[18] In construing section 102, the trial judge apparently viewed the Loprinzi photograph as a "printed publication" which described the Zinkin invention. While neither this Court nor apparently any other tribunal has yet determined whether a photograph in itself constitutes a "printed publication," we believe that a photograph may so qualify for purposes of section 102.[45] In so stating, we reaffirm our pragmatic pronouncement in Philips Electronic and Pharmaceutical Industries Corp. v. Thermal and Electronics Industries, Inc.,[46] that "to restrict our interpretation of section 102(a)'s 'printed' publication requirement solely to the traditional printing press would ignore the realities of the scientific and technological period in which we live * * *."[47] With a photograph, one conversant in a pertinent art could make or construct a purported invention without resorting either to the patent or to his own inventive skills. Under certain circumstances, then, a photograph may so anticipate a patent as to render it invalid.

The question remains, however, whether the photograph of Loprinzi's device anticipated those claims of the Zinkin patent that the defendants challenge. We hold that it does not. In Philips we specified the circumstances under which a prior publication could anticipate a patent: "For a prior publication to be sufficient to defeat a patent it must exhibit a substantial representation of the invention in such full, clear, and exact terms that one skilled in the art may make, construct and practice the invention without having to depend on either the patent or on his own inventive skills."[48]

[19] In the discussion of obviousness in Part III-A, we observed that it would be difficult, if not impossible, to discern the content of the Loprinzi photograph. That observation is applicable here, for it would not be possible for a trial court to ascertain whether the photograph anticipates the Zinkin invention. The photographic representation of the Loprinzi "super-duper pressing apparatus" hardly is "full, clear, and exact." It is questionable whether one skilled in the design of weight-lifting apparatus could produce the Zinkin device, based on an examination of the Loprinzi photograph. Accordingly, the magazine photograph is insufficient to render the patent invalid on the ground of anticipation.

[20] Nor can we hold that the Simmons patent anticipated the Zinkin weight-lifting machine. It is unclear whether the Simmons invention encompasses all or substantially all of the elements of the apparatus under scrutiny in this case. The evidence submitted does not reveal whether one skilled in the design of body-exercising devices, or even in mechanical engineering, could develop the Zinkin weight-lifting apparatus based on the Simmons patent or on his own skills. We conclude, therefore, that the defendants in the present case have failed to demonstrate invalidity of the challenged claims under section 102.

IV.

While the validity of the Zinkin patent is not completely free from doubt, we do not accept the decision reached by the district court. The district court erred in according substantial weight to the testimony of Mr. Lyle. Without such unjustified reliance on that testimony, the trial judge could not properly interpret the prior art. Because the evidence produced by the defendants simply is not sufficient to rebut the presumption of validity accorded patents, we must reverse the rulings of the district court as to obviousness and anticipation, and sustain claims numbered 3 and 4 of the Zinkin patent.

The judgment of the district court will be vacated and the cause remanded for proceedings consistent with this opinion.

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[45] Several courts have held that a *drawing* unaccompanied by verbal description may constitute a description in a printed publication within the meaning of section 102. *See*, e.g., Des Rosiers v. Ford Motor Co., 143 F.2d 907, 911-12, 62 USPQ 320, 323-324 (1st Cir. 1944); In re Bager, 47 F.2d 951, 953, 8 USPQ 484, 486-487 (C.C.P.A. 1931). A photograph may disclose an invention as well as, if not better than a drawing and, consequently, is a "printed publication" for purposes of the statute.

[46] 450 F.2d 1164, 171 USPQ 641 (3d Cir. 1971).

[47] Id. at 1170, 171 USPQ at 645-646.

[48] Id. at 1169, 171 USPQ at 644-645. For similar statements of the "anticipation" standard, see Eames v. Andrews, 122 U.S. 40, 66 (1886); Seymour v. Osborne, 78 U.S. 516, 555 (1970); Rich Products Corporation v. Mitchell Foods, 357 F.2d 176, 180, 148 USPQ 522, 524-525 (2d Cir.), cert. denied 385 U.S. 821, 151 USPQ 757 (1966); Application of LeGrice, 301 F.2d 929, 936, 133 USPQ 365, 371-372 (C.C.P.A. 1962); Deller's Walker on Patents §60 (2d ed. 1964).

Exhibit I

Review by Commissioner of Patents, sua sponte, of question whether decision ordering reexamination should be vacated in view of consent decree in related litigation. Reexamination vacated.

Michael A. O'Neil, and Gardere & Wynne, both of Dallas, Tex., for patent owner.

Louis J. Virelli, J. Walter Schlipp, and Paul & Paul, all of Philadelphia, Pa., for requester.

Tegtmeyer, Assistant Commissioner for Patents.

DECISION VACATING REEXAMINATION PROCEEDING

The above noted reexamination proceeding is before the Office of the Assistant Commissioner for Patents for a determination, sua sponte, of whether the decision ordering reexamination should be vacated in view of a CONSENT DECREE AND PERMANENT INJUNCTION filed February 28, 1984, by the court in related litigation in the U.S. District Court for the Middle District of Pennsylvania styled *Ag-Bag Corp. v. American Bag All Corp. et al*, Civil Action No. CV-83-0374. The court held that claims 1-35 (all claims of the patent) are valid and enforceable against the Defendant-Requester American Bag All Corporation and the other Defendants.

DISCUSSION

[1] The general policy of the Office is that it will act in harmony with the courts and will not "relitigate" in a reexamination proceeding an issue of patentability which has been resolved by a federal court on the merits. See *In re Pearne et al*, 212 USPQ 466 (Com'r. Pat. 1981). While a consent decree is not a decision on the merits pursuant to consideration by the court of the prior art, a consent decree is a "decision on the merits" as to the parties of the litigation. Absent any overriding issue for the Commissioner to continue the reexamination proceeding, it is appropriate that the reexamination proceeding be vacated when a consent judgment affecting all of the claims of the patent is ordered by the court against the reexamination requester. Accordingly, further action in the '436 reexamination proceeding will be in accordance with the decision set forth below.

DECISION

[2] In view of the consent decree issued by the court, the parties no longer have any apparent interest in continuing the '436 reexamination proceeding. As no other indication of interest is present nor any overriding public policy issue is involved, the decision ordering reexamination in Control No. 90/000,436 is *vacated* without prejudice as to any other party filing a request for reexamination based on some or all the prior art before the court. As the decision vacating the reexamination order is equivalent, for fee purposes, to an initial denial of reexamination, a refund of $1,200 will be made to requester.

CONCLUSION

Reexamination proceeding Control No. 90/000,436 is *vacated* and a refund of $1,200 of the filing fee is ordered. The reexamination file will be returned to the Director of Examining Group 240 for action not inconsistent with this decision.

Patent and Trademark Office
Board of Patent Interferences

Wick v. Zindler, et al.

No. 100,191

Decided January 5, 1984
Released February 10, 1986

PATENTS

1. Interference — Reduction to practice — In general (§41.751)

Patentability — Substitution of equivalents (§51.65)

Interference party's argument that pivoted shoe clutch is equivalent to sliding shoe clutch is inapplicable, since doctrine of equivalence does not apply in interference proceedings, nor is argument valid that pivoted shoe clutch is simple invention which did not need to be tested for reduction to practice, since clutch and brake mechanism intended to be used on lawn mower is not type of rare invention that can be reduced to practice by mere construction.

2. Attorneys — Propriety of conduct (§17.7)

Testimony by interference party's counsel, who identified certain documents that inventor used to explain invention during conferences with him, as to when conferences occurred,

and that invention was then explained to, and understood by him, is entitled to sufficient weight to corroborate conception.

Particular patents — Clutches and Brakes

Zindler and Pollow, application, awarded priority against Wick, in counts 4 and 5, and Wick, Patent No. 4,044,533, awarded priority against Zindler and Pollow, in counts 6 and 7.

Patent interference No. 100,191, between Gerald H. Wick, Patent No. 4,044,533, filed May 27, 1976, Serial No. 690,632, and Hugh A. Zindler, and Sheldon D. Pollow, application, Serial No. 654,214, filed February 2, 1976. Priority in subject matter in counts 4 and 5 awarded to party Zindler, and priority of invention of subject matter in counts 6 and 7 awarded to party Wick.

Robert E. Clemency, Gerrit D. Foster, Bayard H. Michael, Paul R. Puerner, Joseph A. Gemignani, Andrew O. Riteris, Glenn A. Buse, and John L. Beard, all of Milwaukee, Wis., for party Wick.

Elwin A. Andrus, Merl E. Sceales, Glenn O. Starke, Eugene R. Sawall, Guenther W. Holtz, Frank S. Andrus, Daniel D. Fetterley, and George H. Solveson, all of Milwaukee, Wis., for party Zindler.

Before Calvert, Urynowicz and Boler, Examiners of Interferences.

Boler, Examiner of Interferences.

This interference involves a patent to Wick assigned to the Outboard Marine Corporation (Outboard) and an unassigned application of Zindler et al. (Zindler). The application that matured into the Wick patent was filed on May 27, 1976. The senior party Zindler file his involved application on February 2, 1976, and he relies on that date for a reduction to practice of all of the counts in issue.

The subject matter involved concerns a clutch and brake mechanism. The only counts in issue are counts 4 through 7 which correspond exactly to claims 15, 16, 19 and 20 of the Wick patent and to claims 19, 20, 22 and 23 of the Zindler application. Counts 4 and 6 depend from count 1 which is no longer an issue in the interference since the claim in the Zindler application corresponding thereto was held to be unpatentable to Zindler by the primary examiner during the motion period. Dissolved count 1 corresponds exactly to claim 11 of the Wick patent. Counts 4 and 6 are reproduced below along with dissolved count 1 from which they depend:

[*Count 1*

A combined brake and clutch mechanism comprising a drive member mounted for rotation and including thereon a clutch drum, a driven member carried for rotation coaxially with and relative to said drive member, a clutch shoe connected to said driven member for common rotation therewith and for movement relative to a position of engagement with said clutch drum, biasing means for urging said clutch shoe toward said position of engagement, a brake surface fixed to said clutch shoe, and a brake member movable between a first position wherein said brake member is spaced from said brake surface, and a second position wherein said brake member engages said brake rotation of said driven member and to displace said clutch shoe from said position of engagement against the action of said biasing means.]

Count 4

A combined brake and clutch mechanism in accordance with count 1 wherein said clutch shoe is connected to said driven member for pivotal movement relative to said driven member.

Count 6

A combined brake and clutch mechanism in accordance with count 1 wherein said clutch drum is located radially outwardly of said clutch shoe and extends in generally parallel relation to the axis of drive shaft rotation and wherein said brake surface is located radially outwardly of and in generally parallel relation to said clutch drum.

Both parties submitted evidentiary records, filed briefs and appeared for oral argument at the final hearing.

Wick's Motion to Strike

On pages 26 through 28 of his main brief, Wick has renewed several motions to strike first raised on the record of the depositions taken by Zindler. Wick moved to strike all of the testimony of Holtz, and objected to ZX 115 to 119, on the ground that Holtz should not be permitted to serve both as counsel for Zindler and as a witness on his behalf. This motion is denied for the reasons given hereinafter in discussing Zindler's case for conception.

Wick also moved to strike answers to leading questions on various noted pages of the Zindler record. Many of the questions objected to on this ground were rephrased and not objected to as rephrased. To the extent that some of the questions may be considered leading, the motion to strike the answers thereto is

denied; however, Wick's arguments have been taken into consideration in assessing the weight to which they are entitled.

Wick moved to strike testimony on certain pages of the Zindler record as being irrelevant. This motion is denied because the testimony related either to Zindler's conception or to his attempt to show that the Wick device relied upon for a reduction to practice had not been adequately tested. Both of these areas of inquiry were relevant to issues involved in this interference.

Wick moved to strike testimony on certain pages of the Zindler record as being offered without compliance with proper procedure. This motion is granted as to the testimony regarding exhibits ZX 110 through 114 which were not timely served under 37 CFR 1.287(a)(1). Zindler stated in his brief that he does not rely on ZX 120 or 121 or the testimony relating thereto for any purpose. Thus, this motion is deemed moot as to the testimony regarding those exhibits. ZX 107 is clearly a copy of a portion of ZX 101 and the original objection to ZX 107 as not having been served under 37 CFR 1.287(a)(1) was withdrawn at ZR 26. The motion is denied as to the testimony regarding ZX 107, 109 and 115 through 119 since copies of all of these exhibits except ZX 107 were properly served and Wick is deemed to have waived any objection he may have had as to the latter exhibit.

Wick further objects to the authenticity of ZX 109 and to the manner in which ZX 122 and WX 74-A were admitted. Holtz received ZX 109 from Zindler at least by February 27, 1975, and thus Holtz established its authenticity as of that date. Wick appears to contend that the exhibit has not been shown to be authentic because it has not been established that it was drawn by Pollow (who did not testify). Zindler said that Pollow showed him a copy of ZX 109 before Zindler made ZX 101. He assumed Pollow made ZX 109, but he did not see Pollow make it. For the purpose of this interference, it does not make any difference whether ZX 109 was drawn by Pollow or some unknown third party since third party inventorship is not ancillary to priority. *Sheffner v. Gallo*, 515 F.2d 1169, 185 USPQ 726 (CCPA 1975). Wick introduced ZX 122 into evidence during cross-examination of Holtz and is considered to have waived any objection to the entry thereof. WX 74-A was identified during Wick's testimony and is deemed to be properly in the record even though not formally offered. *Gunn v. Bosch*, 181 USPQ 758 (Bd.Pat.Int.1973).

Zindler's Motion Under 37 CFR 1.287(d) (1)

A motion by Zindler to rely on certain documents not timely served on Wick was deferred to final hearing (Paper No. 55). Zindler's date for service under 37 CFR 1.287(a)(1) expired on February 8, 1982. On February 11, 1982, Zindler measured some of the components of Wick's Exhibit 64-B and, thereafter, made some calculations regarding the ability of the clutch to kill the engine on the lawn mower used in Wick's alleged reduction to practice under dynamic and static conditions of the clutch shoes. Zindler's deposition was taken on March 2, 1982. The documents prepared by Zindler as a result of the measurements and calculations were not served on Wick until direct examination of Zindler was nearly complete (ZR 52-53). The documents involved are ZX 110 through 114. We deny the motion because 37 CFR 1.287(d)(1) requires that the motion be filed "promptly", and Zindler has failed to show why the documents could not have been served at least several days prior to his deposition thereby allowing Wick an opportunity to prepare for cross-examination.

Wick's Case For Priority

Since the application that matured into Wick's patent was copending with the Zindler application, the junior party, Wick, has the burden of proving his case for priority by a *preponderance of the evidence. Peeler v. Miller*, 535 F.2d 647, 190 USPQ 117 (CCPA 1976).

The record submitted by Wick consists of depositions of the inventor Gerald Wick, of Theodore Holtermann, of Gerald Haft, and of Gerald Betts, together with associated exhibits. Exhibit 1 of the Wick record is a stipulation between the parties as to the authenticity of certain of the exhibits introduced by Wick.

Wick discloses two embodiments in his application. The first embodiment is illustrated in Figures 2 and 3 and comprises clutch shoes 31 which are slidingly connected to the driven member 41. The other embodiment is illustrated in Figures 4 and 5 and comprises clutch shoes 31 pivotally connected to the driven member. Counts 6 and 7 are generic to both embodiments, but counts 4 and 5 are limited to a mechanism wherein the clutch shoes are pivotally mounted to the driven member.

Counts 6 and 7

Wick made a drawing (WX 2) of a clutch and brake mechanism meeting the terms of

counts 6 and 7 sometime prior to June 10, 1975. The drawing was seen and understood by Haft and Holtermann by June 10, 1975. We find, and Zindler does not contend otherwise, that Wick has established conception of the subject matter in counts 6 and 7 by June 10, 1975.

After receiving a copy of WX 2, Haft assigned Holtermann the job of building a clutch and brake mechanism in accordance with the drawing for use on a lawn mower. Holtermann constructed a device which is in evidence as WX 64-B. The mechanism is illustrated in WX 37 and is labelled Type 2. Many of the Wick exhibits are drawings made by Betts under the supervision of Holtermann. Betts testified that he drew the portion of WX 37 relating to the Type 2 mechanism on or before July 14, 1975. This mechanism has sliding clutch shoes and was mounted on the lawn mower shown in WX 59 through 66. The mechanism was tested at Outboard's facilities in Milwaukee prior to September 15, 1975, where Holtermann and Haft were employed, and further tested at Lawn-Boy Engineering (Lawn-Boy) in Galesburg, Illinois, where Wick was employed, on September 25, 1975. Lawn-Boy is a part of Outboard.

The mechanism as installed on the lawn mower was arranged so that the brake was normally spring biased into engagement thereby normally maintaining the blade stationary during operation of the engine. A linkage (deadman control) under the control of the operator could be actuated to release the brake and engage the clutch to drive the blade. Holtermann and Haft testified that the lawn mower was used to cut weeds and grass in September 1975. The brake held the blade stationary except when the operator purposely released it, and the clutch picked up the blade when the brake was released. Both considered the tests to be successful, but indicated that there was some dissatisfaction with the noise on engagement and disengagement (WR 107-108, 204-205).

Zindler concedes that counts 6 and 7 read on the mechanism tested on behalf of Wick in September 1975, but he contends that the testing was inadequate to establish an actual reduction to practice; that the opinion testimony of Holtermann and Haft six years after the tests is insufficient to prove that they were successful; and the fact that Holtermann started working on the pivoted shoe embodiment shortly after the September tests supports Zindler's contention that the September tests were nothing but an abandoned experiment.

Zindler relies on his own testimony as well as that of Holtermann to the effect that in the circumstance where the blade could not turn, for example, due a plugged discharge chute or some other obstruction, the lawn mower engine used in the September tests would overpower the clutch and cause it to slip with the result that the clutch could overheat and be destroyed in a short period of time. Zindler's testimony was based on calculations set forth in ZX 110 through 114. We have not accorded these exhibits or Zindler's testimony with respect thereto any weight because the exhibits were not timely served under 37 CFR 1.287(a)(1), and we hereinabove denied Zindler's motion under 37 CFR 1.287(d)(1) to have the late service of copies of ZX 110 through 114 excused. Holtermann testified that the problem alluded to by Zindler did not arise during the testing of WX 64-B, but he was of the view that if it did occur the operator would realize that the blade was not turning within 10 or 15 seconds and release the clutch before any damage would occur thereto (WR 242-243). Moreover, Holtermann testified that the lawn mower was tested under load by pushing it into heavy grass and weeds before engaging the clutch and that the clutch picked up the blade to cut the grass as intended (WX 107-108, 242). In our view, the testimony of Holtermann and Haft is clear and definite to the effect that the WX 64-B clutch and brake mechanism successfully performed its intended function in September 1975 and their testimony is sufficient to corroborate an actual reduction to practice on behalf of Wick at that time with respect to the subject matter in counts 6 and 7. The case cited by Zindler, *Konet v. Haskins*, 179 F.2d 1003, 84 USPQ 461 (CCPA 1950) is not controlling here for in that case the Court said that the testimony of the witness was "too indefinite, both as to the parts of the instrument, their relationship inside the instrument, as to just how such parts were functioning, to constitute satisfactory proof of reduction to practice."

The evidence relied upon by Zindler for his contention that the sliding shoe mechanism (WX 64-B) was merely an abandoned experiment consists of a letter (WX 21) from Mr. Comstock, house counsel for Outboard, to Mr. Clemency, outside counsel, Wick's notes (WX 29) regarding some testing which took place in March 1976, and a memo (WX 30) from Holtermann to Wick in March 1976, together with the fact that shortly after the September tests Holtermann started working on a pivoted shoe arrangement. In WX 21, dated November 21, 1975, Comstock noted that he had sent Clemency a drawing of the sliding shoe embodiment on October 13, 1975 and then stated that, "[w]e apparently had some difficulty with this design and have now gone to a pivoted shoe arrangement as shown at the top left of [WX 37]. This arrangement (top left) is now our preferred form of this invention." In

WX 29, dated March 10, 1976, Wick stated with respect to the testing in early March 1976, "[t]he sliding shoe type was noisy both engaged and unengaged. We did not use this clutch very much." In WX 30, dated March 12, 1976, Holtermann stated, "[e]nclosed are layouts and details of . . . the 'Wick' centrifugal clutches which should be sufficient to allow you to develop cost figures." Holtermann then went on to state that the Type I clutch had been built as shown, and that the shoulder bolts shown on the Type 3 clutch had been replaced with welded-in solid pins. Both the Type 1 and 3 clutches have pivotal shoes. Since the Type 2 clutch was not specifically mentioned in WX 30, Zindler concludes that it had been abandoned by then. On the other hand, Holtermann testified that the term "clutches" in the second line of the memo included both types of clutches (WR 114).

The evidence relied upon by Zindler does not show that Wick abandoned the sliding shoe embodiment but merely indicates that the pivoted shoe form was preferred. Comstock did not testify, therefore, the "difficulty" mentioned in WX 21 has not been explained but there is nothing in the record to indicate that he was referring to anything other than the noise generated by the operation of WX 64-B, which was referred to in the testimony of Wick, Haft and Holtermann. The sliding shoe mechanism was tested in September 1975, again in March 1976, and was illustrated and described in the Wick patent application filed in May 1976. This conduct by Wick is not consistent with Zindler's theory that the September tests were abandoned experiments.

Accordingly, we hold that Wick has established that he conceived and reduced to practice the invention in counts 6 and 7 by September 25, 1975.

Counts 4 and 5

Wick did not test a mechanism meeting the terms of counts 4 and 5 on a lawn mower until March 1976, that is, after Zindler's filing date of February 2, 1976. Wick argues that the pivoted shoe clutch is equivalent to the sliding shoe clutch; that a pivoted shoe clutch was assembled prior to Zindler's filing date; and that the pivoted shoe clutch is a simple invention which did not need to be tested for a reduction to practice, particularly in view of the fact that the sliding shoe embodiment had already been successfully tested.

[1] The doctrine of equivalence does not apply in interference proceedings. *Wetmore v. Quick*, 536 F.2d 937, 190 USPQ 223 (CCPA 1976). In our view, a clutch and brake mechanism intended to be used on a lawn mower is not the rare type of invention that can be reduced to practice by mere construction. Since Wick did not test the pivoted shoe clutch prior to March 1, 1976, he has failed to establish an actual reduction to practice of the subject matter in counts 4 and 5 prior to Zindler's filing date. *Elmore v. Schmitt*, 278 F.2d 510, 125 USPQ 653 (CCPA 1960).

It is not clear from the record when Wick first became aware of the fact that Holtermann was working on the pivoted shoe clutch, but the earliest date which we could possibly find for conception by Wick of the pivoted shoe clutch would be late October 1975 when Betts drew the views labelled Type 1 and 3 on WX 37 under Holtermann direction (WR 227-228). We need not consider Wick's case for conception coupled with diligence as to counts 4 and 5 because we hold hereinafter that Zindler was the first to conceive as well as the first to reduce to practice by filing with respect to those counts.

Zindler's Case for Conception

The record submitted by Zindler consists of the deposition of one of the inventors, Hugh A. Zindler, and of his patent attorney Guenther W. Holtz, along with several documentary exhibits. Sheldon D. Pollow, the other inventor, did not testify.

Zindler made a drawing (ZX 101) in December 1974 and took it to his patent attorney in January of 1975. Additional drawings (ZX 102, 103 and 104) and a written description (ZX 105) were taken by Zindler to his patent attorney in February 1975. Zindler read the counts element for element on ZX 101 and 102 and wrote legends on ZX 107 designating the various elements. Zindler testified that he had known Pollow for a number of years prior to the invention; that Pollow came to him in the fall of 1974 to discuss a problem in the design of a clutch and brake mechanism; that since they lived twenty miles from each other they worked independently on the problem after discussing a number of possible solutions; and that Pollow showed him a copy of the drawing in evidence as ZX 109 before Zindler made ZX 101.

Holtz corroborated Zindler's testimony to the effect that he received a copy of ZX 101 in January 1975 and received copies of ZX 102, 103, 104 and 105 in February 1975. Holtz said he also received a copy of ZX 109 but he was not sure whether he received it when he met with Zindler in January or February 1975. He believes that he received it in February 1975 because the invention was logged into the firm records in January with Zindler listed

as the inventor and that Pollow would have also been listed as an inventor if Holtz then realized that the disclosure brought in by Zindler involved a joint conception. Holtz testified that Pollow was expected to be a witness in this case, but that he requested not to be called to testify due to the fact that he was in poor health.

[2] In our view, Holtz has adequately corroborated conception on the part of Zindler and Pollow as of at least February 27, 1975. Wick contends that the testimony of Holtz should be given no weight because it is against the canons of ethics of the American Bar Association and the State Bar of Wisconsin for an attorney to testify as a fact witness for a client he is representing. However, whatever the ethical considerations may be, an attorney is competent to serve as a witness for or against his client. 97 C.J.S. Witnesses Sec. 71, p. 467, reproduced in *Wilder v. Snyder*, 201 USPQ 927, 934 (Bd.Pat.Int.1977). Of course, the role of advocate is inconsistent with that of an unbiased witness and, therefore, an attorney testifying for his client can expect his testimony to be discounted. Nevertheless, under the circumstances of this case where Holtz has identified certain documents that the inventor used to explain the invention during conferences with him, we believe that his testimony as to when the conferences occurred and that the invention was then explained to and understood by him is entitled to sufficient weight to corroborate conception. We note that Holtz supported his testimony with documentary evidence in the form of calendar entries (ZX 115 and 116) and entries in his law firm's log of invention disclosures (ZX 117 and 118).

Wick also argues that Holtz has not corroborated conception by Zindler and Pollow prior to the filing date of the Zindler application because Holtz was apparently under the impression that Zindler was a sole inventor when Zindler explained the invention to him. However, Zindler acknowledges that he met with Pollow to discuss the invention prior to his first meeting with Holtz, and he concedes that Pollow is a joint inventor. The application executed by Zindler and Pollow contains drawings which are nearly identical to ZX 101 and 102 which were shown to Holtz in January and February 1975. No more is required to establish joint conception of the invention in issue by Zindler and Pollow as of February 27, 1975. *Haskell v. Colebourne*, 671 F.2d 1362, 213 USPQ 192, 195 (CCPA 1982).

Thus, we hold that Zindler has established conception of the invention in counts 4 through 7 as of February 27, 1975, and that he was the first to reduce to practice the invention in counts 4 and 5 by filing his patent application on February 2, 1976.

Wick's Request to Dissolve as to Counts 4 and 5

Wick contends that if he is not found to be the first inventor of the subject matter in counts 4 and 5, the interference should be dissolved as to those counts because they are not patentable over the prior art and in addition they are not patentable over counts 6 and 7. The primary examiner at one point in these proceedings dissolved the interference as to counts 4 and 5 on the ground that Zindler's claims corresponding thereto were not patentable over the prior art. Zindler requested reconsideration, and the primary examiner reinstated counts 4 and 5 stating that he found the subject matter therein to be patentable to Zindler over the art previously relied upon. Wick contends that the primary examiner did not consider Wick's opposition when he reinstated counts 4 and 5. We note, however, that the entire interference file is sent to the primary examiner when he is required to render a decision. Since Wick's opposition (Paper No. 26) was in the file at the time of the reconsideration, the primary examiner would have, as a matter of course, considered the opposition in reaching his decision. The question of patentability over the prior art is not ancillary to priority and, accordingly we have no authority to decide that issue. *Anderson v. Scinta*, 372 F.2d 523, 152 USPQ 584 (CCPA 1967).

Counts 4 and 5 are not anticipated by the subject matter in counts 6 and 7 and Zindler maintains that they are in fact patentably distinct therefrom. The question of patentable distinctness between counts has been held to be ancillary to priority in an interference involving only applications. *Hester v. Allgeier*, 646 F.2d 513, 209 USPQ 370 (CCPA 1981). That decision is not deemed to be applicable to an interference involving a patent, as here, in view of the provision in 37 CFR 1.205(a) to the effect that an applicant must present in his application copies of all of the claims of the patent which also define his invention, and the long standing practice of using all of the copied claims as counts of the interference because the patent is outside the jurisdiction of the Patent and Trademark Office except for the question of priority. I Rivise and Caesar, *Interference Law and Practice*, Section 54, p. 105, (Michie Co. 1940). Under 35 USC 135(a), the claims of a patent corresponding to lost counts in an interference are cancelled by operation of law. Claims 15 and 16 of the Wick patent would not be cancelled pursuant to the statute if the interference were dissolved with respect to counts 4 and 5 as requested by Wick. In any event, we have no authority to dissolve counts

of an interference. *Nitz v. Ehrenreich*, 537 F.2d 539, 190 USPQ 413 (CCPA 1976). The most that we could do is recommend dissolution to the Commissioner of the Patent and Trademark Office under 37 CFR 1.259, but we are not persuaded by Wick's arguments that we should make such a recommendation in this case.

Award of Priority

Priority of invention of the subject matter in counts 4 and 5 is awarded to Hugh A. Zindler and Sheldon D. Pollow, the senior party; and priority of invention of the subject matter in counts 6 and 7 is awarded to Gerald H. Wick, the junior party.

District Court, S. D. New York

Ballet Makers, Inc. v.
The United States Shoe Corporation, et al.

No. 85 Civ. 8622 (MEL)

Decided May 5, 1986

TRADEMARKS

1. Infringement — Tests of (§67.439)

Dance footwear and dance accessory items produced by defendant company which was authorized by trademark owner to use owner's mark on its goods were not, as matter of law, imitations, but rather genuine product, sponsored by and produced for trademark owner, and use of mark accurately designated correct source of goods and did not create likelihood of confusion within meaning of Lanham Act, despite allegation that trademark owner had previously given exclusive license to plaintiff.

Action by Ballet Makers, Inc., against The United States Shoe Corporation, and J. P. Manning, Inc., for trademark infringement, Lanham Act violations, and breach of contract. On defendants' motion to dismiss or for summary judgment. Motion granted in part.

Edward A. Mailman, and Ostrolenk, Faber, Gerb & Soffen, both of New York, N.Y. (Mark Garscia, Lawrence Freedman, and Koenig, Ratner & Mott, P.C., all of New York, N.Y., of counsel) for plaintiff.

Brumbaugh, Graves, Donohue & Raymond, New York, N.Y. (Joseph D. Garon, Robert Neuner, and Doreen J. Leavens, all of New York, N.Y., of counsel) for defendant The United States Shoe Corporation.

John P. Reiner, and Townley & Updike, both of New York, N.Y. (David O. Simon, New York, N.Y., of counsel) for defendant J. P. Manning, Inc.

Lasker, District Judge.

This litigation concerns the use of the trademark CAPEZIO.[1] Ballet Makers, Inc. ("Ballet Makers"), a New York corporation which manufactures dance and recreational footwear and accessories, was originally established as a manufacturing division of Capezio, Inc. In 1964 Ballet Makers was spun off and given the right to sell and manufacture certain CAPEZIO products. In 1973, Capezio, Inc., then experiencing financial difficulties, sold the title to the CAPEZIO trademark, which, in December of that year, came to be owned by United States Shoe Corporation ("U.S. Shoe"), a corporation established under the laws of Ohio. On February 13, 1974 U.S. Shoe and Ballet Makers entered into an agreement granting Ballet Makers a license to sell and distribute certain CAPEZIO products ("the 1974 agreement"). Ten years later, U.S. Shoe entered into another licensing agreement, this time with J.P. Manning, Inc. ("Manning"), a New York corporation ("the Manning agreement"). Ballet Makers' claim that the Manning agreement encroaches on Ballet Makers' rights under the 1974 agreement lies at the heart of this litigation. Specifically, Ballet Makers alleges violations of the Lanham Act, §§ 32 and 43(a), 15 U.S.C. §§ 1114 and 1125(a) respectively, and breach of contract. It seeks damages as well as injunctive relief. Jurisdiction is asserted under 15 U.S.C. §1121, 28 U.S.C. § 1338, 28 U.S.C. § 1332 and based upon the doctrine of pendant jurisdiction.

[1] According to the complaint, there are several registrations of the trademark, "including but not limited to Reg. Nos. 662,280 and 893,346." Complaint at ¶ 7. "CAPEZIO," as used throughout this decision, refers to all of the relevant registrations.

Exhibit J

make nebulous reference to "extensive" advertisement on radio and in newspapers and to prominent display of the mark on signs outside applicant's store).

Applicant in this case also presses upon the Board the fact that it has been issued a state trademark registration for "OFF THE RACK" and maintains that this must be taken as prima facie evidence of distinctiveness (inherent or acquired), especially since the state statute involved has substantially the same registration standards as the Lanham Act. However, it is well-established that in trademark proceedings before the Unites States Patent and Trademark Office, state registrations are neither controlling on the question of trademark usage nor on the question of federal registrability of a mark. See T.J. McCarthy, Trademarks and Unfair Competition, §22.2 at p. 27 (2d ed., 1984); Philip Morris Inc. v. Liggett & Myers Tobacco Co., 139 USPQ 240 (TTAB 1963) ("COUPON" held merely descriptive of cigarettes containing premium redemption coupons despite state registration); In re Illinois Bronze Powder & Paint Co., 188 USPQ 459 (TTAB 1975) (slogan mark held not registrable on basis of secondary meaning despite submission of state registration, 5-year use declaration, and litigation consent agreement). Nor does the Board view applicant's successful litigation in federal courts, based on its state registration and general "unfair competition" doctrine, as relevant to the question of inherent or acquired distinctiveness since that issue was not involved in such litigation. That distinctiveness may have been assumed by the Court therein (i.e., within the particular meaning and requisites of the Lanham Act) is purely speculative since it was the Court's function only to adjudicate the claims and contentions before it. These focussed on concepts and issues of priority, natural expansion, false designation, and confusing similarity in a context not involving federal registration rights but did not deal with the question of possible descriptiveness of the designations involved.

By any standard, applicant's case for acquired distinctiveness is a weak one (and in no event entitled to a presumption of distinctiveness based on five years of continuous and substantially exclusive use since the federal statute requires such use prior to application filing). The case, moreover, is "thin" on manner and extent of use of the mark and even "thinner" on its evidence of a significant body of recognition of source-indicating capacity. Whatever applicant's actual record of sales, advertising and generation of secondary meaning for "OFF THE RACK" in the minds of purchasers may be, what is established on this record is, in our view, inadequate to make the Section 2(f) case. We conclude that the Examining Attorney's determination to that effect was correct and proper.

Decision:

The refusal to register is affirmed.

District Court, N.D. New York

SMI Industries Canada Ltd. v. Caelter Industries, Inc. et al.

No. 83-CV-1515

Decided May 21, 1984

PATENTS

TRADEMARKS

UNFAIR COMPETITION

1. Attorneys — Propriety of conduct (§17.7)

Party's receipt of assets, including patent and trademark rights, from company that opposing party's attorney once represented, does not confer "former client" status upon that party within meaning of Canon 4 of Code of Professional Responsibility, absent any other previous attorney-client relationship between attorney and party receiving those assets.

PATENTS

TRADEMARKS

2. Attorneys — Propriety of conduct (§17.7)

Disqualification of counsel in patent and trademark action is not required under Canon 5 of Code of Professional Responsibility for attorney who formerly represented intellectual property interest of company whose assets were acquired by party requesting disqualification, absent evidence that attorney "ought to" testify in pending action, according to DR 5-102(a), and absent evidence that

continued represent
party seeking disqual

PATENTS

TRADEMARKS

3. Attorneys — F
(§17.7)

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PATENTS

4. Injunction — P
(§40.5)

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that patent is valid "

TRADEMARKS

5. Title — Assignm

Trust deed that
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not amount to actual
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6. Abandonment —

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UNFAIR COMPETI

7. Injunction —
(§40.9)

Injunctive relief is
cused whose letter t

continued representation would prejudice party seeking disqualification.

PATENTS

TRADEMARKS

3. Attorneys — Propriety of conduct (§17.7)

There is no "appearance of impropriety," under Canon 9 of Code of Professional Responsibility and no legal inconsistency in argument by one party's attorney, who formerly represented opposing party's predecessor in interest, that patents he originally helped to secure for predecessor in interest are invalid based upon newly discovered art or that trademark rights that opposing party asserts do not belong to it, or are abandoned.

PATENTS

4. Injunction — Preliminary injunction (§40.5)

Preliminary injunction enjoining patent use is not warranted, without demonstration that patented product is widely accepted in industry or that it generates large profits, and that patent is valid "beyond question."

TRADEMARKS

5. Title — Assignments (§67.863)

Trust deed that used trademark rights merely to secure indebtedness, but that did not amount to actual transfer of control over trademarks to trust company, did not constitute invalidating in gross transfer, nor did later purchase agreement reciting sale of trademark and various company assets, since goodwill was plainly acquired appurtenant to acquisition of trademarks.

6. Abandonment — In general (§67.031)

Fact that trademark owner with knowledge of accused's use of trademark waited some three and one-half months before formally notifying accused to "cease and desist" does not amount to "uncontrolled and naked licensing," considering realities of modern business practices and fact that trademark owner was Canadian corporation struggling to establish subsidiary at time of alleged infringement.

UNFAIR COMPETITION

7. Injunction — Unfair competition (§40.9)

Injunctive relief is appropriate against accused whose letter to customers and news release misleadingly implies that competitor is "carpet bagger" disrupting accused's business, but fails to disclose existence of competitor's competing claims to intellectual property.

Particular patents — Anti-shimmy Devices

4,178,007, Martineau, Hydraulic Anti-shimmy Device for Caster Wheels, preliminary injunction denied.

Action by SMI Industries Canada Ltd., against Caelter Industries, Inc., for trademark and patent infringement and unfair competition, in which defendant counterclaims for unfair competition. On plaintiff's motions for disqualification of defendant's counsel, and for preliminary injunction. Motions denied.

Hiscock, Lee, Rogers, Henley & Barclay, New York, N.Y. (J. Eric Charlton, New York, N.Y., of counsel) for plaintiff.

MacKenzie, Smith, Lewis, Mitchell & Hughes, Syracuse, N.Y., and Limbach, Limbach & Sutton, San Francisco, Calif. (Dennis P. Hennigan, Syracuse, N.Y., and George C. Limbach and Marie S. Cefalu, both of San Francisco, Calif., of counsel) for defendant.

Munson, District Judge.

This is an action for trademark and patent infringement as well as unfair competition. Plaintiff, a Canadian corporation, is engaged in the manufacture, sale and distribution of commercial snow removal and airport rescue equipment. Defendant, a New York corporation, is engaged in the same industry. At issue in the instant lawsuit are the trademarks "SMI," "Snowmaster" and "Firemaster," all names used on various products manufactured by the parties herein. The patent at issue, U.S. Patent No. 4,178,007, concerns what the parties commonly refer to as a "Hydraulic Anti-Shimmy Device for Caster Wheels." This device is apparently used to aid in removal of snow with large snow removal vehicles. Lastly, the unfair competition claim concerns defendant's alleged defamation of plaintiff and its products. Defendant has answered plaintiff's complaint and has counterclaimed for both federal and state statutory unfair competition.

Presently before the court are plaintiff's motions for an order disqualifying the law

firm of Limbach, Limbach & Sutton from representing the defendant Caelter Industries, Inc., and for a preliminary injunction pending a trial on the merits. See Fed. R. Civ. P. 65. Before addressing the motions the court believes that the complex factual background of this case must be set forth in some detail.

I. Facts

Caelter Enterprises, Ltd., a now bankrupt Canadian corporation, was the owner of the intellectual property at issue in this lawsuit. Prior to May of 1977 Caelter Enterprises licensed these properties to its wholly owned subsidiary Caelter Industries, Inc. for use in the latter's Watertown, New York business, operating under the name of SMI New York. In May of 1977 when Caelter Enterprises was encountering severe financial difficulties, Caelter Enterprises President Walter O. Lampl entered into an agreement known as a Trust Deed with the Royal Trust Company of Montreal. The purpose of this agreement was to secure the bond obligations of Caelter Enterprises with the Royal Trust Company acting as a trustee for the bondholders. As collateral for the Trust Deed, Caelter Enterprises gave the Royal Trust Company the equivalent of a security interest in its intellectual property and other assets, including most, if not all, of the patents and trademarks at issue herein.

Caelter Enterprises continued with its financial difficulties until the company finally went bankrupt in December of 1982. At that time the Royal Trust Company and Bank of Montreal, a bondholder, assumed possession and control over all of the assets of Caelter Enterprises. Following the bankruptcy of Caelter Enterprises, another Canadian corporation, operating under the name 123517 Canada, Inc. purchased most of the assets of Caelter Enterprises from the Royal Trust Company and the Bank of Montreal. The purchaser corporation, 123517 Canada, Inc., later assumed its present name of SMI Industries Canada Ltd. and is the plaintiff in this action.

Plaintiff SMI Industries Canada Ltd. formed an American corporation known as S.M.I. Industries, U.S.A., Inc. in or about September of 1983. S.M.I Industries, U.S.A., Inc. is the counterclaim defendant herein and operates its business in Watertown, New York under that name. Thus, there is relatively little difference between the operating names of plaintiff's and defendant's facilities, and it is undisputed that both parties distribute competitive products. It is both the similarity in names and in products that give rise to the instant lawsuit.

With regard to the defendant Caelter Industries, Inc., the court notes that one hundred percent of the stock of this corporation is currently held by the Royal Trust Company. Walter O. Lampl, the President of Caelter Industries, Inc., who was also the President of Caelter Enterprises, Ltd., presently has an agreement to purchase this stock from the Royal Trust Company. Thus, the control of both Caelter Industries and Caelter Enterprises in terms of their day-to-day operations has always been with Mr. Lampl.

Caelter Industries, Inc. does business through its two divisions, the Snowblast Division in Denver, Colorado and the SMI New York Division in Watertown, New York. The corporation traces its roots back to two distinct corporations, the American Snowblast Corporation of Denver, Colorado and Sicard Industries, Inc. of Watertown, New York. Through various mergers and/or acquisitions not pertinent to this lawsuit, the current defendant Caelter Industries, Inc. was formed in 1977.

Following the bankruptcy of Caelter Enterprises, Ltd., the Royal Trust Company, through its accounting firm Coopers & Lybrand, prepared a brochure describing the assets of Caelter Enterprises for prospective bidders. This brochure was dated February 11, 1983 and described the Caelter Enterprises assets in twenty-eight general lots or categories. During the pendency of the sale period, Caelter Enterprises' American subsidiary corporation, Caelter Industries, continued to operate its two divisions in Denver and Watertown. It is also undisputed that Caelter Industries continued to use, as it had in the past, all of the intellectual property at issue herein.

On or about May 24, 1983 plaintiff SMI Industries Canada Ltd. (then known as 123517 Canada, Inc.) entered into the contract which purportedly gave it the intellectual property that it now claims is being infringed by defendant. The contract specifically lists the trademarks "SMI" and "Snowmaster" in addition to U.S. Patent No. 4,178,007 for the "Hydraulic Anti-Shimmy Device for Caster Wheels." The contract also makes specific reference to the Coopers & Lybrand brochure described above. Noticeably absent from the contract, however, is any mention of the trademark "Firemaster." Following the May 24, 1983 purchase plaintiff notified defendant of its acquisition of these properties and demanded that defendant cease its use thereof. In due course this action was commenced on November 17, 1983. See Fed.R.Civ.P. 3.

II. Motion to Disqualify Defendant's Counsel

The court will first address plaintiff's motion to disqualify the law firm of Limbach, Limbach & Sutton [Limbach firm]. Plaintiff alleges that the Limbach firm's representation of defendant in this action violates Canons 4, 5 and 9 of the New York State Bar Association's Code of Professional Responsibility and certain Disciplinary Rules promulgated thereunder. Each of plaintiff's challenges stems from the Limbach firm's prior representation in patent and trademark matters of Caelter Enterprises, the parent corporation of the defendant and predecessor-in-interest of the plaintiff.

The Limbach firm's representation of defendant's parent corporation in this specialized area of law began in 1967 and continued until 1982 when Caelter Enterprises was forced into bankruptcy. During the period in question the Limbach firm was closely involved in the process of securing for Caelter Enterprises the patents and trademarks which plaintiff claims to have purchased in 1983. Defendant, who now challenges the validity of these patents as well as plaintiff's ownership rights in the trademarks, has itself been a client of the Limbach firm since 1968. As a result of these long-standing attorney-client relationships, the Limbach firm has gained an intimate knowledge of the business operations of the defendant and its parent corporation. Plaintiff contends that the Limbach firm's long-standing relationship with the defendant's parent corporation gives rise to a number of ethical violations in this case. Plaintiff posits three distinct arguments in favor of disqualification.

First, plaintiff argues that since it succeeded to the patent and trademark rights of the defendant's parent corporation, the representation by the Limbach firm presents a serious conflict of interest and the distinct possibility that confidential information obtained during the former representation will be used to the detriment of the plaintiff in violation of Canon 4.

Second, plaintiff argues that the Limbach firm's representation of the defendant violates Canon 5 because it is evident that members of that firm ought to be called as witnesses at trial. This argument stems from the fact that the Limbach firm represented the defendant's parent corporation in the application for and ownership of the patents and trademarks made the subject of this litigation.

Third, plaintiff argues that the Limbach firm cannot represent the defendant in this action because such representation creates the appearance of professional impropriety in violation of Canon 9. Specifically, plaintiff claims that representation of the defendant places the Limbach firm in the anomolous position of challenging the validity of patents which is secured for a former client and the ownership of trademarks which is registered for the client.

For the reason set forth below, the court concludes that no ethical violations are present in this case and thus the motion to disqualify is hereby denied.

A. *Introduction*

As a preliminary matter the court notes that district courts not only have the inherent power to ensure compliance with the ethical standards set forth in the Code of Professional Responsibility, but also the duty and the responsibility to disqualify counsel for unethical conduct prejudical to his or her adversaries. General Motors Corp. v. City of New York, 501 F.2d 639, 643 n. 11 (2d Cir. 1974); Emle Industries, Inc. v. Patentex, Inc., 478 F.2d 562 (2d Cir. 1973); United States ex. rel. Sheldon Elec. Co. v. Blackhawk Heating & Plumbing Co., 423 F.Supp. 486, 488 (S.D.N.Y. 1976).

The courts of this Circuit, however, are quite hesitant to disqualify an attorney and will do so only upon a showing that the attorney's conduct will "tend to taint the underlying trial." Board of Educ. of the City of New York v. Nyquist, 590 F.2d 1241, 1246 (2d Cir. 1979). The reason for this judicial reluctance is that disqualification has a serious and immediate adverse effect in that it denies the client his choice of counsel. Society of Goodwill to Retarded Children, Inc. v. Carey, 466 F.Supp. 722 (E.D.N.Y. 1979). Moreover, the judiciary has come to recognize that disqualification motions are often interposed for tactical reasons, and even when brought in good faith, such motions often result in delay and add substantially to litigation costs. Id. at 724.

The determination of a motion to disqualify counsel requires a careful balancing of the client's right to retain the counsel he has chosen, the opposing party's right to untainted litigation, and society's need to maintain the highest standards of professional responsibility for attorneys. Waterbury Garment Corp. v. Strata Productions, Inc., 554 F.Supp. 63, 66 (S.D.N.Y. 1982). The court should not apply these standards mechanically, but should give due regard to the function of regulating the Bar in the interests of justice to all concerned. J.P. Foley & Co. v. Vander-

bilt, 523 F.2d 1357, 1360 (2d Cir. 1975). The court's task in disposing of motions to disqualify counsel, then, is to determine for itself the ends sought to be furthered by the Code provisions invoked, together with the question of whether disqualification in the case sub judice will further those ends.

B. *Canon 4*

Canon 4 of the New York State Bar Association's Code of Professional Responsibility provides that a lawyer "should preserve the confidence and secrets of a client." Disciplinary Rule 4-101(B) specifically enjoins a lawyer from knowingly using such confidence and secrets to the disadvantage of his client or for the advantage of himself or a third party unless the client gives his consent. The self-evident purpose of this ethical precept is to encourage unbridled communication between clients and their attorneys. Without strict enforcement of such high ethical standards, "a client would hardly be inclined to discuss his problems freely and in depth with his lawyer, for he would justifiably fear that information he reveals to his lawyer one day may be used against him on the next." Emle Industries, Inc. v. Patentex, Inc., 478 F.2d at 570-71.

As noted previously, plaintiff contends that the Limbach firm should be disqualified in this case because plaintiff allegedly has succeeded to the interest of defendant's parent corporation, which the Limbach firm has formerly represented in patent and trademark matters. This is a completely novel theory of disqualification. Plaintiff argues that even though the Limbach firm never represented the plaintiff or any of its affiliated companies, the firm's representation of the instant defendant is adverse to its interests within the meaning of Canon 4 because it "stands in the shoes of the Limbach firm's former client, its predecessor-in-interest."

1. Standing

The defendant argues that plaintiff has no standing to challenge the Limbach firm's representation of Caelter Enterprises because no attorney-client relationship ever existed between the Limbach firm and the plaintiff. The court disagrees.

The court believes that the general rule which restricts standing to raise a Canon 4 disqualification motion to one who is a client or former client of the challenged law firm must give way to a maxim that adequately addresses the need to ensure both clients and the general public that lawyers will act within the bounds of ethical conduct. Any attorney has the right and the obligation to bring to the court's attention an alleged violation of a disciplinary rule. Indeed, the Code of Professional Responsibility expressly requires that an attorney come forward if he has knowledge of an actual or potential violation of a disciplinary rule.

Disciplinary Rule 1-103(A) specifically provides that "a lawyer possessing unprivileged knowledge of a violation * * * shall report such knowledge to an [appropriate] tribunal . * * *." The First, Fourth and Fifth Circuits have concluded that DR 1-103(A) confers standing on any attorney to challenge a lawyer's representation of a client when he is privy to facts which justify disqualification. See Kevlik v. Goldstein, 724 F.2d 844 (1st Cir. 1984); United States v. Clarkson, 567 F.2d 270, 271 n. 1 (4th Cir. 1977); Brown & Williamson Tobacco Corp. v. Daniel Int'l Corp., 563 F.2d 671, 673 (5th Cir. 1977); see also Dunton v. County of Suffolk, 729 F.2d 903, No. 83-7384, slip op. (2d Cir. Feb. 28, 1984) (attorneys are officers of the court and are obligated to adhere to all disciplinary rules and to report incidents of which they have unprivileged knowledge involving potential violations of the disciplinary rules). Defendant's standing argument is thus without merit.

2. Disclosure of Confidences

Ordinarily an attorney may not "knowingly reveal a confidence of his client or use a confidence of his client to the disadvantage of the client." Evans v. Artek Systems Corp., 715 F.2d 788 (2d Cir. 1983); Fund of Funds, Ltd. v. Arthur Anderson & Co., 567 F.2d 225, 227 n. 2 (2d Cir. 1977). To endure faithful compliance with this broad ethical precept, any attorney may be disqualified from representing a client if: (1) the moving party is a former client of the adverse party's counsel; (2) there is a substantial relationship between the subject matter of the counsel's prior representation of the moving party and the issues in the present lawsuit; and (3) the attorney whose disqualification is sought had access to, or was likely to have access to, relevant privileged information in the course of his prior representation of the client. Evans v. Artek Systems Corp., 715 F.2d at 791; Gheng v. G.A.F. Corp., 631 F.2d 1052, 1055-56 (2d Cir. 1980), judgment vacated on other grounds, 450 U.S. 903 (1981); Code of Professional Responsibility, Canon 4, DR 4-101(B).

Although plaintiff was never represented by the Limbach firm, and thus is not a

"former client" within the meaning of Canon 4, it argues nevertheless that by virtue of being an assignee of the defendant's parent corporation it succeeds to the rights of the Limbach firm's former client. Such rights, it is argued, include the attorney-client privilege which formerly existed between defendant's parent and the firm. Although interesting, plaintiff's argument is without merit and unsupported by the case law. Indeed, plaintiff has failed to cite a single case in support of the proposition that an assignee of assets stands in the shoe of its assignor for purposes of Canon 4. The court has, however, located several cases which hold that an assignment of intellectual property does not assign the assignor's attorney to the assignee. See In re Yarn Processing Patent Validity Litigation, 530 F.2d 83, 190 USPQ 523 (5th Cir. 1976); Beghin-Say v. Rasmussen, 212 U.S.P.Q. 614 (Comm. Dec. 1980).

The court in In re Yarn Processing Patent Validity Litigation was faced with arguments similar to those advanced by plaintiff. In that case the purchaser of patent rights from an inventor sought to disqualify opposing counsel, who had previously represented the inventor, on the basis of potential violations of Canon 4. The challenged law firm had no relationship whatsoever with the purchaser. However, the purchaser maintained that it has a right to expect that the validity of the patents would not be attacked by the inventor's former counsel. The court disagreed, noting that:

> [P]laintiff * * * confuses the nature of the rights and duties implicit in the assignment of the patents with the nature of the rights and duties which arises between an attorney and client. Assignment of the patent does not asign [the law firm] along with it . * * * The prohibition applied to attorneys against representation of conflicting interests rests on the duties of an attorney arising from the attorney-client relationship. In the absence of this relationship, the duties of loyalty and confidentiality do not arise . * * * When [plaintiff] was assigned the * * * patent it did not receive any assignment of any rights against [the law firm].

Id. at 90, 190 USPQ at 527; see also Black v. State of Missouri, 492 F.Supp. at 864 (plaintiffs cannot succeed to position of conflict with attorneys who have never represented them); International Electronics Corp. v. Flash, 527 F.2d 1288 (2d Cir. 1975) (merger of law firm's former corporate client with plaintiff constituted a sale which did not prevent law firm from representing former stockholders of purchased corporation against plaintiff).

[1] In the present case the court fails to see how the plaintiff's receipt of assets from the Limbach firm's former client confers "former client" status upon it within the meaning of Canon 4. No attorney-client relationship has ever existed between plaintiff and the Limbach firm and, therefore, no potental violation of Canon 4 can occur in this case. Were this court to accept plaintiff's arguments it would open the courts to a deluge of spurious disqualification motions without advancing any of the policies which underlie Canon 4. Any purchaser of another firm's assets would be able to raise the adverse representation claim against the seller's counsel in any subsequent litigation involving the transferred assets. Plaintiff's motion brought pursuant to Canon 4 is thus denied.

C. *Canon 5*

Plaintiff next seeks disqualification based upon Canon 5. The Limbach firm, as specialists in the areas of patent and trademark law, formerly represented Caelter Enterprises with respect to the application and registration of the patents and trademarks which are the subject of this litigation. Because the defendant has challenged the validity of the patents and the plaintiff's ownership rights to the trademarks in its affirmative defense, the plaintiff argues that the Limbach firm will be forced to testify a trial and, therefore, must be disqualified.

Canon 5 of the New York State Bar Association Code of Professional Responsibility expressly prohibits an attorney who ought to be called as a witness in a trial from participating in that trial. This prohibition is set forth in DR 5-102(A), which provides as follows:

> If, after undertaking employment in contemplated or pending litigation, a lawyer learns or it is obvious that he or a lawyer in his firm ought to be called as a witness on behalf of his client, he shall withdraw from the conduct of the trial and his firm, if any, shall not continue representation in the trial, except that he may continue the representation and he or a lawyer in his firm may testify in the circumstances enumerated in DR 5-101(b)(1) through (4).

Even if a member of a firm ought to be called as a witness, DR 5-101(B) provides that representation may continue

(1) If the testimony will relate solely to an unconstested matter.

(2) If the testimony will relate solely to a matter of formality and there is no reason to believe that substantial evi-

dence will be offered in opposition to the testimony.

(3) If the testimony will relate solely to the nature and value of legal services rendered in the case by the lawyer or his firm to the client.

(4) As to any matter, if refusal would work a substantial hardship on the client because of the distinctive value of the lawyer or his firm as counsel in the particular case.

The test for disqualifying counsel under DR 5-102(A) is not whether counsel *will* be called as a witness, but whether he *ought* to be called as a witness in the proceeding. McArthur v. Bank of New York, 524 F.Supp. 1205 (S.D.N.Y. 1981); Eurocom, S.A. v. Mahoney, Cohen & Co., 522 F.Supp. 1179 (S.D.N.Y. 1981); Bottaro v. Hatton Associates, 528 F.Supp. 1116, 1118 (E.D.N.Y. 1981). The phrase "ought to be called as a witness" has been narrowly construed to refer to an attorney "who has crucial information in his possession which must be divulged" in the course of a trial. Universal Athletic Sales Co. v. American Gym, Recreational & Athletic Equip. Corp., 546 F.2d 530, 539 n. 21 (3d Cir. 1976), cert. denied, 430 U.S. 984 (1977).

[2] In the instant case the court fails to see how members of the Limbach firm ought to be called as witnesses at trial. The issues raised in defendant's affirmative defenses relate to newly discovered prior art which is alleged to render the subject patents void for non-obviousness. Any testimony on the part of the Limbach firm with respect to why the patent office may have failed to discover the existence of any prior art references would be totally irrelevant in this case. The issue before the court is whether the patents are indeed valid, not whether the Limbach firm properly procurred the patent licenses in the first instance. The process by which the Limbach firm secured these patents is simply not relevant to any material issue in this litigation.

Even assuming, arguendo, that members of the Limbach firm ought to be called as witnesses at trial, the court concludes that disqualification is not appropriate in this case. As noted previously, DR 5-101(B)(4) provides that an attorney may continue representation of his client in a proceeding in which the attorney is called upon to testify if disqualification would work a special and unwarranted hardship on the client by virtue of the distinctive value of the lawyer or his firm as counsel in the case.

In the present case George Limbach has represented the related predecessor corporation of defendant in patent and trademark matters since 1967, and the Limbach firm has represented defendant and its related companies since early in 1968. The attorney-client relationship has become intimate, and the firm has acquired specialized knowledge of defendant, defendant's related companies, and their operations. The Limbach firm's representation of defendant in the present action involves a complex set of legal and factual issues which the firm has been familiar with for many years. At this late juncture it would work a substantial hardship upon the defendant to require it to retain new counsel. Moreover, there is no basis for concluding that the continued representation by the Limbach firm will prejudice the plaintiff in this proceeding in any way or taint the underlying trial. Accordingly, plaintiff's motion to disqualify pursuant to Canon 5 is denied.

D. *Canon 9*

Plaintiff's final argument in favor of disqualification is based upon Canon 9 of the Code of Professional Responsibility which requires an attorney to avoid "even the appearance of impropriety." Plaintiff alleges that the Limbach firm's present challenge to the validity and ownership of patents and trademarks which it originally helped to secure for its former client constitutes conduct giving rise to an appearance of impropriety.

While a motion to disqualify opposing counsel may be granted under Canon 9 in the absence of an actual breach of ethics, there must be at least a reasonable possibility that some specifically identifiable impropriety will occur. Board of Educ. of the City of New York v. Nyquist, 590 F.2d 1241 (2d Cir. 1979); R-T Leasing v. Ethyl Corp., 484 F.Supp. 950 (S.D.N.Y. 1979); aff'd, 633 F.2d 206 (2d Cir. 1980). This requirement that a lawyer avoid even the appearance of impropriety reflects the bar's concern that some conduct which is in fact ethical may appear to the layman as unethical and thereby erode public confidence in the judicial system and the legal profession. Woods v. Covington City Bank, 537 F.2d 804 (5th Cir. 1976).

[3] A realistic view of the present litigation convinces the court that the public's perception of the integrity of the bar and the judicial system is not likely to be undermined by the Limbach firm's present representation of the instant defendant. The court agrees with the defendant that plaintiff's challenges under Canon 9 are a function of a mistaken belief that the Limbach firm is now taking a position with respect to the patents and trade-

marks which is contrary to the position taken during the procurement of these properties.

With respect to the patent issues in this case, defendant is merely arguing that the patents may be invalid based upon newly discovered art whose existence was not known before or during the pendency of the patent application. As the defendant correctly points out, had these prior art references been known to the Limbach firm prior to the issuance of the patent, both the applicant and the firm would have been duty bound to disclose such information to the Patent Office. There is no suggestion here that this information was available to either the applicant or the Limbach firm during the pendency of the patent application.

The plaintiff's argument with respect to the trademarks in this case is similarly misplaced. The defendant is not claiming, as plaintiff contends, that the trademarks which it registered for its former client are void ab initio or that the former client never had a valid ownership interest in the trademarks. Rather, the defendant is challenging plaintiff's rights to the trademarks based upon the argument that plaintiff simply does not have legal ownership of the trademarks or in the alternative that plaintiff lost all rights in the trademarks by failing to exercise quality control over the use of the trademarks by its licensees.

There is simply no appearance of impropriety in the Limbach firm positing these legal theories. Moreover, contrary to the arguments set forth by plaintiff, these legal theories are not inconsistent with the firm's former representation of the defendant's parent corporation. Accordingly, the plaintiff's motion to disqualify based upon Canon 9 is hereby denied.

III. Motion for a Preliminary Injunction

It is well established that the object of a preliminary injunction is to preserve the status quo until there can be a hearing on the merits. Guiness & Sons, PLC v. Sterling Publishing Co., 732 F.2d 1095, No.83-9056, slip op. at 2995-96 (2d Cir. Apr. 16, 1984); Sierra Club v. United States Army Corps of Eng'rs, 732 F.2d 253, No. 83-6321, slip op. at 2252-53 (2d Cir. Mar. 7, 1984); Diversified Mortgage Investors v. United States Life Ins. Co. of New York, 544 F.2d 571, 576 (2d Cir. 1976); Hamilton Watch Co. v. Benrus Watch Co., 206 F.2d 738, 742 (2d Cir. 1953). In this Circuit a party requesting a preliminary injunction must meet the test set forth in Jackson Dairy, Inc. v. H.P. Hood & Sons, Inc., 596 F.2d 70 (2d Cir. 1979) (per curiam), namely, a demonstration of irreparable harm and "either (1) likelihood of success on the merits or (2) sufficiently serious questions going to the merits to make them a fair ground for litigation and a balance of hardship tipping decidely toward the party requesting the preliminary relief." Id. at 72. See also Sadowsky v. City of New York, 732 F2d 312, No. 84-7055, slip op. at 3172-73 (2d Cir. Apr. 19, 1984); FMC Corp. v. Taiwan Tainan Giant Indus. Co., Ltd., No. 83-7945, slip op. at 2182 (2d Cir. Mar. 6, 1984). Moreover, such a showing is closely scrutinized in patent litigation and the moving party must demonstrate that the patent is "valid beyond question" and infringed. Bose Corp. v. Linear Design Labs, Inc., 467 F.2d 304, 307, 175 USPQ 385, 388 (2d Cir. 1972); Carter-Wallace, Inc. v. Davis-Edwards Pharmacal Corp., 443 F.2d 867, 871, 169 USPQ 625, 626 (2d Cir. 1971), cert. denied, 412 U.S. 929 (1973); see also Smith Int'l, Inc. v. Hughes Tool Co., 718 F.2d 1573, 1578, 219 USPQ 686, 690 (Fed. Cir. 1983).

In the present case plaintiff seeks a preliminary injunction enjoining defendant from utilizing (1) U.S. Patent No. 4,178,007; (2) the various "drawings, designs, patterns, models, dies, matrices and molds" used and destined for use in the manufacture of products bearing the trademark "SMI"; and (3) the trademarks "SMI." "Snowmaster" and "Firemaster." Plaintiff further seeks to enjoin defendant from contacting any customers or potential customers of plaintiff in such a way as to impugn the basic integrity of plaintiff's business. Due to the complexity of these requests and the multiplicity of issues contained therein, the court will address these topics separately.

A. U.S. Patent No. 4,178,007

Registered patents carry with them a presumption of validity that requires the party asserting invalidity to bear the burden of overturning that presumption. See 35 U.S.C. § 282. Nevertheless, in the context of motions for preliminary injunctions, the moving party bears the heavy burden of demonstrating that the patent is "valid beyond question" and infringed. Bose Corp. v. Linear Design Labs, Inc., 467 F.2d at 307, 175 USPQ at 388. To make such a showing the courts have required either a prior adjudication of the patent's validity or long acquiescence to its validity by industry. Id.; Frommelt Indus., Inc. v. W.B. McGuire Co., Inc., 504 F.Supp. 1180, 212 USPQ 449 (N.D.N.Y. 1981). In the absence of the above, direct technical evidence proving the patent's validity is sufficient to

warrant the granting of preliminary injunctive relief. Smith Int'l, Inc. v. Hughes Tool Co., 718 F.2d at 1573, 219 USPQ 686; Jenn-Air Corp. v. Modern Maid Co., 499 F. Supp. 320, 323, 209 USPQ 295, 298 (D. Del.), aff'd, 659 F.2d 1068 (3d Cir. 1981) (mem.).

In the present case it is undisputed that there has been no prior adjudication of the validity of U.S. Patent No. 4,178,007. Thus, for plaintiff to obtain its injunction it must demonstrate either long acquiescence to the patent's validity by industry or supply direct technical evidence of the patent's validity through some other source.

Defendant opposes the injunction on numerous grounds. To begin with, defendant argues that the preliminary injunction should not issue because of the undue delay by plaintiff in bringing the instant motion. As to the validity of the patent, defendant argues that there was no acquiescence by industry of the disputed patent. Further, defendant asserts that it has discovered two prior art patents which serve to defeat the subject patent as non-obvious pursuant to 35 U.S.C. § 103. Lastly, defendant claims that plaintiff has failed to prove infringement. Alternatively, defendant has offered to place into escrow a five percent royalty of the value of the anti-shimmy device on the caster of any product sold in the future which incorporates defendant's current design of the anti-shimmy device. These arguments will be explored seriatim.

As a preliminary matter the court disagrees with defendant's contention that plaintiff is guilty of undue delay in bringing the instant motion. Plaintiff purchased the assets of Caelter Enterprises on May 24, 1983 and brought this lawsuit on November 17, 1983. In this six month period, plaintiff contacted defendant and demanded that defendant cease using the subject intellectual property. Considering the difficulties plaintiff has encountered in obtaining proper documentation from its Canadian representative and the relative complexity of the issues presented by this lawsuit, the court finds that plaintiff's motion for a preliminary injunction is properly before the court. This is so with regard to not only the patent phase of the litigation, but also the trademark, commercial defamation and "drawings, designs * * * and molds" phases.

With regard to plaintiff's argument that the subject patent has been considered valid by the relevant industry for a sufficient period of time, the court has carefully examined the case law and concludes otherwise. While some courts have found commercial acquiescence in such short periods of time as five and one-half years, see Zenith Laboratories, Inc. v. Eli Lilly & Co., 460 F.Supp. 812, 201 USPQ 324 (D.N.J. 1978), most courts have required substantially more market time than the four year period present in the instant action. See, e.g., Premo Pharmaceutical Laboratories, Inc. v. USV Laboratories, Inc., 481 F.Supp. 193, 203 USPQ 853 (S.D.N.Y.) (16 years), aff'd,. 615 F.2d 1351 (2d Cir. 1979) (mem.); Eli Lilly & Co. v. Generix Drug Sales, Inc., 324 F.Supp. 715, 169 USPQ 13 (S.D.Fla. 1971) (period in excess of 11 years), aff'd, 460 F.2d 1096, 174 USPQ 65 (5th Cir. 1972). See also Rohm & Haas Co. v. Mobil Oil Corp., 525 F.Supp. 1298, 212 USPQ 354 (D.Del. 1981) (preliminary injunction denied where patented product not yet manufactured).

In the present case U.S. Patent No. 4,178,007 was granted by the United States Patent Office on December 11, 1979. The record reveals that the device is not widely utilized in the snow removal industry and is not particularly cost effective. As such, there was not a great deal of industry motivation to attach and/or challenge the patent's validity. H.J. Ashe Co. v. Bridgeport Metal Goods Mfg. Co., 273 F.Supp. 196, 199–200, 154 USPQ 165, 16–167 (S.D.N.Y. 1967).

[4] Unlike the case of Eli Lilly & Co. v. Generix Drug Sales, Inc., plaintiff has not demonstrated that the patented product is widely accepted in the industry. Nor has plaintiff shown that the patented product generates large profits. 324 F.Supp. at 718, 169 USPQ at 16. See also H.J. Ashe Co. v. Bridgeport Metal Goods Mfg. Co., 273 F.Supp. at 200, 154 USPQ at 168 (noting the high costs of patent litigation and the absence of incentives to challenge certain types of patents). These facts, coupled with plaintiff's failure to provide affirmative technical evidence of the patent's validity and defendant's proof of the patent's obviousness, leads the court to conclude that preliminary injunctive relief is not warranted for U.S. Patent No. 4,178,007. Plaintiff must demonstrate that the patent in question is valid "beyond question" and infringed. In view of this court's finding that plaintiff has not shown validity "beyond question," the court makes no finding with respect to infringement. Accordingly, plaintiff's motion for a preliminary injunction enjoining defendant from utilizing U.S. Patent No. 4,178,007 is denied.

B. *Drawings, Designs and Molds*

Paragraph 15(III) of the May 24, 1983 agreement between plaintiff and the representatives of the Coopers and Lybrand recites the transfer of the following properties:

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> All of the drawings, designs, patterns, models, dies, matrix and moulds, located throughout the world used and destined for use in the manufacturing of the following products: SMI, Sicard and/or Snowblast.

At first blush it would seem as though plaintiff purchased these assets and would certainly be entitled to an injunction restraining others from utilizing these drawings. However, as will be explored below, there are serious factual questions regarding the interpretation of paragraph 15(III) of the May 24, 1983 agreement.

By an affidavit dated January 4, 1984, Walter O. Lampl, President of defendant Caelter Industries, stated that Caelter Enterprises did not own the subject drawings at the time of the sale. Rather, Lampl urges that his present corporation Caelter Industries purchased these drawings *prior* to their purported transfer on May 24, 1983. Not surprisingly, Robert S. MacKenzie, President of S.M.I. Industries, U.S.A., the American subsidiary of plaintiff, has supplied the court with an affidavit dated January 9, 1984 stating that defendant never owned the drawings but merely used them under a revocable license from Caelter Enterprises. MacKenzie bases his affidavit from his own personal knowledge garnered from his prior employment with defendant.

At this stage of the proceedings the court has before it a significant factual dispute that is incapable of resolution based upon the present record. This court has recognized long ago that it is unusual to issue preliminary injunctive relief prior to the holding of an evidentiary hearing. Menley & James Laboratories Ltd. v. Approved Pharmaceutical Corp., 438 F.Supp. 1061, 1065, 195 USPQ 766, 768-769 (N.D.N.Y. 1977). See also Forts v. Ward, 566 F.2d 849 (2d Cir. 1977); SEC v. Frank, 388 F.2d 486 (2d Cir. 1968); Sugarhill Records Ltd. v. Motown Record Corp., 570 F.Supp. 1217 (S.D.N.Y. 1983). Here, determination of the ownership of the subject drawings must come, if at all, after the receipt of the appropriate testimony and/or documentary evidence. Accordingly, plaintiff's motion for a preliminary injunction enjoining defendant from utilizing the drawings referred to in paragraph 15(III) of the May 24, 1983 agreement is denied.

C. *"SMI," "Snowmaster" and "Firemaster"*

Plaintiff's motion for a preliminary injunction enjoining defendant from use of these three trademarks is the most hotly contested aspect of this lawsuit. As such, the court must carefully consider the propriety of issuing injunctive relief prior to conducting an evidentiary hearing. Menley & James Laboratories Ltd. v. Approved Pharmaceutical Corp., 438 F.Supp. at 1065, 195 USPQ at 769; see also SEC v. Frank, 388 F.2d at 491.

Defendant's principal objection in this regard concerns its characterization of the transfers of these trademarks. It is argued that the transfer from Caelter Enterprises to the Royal Trust Company and then to plaintiff was a transfer *in gross* and, therefore, invalid. Defendant asserts that since the trademarks were not transferred along with the goodwill of Caelter Enterprises, the transfers amounted to nothing more than a "naked license" and thus were invalid under the Lanham Act, 15 U.S.C. § 1051, et seq. To the contrary, plaintiff asserts that the transfer of the trademarks from Caelter Enterprises to the Royal Trust Company and then to plaintiff was proper and that its entitlement to a preliminary injunction is unquestioned. The court notes that the parties have not questioned the validity of the trademarks per se and that the propriety of their registration is not at issue in this lawsuit.

Although plaintiff's motion for a preliminary injunction seeks to restrain defendant from using all three of these trademarks, the court believes that a separate discussion of the "Firemaster" trademark is in order. The May 24, 1983 purchase agreement between plaintiff and the agents for the Royal Trust Company recited in great detail those assets of Caelter Enterprises that were being transferred. While "SMI" and "Snowmaster" are mentioned, the court observes that the trademark "Firemaster" is not present in the agreement.

At oral argument on this motion plaintiff's counsel referred to this absence as a "mere scrivener's error." Be that as it may, this is a motion for a preliminary injunction, and the court must adhere to the standards set forth in the Jackson Dairy case. With regard to the likelihood of succeeding on the merits, the court at this time can come to no other conclusion but that preliminary injunctive relief should not issue as to the "Firemaster" trademark. This trademark is not mentioned in the purchase agreement, and this court has been supplied with no evidence to support plaintiff's claim of purchase. Though such proof may surface prior to trial, it is not present at this stage of the proceedings, and the court must deny plaintiff's motion to enjoin defendant from using the "Firemaster" trademark.

Defendant's argument with respect to the "SMI" and "Snowmaster" trademarks is three-fold. First, defendant argues that the

execution of the trust deed between Caelter Enterprises and the Royal Trust Company in 1977 constituted an *in gross* transfer. Second, defendant argues that even if the 1977 trust deed did not effect a transfer, the May 14, 1983 purchase of Caelter Enterprises' assets by plaintiff constituted an *in gross* transfer. Lastly, defendant argues that, notwithstanding the above, plaintiff "abandoned" its rights to these trademarks by failing to exercise control over the use of the trademarks following their alleged purchase.

[5] With regard to defendant's first argument, the court agrees with plaintiff that the 1977 trust deed did not amount to a transfer at all. Although trademarks are freely assignable as tangible assets, see generally J. McCarthy, *Trademarks and Unfair Competition*, §18.1 (1973), this particular transaction did not amount to an actual transfer of the trademarks from Caelter Enterprises to the Royal Trust Company. Rather, the trademarks were merely used by Caelter Enterprises to secure its indebtedness. The Royal Trust Company never exercised any control over the operation of Caelter Enterprises in terms of the company's use of these trademarks. Moreover, Caelter Enterprises never changed its position vis-a-vis these trademarks following the execution of the trust deed. Thus, since neither of the parties intended the transaction to be a transfer nor treated it as such, this court finds defendant's argument to be without merit.

With regard to defendant's second argument, the court finds that the May 24, 1983 purchase agreement did not amount to an *in gross* transfer of the trademarks. A transfer of a trademark *in gross* is simply one effected without a simultaneous transfer of the goodwill appurtenant to that trademarks. A trademark is merely a symbol of goodwill, United Drug Co. v. Theodore Rectanus Co., 248 U.S. 90 (1918), and "has no independent significance apart from the good will it symbolized." J. McCarthy, supra (citing Prestonettes, Inc. v. Coty, 264 U.S. 359 (1924)). Thus, when a trademark is the subject of an *in gross* transfer, the purchaser obtains only the symbol but not the reality. Since the Lanham Act places an affirmative duty on trademark owners to exercise some degree of control over the trademarks they license, Dawn Donut Co. v. Hart's Food Stores, 267 F.2d 358, 121 USPQ 269 (2d Cir. 1959), the courts have required a simultaneous transfer of both the trademark and its goodwill in order to preserve the validity of the trademark.

In the present case the May 24, 1983 purchase agreement recites the sale of the "SMI" and "Snowmaster" trademarks as well as a vast majority of the assets of Caelter Enterprises. This additional transfer of assets is an important consideration for the court in determining whether Caelter Enterprises' goodwill was also transferred with the trademarks. J. McCarthy, supra, §18:7 Haymaker Sports, Inc. v. Turian, 581 F.2d 257, 261 & n. 7, 198 USPQ 610, 613 & n. 7 (C.C.P.A. 1978). After a careful review of the purchase agreement, it appears plain that plaintiff acquired the goodwill appurtenant to these trademarks. This acquisition is evidenced by the complete diversity of assets that were the subject of the purchase agreement. Such assets include: a parts inventory; work in progress; finished goods; machinery, tools and equipment; office furniture and equipment; rolling stock; tools, stock in trade and rolling stock; and trademarks, patents, rights, titles and interests. Moreover, the court notes that the assets were found at two different locations and a fair reading of the purchase agreement leads the reader to conclude that the transfer of assets was intended to be all inclusive rather than partial.

This same conclusion is reached with respect to defendant's secondary assertion that an *in gross* transfer was effected when the Royal Trust Company succeeded to the ownership of Caelter Enterprises' assets upon the bankruptcy of the latter in December of 1982. Clearly, a trustee in bankruptcy, a position analogous to that of the Royal Trust Company in December of 1982, has the power to transfer the intellectual property of a debtor. When Caelter Enterprises went bankrupt the Royal Trust Company assumed ownership of all of the assets of Caelter Enterprises. This was done in accordance with the terms of the 1977 Trust Deed which had granted a security interest to the Royal Trust Company. Inasmuch as the 1977 Trust Deed did not amount to a transfer of asets, the failure of Caelter Enterprises to fulfill its loan obligations caused an automatic transfer of assets. Again, this was a complete transfer of assets rather than a partial transfer of the trademarks without their attendant goodwill. As such the court must reject in toto defendant's assertion that the subject trademarks were rendered invalid by virtue of an *in gross* transfer.

[6] Lastly, the court must address defendant's argument that plaintiff abandoned whatever interest it possessed in the trademarks by failing to exercise direct control over those trademarks. As noted above, the owner of a trademark must protect that trademark from dissolution by controlling those persons authorized to use it. Failure to do so renders the trademark invalid as a mere "naked license." Societe Comptoir v. Alexander's

Dept. Store, 299 F.2d 33, 132 USPQ 475 (2d Cir. 1962) (holding grant of "naked license" to be a fraud on the public and unlawful). Defendant contends in the instant case that abandonment is evidenced by plaintiff's failure to halt defendant's use of the trademarks immediately following the May 24, 1983 purchase agreement.

Defendant argues that since plaintiff was aware of the license agreement between Caelter Enterprises and Caelter Industries *prior* to plaintiff's execution of the purchase agreement, plaintiff should have taken affirmative steps to prevent defendant from continuing to use the trademarks. Instead, defendant argues, plaintiff waited until mid-September to contact defendant and demand that defendant cease its use of the trademarks. In addition, defendant points out that plaintiff waited until November 17, 1983 to commence this action and until December 16, 1983 to file the instant motion for a preliminary injunction. While such arguments appear colorable on their face, they fall short when considered in light of the facts of this case.

Defendant's President Walter O. Lampl was also President of Caelter Enterprises. Mr. Lampl was intimately familiar with the financial problems being experienced by Caelter Enterprises and knew of the purchase of Caelter Enterprises' assets by plaintiff. Thus, defendant's thinly veiled assertion that it is an innocent victim of plaintiff's outrageous and aggressive conduct is belied by the record.

Defendant knew full well that the intellectual property of Caelter Enterprises had been purchased by plaintiff, but defendant continued to use it nevertheless. Moreover, the court believes that the period from May 24, 1983, the date plaintiff purchased the trademarks at issue, until it first *formally* notified defendant that defendant should case and desist, should not be considered as one of "uncontrolled and naked licensing." This is a relatively short amount of time considering the realities of modern business practices and also considering the fact that plaintiff is a Canadian corporation that was struggling to establish its American subsidiary at the same time that it was attempting to restrain defendant's actions.

Plaintiff can hardly be said to have slept on its rights against defendant when defendant did not either rely on the passage of time or take some action in detrimental reliance on plaintiff's failure to act. Indeed, the record indicates that defendant considered changing its operating name following the purchase by plaintiff of Caelter Enterprises' assets so as to avoid the possibility of receiving a cease and desist letter. See Reply Affidavit of Robert S. MacKenzie dated Jan. 9, 1984 at ¶18. Based upon these facts, together with a review of the record as a whole, the court concludes that plaintiff did not abandon its interest in the trademarks at any time and more specifically in the time between its purchase of Caelter Enterprises' assets and the commencement of this action.

Returning to the standards for a preliminary injunction as set forth in Jackson Dairy, Inc. v. H.P. Hood & Sons, Inc., 597 F.2d at 72, the courlt believes that plaintiff has demonstrated both irreparable harm and a likelihood of success on the merits with respect to its trademark claims for "SMI" and "Snowmaster." Irreparable harm is present in that there is substantial likelihood of confusion between the plaintiff and the defendant's use of the trademarks. In addition, plaintiff cannot control the quality of goods being sold by defendant under these two trademarks. Lastly, irreparable harm can be presumed from the demonstration of plaintiff's ability to succeed on the merits. See generally Guinness & Sons, PLC v. Sterling Publishing Co., 732 F.2d 1095, No. 83-9056, slip op. at 2996.

As to the success on the merits, the court believes that the May 24, 1983 purchase agreement was valid and not a transfer *in gross*. Defendant has not denied that it is presently utilizing the "SMI" and "Snowmaster" trademarks. Accordingly, the court believes that preliminary injunctive relief should issue, and defendant is hereby restrained from using the trademarks "SMI" and "Snowmaster" during the pendency of this action or until further order of this court. Pursuant to Fed.R.Civ.P. 65(c), the parties are hereby directed to appear before the court on May 24, 1984 at 4:30 p.m. for the purposes of setting an appropriate bond for the payment of costs and damages.

D. *Commercial Defamation*

The essence of this aspect of plaintiff's motion for a preliminary injunction centers around a letter defendant sent to its customers on or about October 19, 1983. The letter, signed by defendant's President Walter O. Lampl, is set forth in full below.

> You probably have been contacted recently by a new company having a name similar to ours, and operating out of the same geographic area as we do. There were probably some statements made to your claiming that this new company has a acquired certain drawings, patents, etc., relating to SMI equipment. We understand

that this has created a lot of confusion among our customers. We would like to set the record straight as follows:

1. SMI New York, a division of Caelter Industries, Inc. has not sold and has no intention of selling any of its drawings or other manufacturing records, nor does it for this matter have any intention to sell any of its other assets.

2. Caelter Industries, Inc., through its SMI New York division is the *only* company which has in its files the specific drawing bills of material, etc. which were used to produce the specific machine(s) used by your organization. Only SMI New York maintains a specific and complete history file for each piece of equipment ever sold.

Enclosed you will find a news release recently issued by our company. I trust this will shed additional light on the present situation.

We are most appreciative of your past business and hopeful to be able to serve you in the future.

The news release referred to in the later portion of the letter concerns a state court injunction against two former employees of defendant now employed by plaintiff's Watertown, New York subsidiary. Specifically, the injunction restrained these two employees from interfering with their former employer's business or contractual relations. The former employees were further enjoined from divulging any confidential information or trade secrets.

As only a cursory reading of the above discloses, the parties and their subsidiary companies are currently embroiled in a bitter fight over both products and territory. Robert S. MacKenzie, currently the President of plaintiff's subsidiary S.M.I. Industries U.S.A., Inc., was one of the former employees who was the subject of the above-described state court injunction. Thus, MacKenzie left defendant's employ and became a principal in its newly created competitor company.

[7] With regard to the letter itself, the court notes that it was sent approximately one month prior to the commencement of this action on November 17, 1983. In addition, it would appear as though the statements contained therein are true insofar as they state that defendant has not sold nor does it intend to sell any of its drawings or designs. Moreover, as the affidavit of Dennis P. Hennigan confirms, a state court injunction was in fact obtained against MacKenzie and another former employee of defendant Caelter Industries, Inc. The problem with the letter and its tone, however, is that its implication is one that plaintiff is a carpetbagger who has come into the area solely to disrupt defendant's business. Such a portrayal is clearly not true as plaintiff is a legitimate business concern that claims rightful ownership of the intellectual property which is the subject of this lawsuit.

While the court recognizes that the letter and accompanying news release were sent *prior* to the institution of these proceedings, defendant was surely aware at the time that plaintiff disputed its rightful ownership of the drawings and patents. As such, it was misleading for defendant not to have included in its letter a claim that "the other business" has asserted a claim to this property. Defendant need not have stated that it believed plaintiff's claims to have substance, but it should have at least disclosed the existence of such claims.

Since the failure of defendant to disclose the existence of competing claims to the intellectual property at issue in this lawsuit may have the tendency to impugn the basic integrity of plaintiff's business, the court believes that injunctive relief is appropriate. Thus, the question remains as to the form such injunctive relief should take. Plaintiff has not requested that defendant cease contacting any of its customers. Rather, plaintiff merely requests an injunction restraining defendant from portraying plaintiff is a false light. Such a request is eminently reasonable and will prove to be no hardship to defendant. Accordingly, during the pendency of this action or until further order of this court, defendant shall be enjoined from contacting customers in the relevant market in such a way as to portray plaintiff and its business in a false light. Contacts with customers should, consistent with this decision, be fair and accurately explain the facts of this litigation.

IV. Conclusion

In sum, the court hereby denies plaintiff's motion for an order disqualifying the law firm of Limbach, Limbach & Sutton from representing defendant in this action. The court finds that the Limbach firm has breached no ethical duties it owes to any present or former clients and has violated no Canons of the Code of Professional Responsibility. With respect to plaintiff's motion for a preliminary injunction, the court hereby grants the motion in part and enjoins defendant from utilizing the trademarks "SMI" and "Snowmaster" during the pendency of this litigation or until further order of this court. Defendant is further enjoined from contacting present or future customers of plaintiff in such a way as to portray plaintiff and its business in a false light. The motion

for a preliminary injunction is hereby denied in all other respects.

The parties are hereby directed to appear before the court on May 24, 1984 at 4:30 p.m. for the purposes of determining the amount of a bond to be posted by plaintiff pursuant to Rule 65(c) of the Federal Rules of Civil Procedure.

It is so Ordered.

District Court, M. D. Georgia, Macon Div.

Engelhard Minerals and Chemicals Corporation
v. Anglo-American Clays Corporation et al.

No. 80-187-MAC

Decided Apr. 25, 1984

PATENTS

1. Defenses — Fraud (§30.05)

Failure to disclose to Patent Office prior art that would not have diminished uniqueness of patent's claims, and inaccuracies in disclosure that were not shown to be intentional and do not materially alter patent's novelty, do not mandate finding of patent invalidity.

2. Specification — Sufficiency of disclosure (§62.7)

Conduct of patentee who stated range of temperatures that was knowingly inaccurate in patent relating to industry in which, due to differences in equipment utilized, practice was to experiment with temperatures, is not so culpable as to warrant finding of patent invalidity.

Particular patents — Pigments

3,586,523, Fanselow and Jacobs, Calcined Kaolin Clay Pigment, valid.

Action by Engelhard Minerals and Chemicals Corporation, against Anglo-American Clays Corporation, Freeport Minerals Co., Freeport Kaolin Co., and Yara Engineering Corp., for patent infringement, in which defendants counterclaim for attorney fees. Judgment for plaintiff on issue of patent validity.

Frank C. Jones, Atlanta, Ga., and Kurt E. Richter, New York, N.Y., for plaintiff.

Jerry B. Blackstock, Atlanta, Ga., Stefan J. Klauber, Paramus, N.J., George C. Grant and John B. Harris, Jr., both of Macon, Ga., Allan H. Bonnell, Dana M. Raymond, and Michael T. Schaffield, all of New York, N.Y., and Raul V. Fonte, Belle Chasse, La., for defendants.

Owens, District Judge.

Plaintiff, an assignee of United States Patent Number 3,586,523 (copy reproduced as an Appendix to this opinion), commenced the instant action seeking injunctive relief and damages due to defendants' alleged infringements of the patent in suit. The defendants assert that the patent is invalid, and counterclaim for attorney fees incurred to prove invalidity. The issue of patent validity was tried separately before this court on September 7 through 22, 1983. This constitutes this court's findings of fact and conclusion of law as to the issue of patent validity.

Introduction

The central Georgia area contains some of the world's large deposits of kaolin, a type of clay predominantly comprised of the mineral kaolinite. In the paper making industry kaolin is used as a pigment to impact a bright white color and opacifying properties to the pulp fibers which make up finished paper. Prior to the use of kaolin, synthetic titanium dioxide (TiO_2) was the chief pigment used by the paper industry. Beginning in the 1950's and continuing throughout the 1970's the price of TiO_2 escalated to levels which created a commercial need for an extender or substitute pigment. During this period the major kaolin companies expended considerable resources in an effort to develop a competitive pigment produced from their abundant supplies of kaolin. Since the paper industry was very satisfied with the performance of Tio_2, the production of a kaolin pigment which could match this performance, but at a lower cost, became the goal of all of the parties herein.

There are four physical properties (two of primary importance and two of secondary importance) which the market demands of a paper pigment:

Properties of Primary Importance

1. *High Brightness*: A pigment must be substantially white and very bright, i.e., light reflective.[1]

[1] The brightness of a pigment is measured by the degree (expressed as a percentage) to which it will reflect light as compared to a standard value. In the kaolin and paper industries, the standard measuring device is a brightness meter manufactured by the General Electric Company. A "sub-

#101

49-111-0

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

WATTANASIN	:	
	:	INTERFERENCE NO.: 102,648
V.	:	EXAMINER-IN-CHIEF:
FUJIKAWA ET AL	:	MICHAEL SOFOCLEOUS

FUJIKAWA REPLY TO THE WATTANASIN OPPOSITION TO THE MOTION FOR SANCTIONS

HONORABLE COMMISSIONER OF PATENTS AND TRADEMARKS
WASHINGTON, D.C. 20231
BOX INTERFERENCE

SIR:

Apart from a brief and unsupported attempt to argue that the applicable Rules which serve as the predicate for the Fujikawa Motion for Sanctions, 37 CFR §10.62(b) and §10.63(a) does not apply to the instant situation, because the Patent and Trademark Department of Sandoz does not constitute a "firm" for the purpose of the Rules, Sandoz relies only on the exceptions to the general Rule of 37 CFR §10.62(b) for authorizing the simultaneous testimony by Kassenoff, and his participation as Counsel in this matter.

Neither the straw man argument that the Sandoz Patent and Trademark Department is not a firm, nor the argument with respect to the exceptions, is adequately supported by fact or law, and accordingly, the entry of sanctions is believed appropriate.

I. THE SANDOZ PATENT DEPARTMENT IS A "FIRM" FOR THE PURPOSES OF THE RULES

Without authority, or indeed without relevant facts, Sandoz urges that the Sandoz Patent and Trademark Department is not a firm, and thus, 37 CFR §10.62 and §10.63 do not apply to the Sandoz Patent and Trademark Department. Page 7 of the Opposition. The argument is nonsense, and Sandoz offers no legal support for its position. It would be an enormous elevation of form over substance if each and every corporate patent applicant could avoid the Rules of Conduct prescribed by and for the Patent Office simply by temporarily expanding its "legal department" to embrace all necessary attorneys, and thereafter return them to legal practice. Wattanasin offers neither precedent nor logic to support its view, and the same must be rejected.

II. TO THE EXTENT THE FOUR EXCEPTIONS APPLY, THE TESTIMONY MAY BE ADMITTED WITHOUT SANCTION

The four exceptions to 37 CFR §10.62(b) and §10.62(a) do not substantially apply to the testimony that is the basis for the Fujikawa Motion for Sanctions. Each of the exceptions is discussed, in turn, below. To the limited extent they do apply, that limited testimony may be admitted without sanctions.

(1) Exception one permits introduction of the testimony by an attorney acting on behalf of the party for whom it is introduced if the testimony relates solely to an uncontested matter. By Wattanasin's own admission, the testimony of Melvyn M. Kassenoff (Kassenoff) relates specifically to the issue of abandonment, suppression or concealment. This is very much a contested issue. See the Wattanasin Opposition, pages 3-4. Quite clearly, exception one is not applicable, and Wattanasin does not really argue to the contrary.

(2) Exception two pertains to testimony with respect to matters of formality. Wattanasin urges that certain of Mr. Kassenoff's testimony relates to essential formalities, establishing the existence of his handwriting in certain documents. See the Wattanasin Reply, page 8. Accordingly, Fujikawa hereby

indicates that if the Kassenoff testimony is otherwise acceptable to the EIC, it modifies its request for sanctions to the extent that the Kassenoff testimony at Wattanasin Record 230, lines 5-7, confirming the presence of Kassenoff's handwritten notations on Exhibit N, and WR-231, lines 8-11, again confirming the presence of Kassenoff's handwriting, may be admitted without sanction.

As Wattanasin does not suggest that any other part of the Kassenoff testimony qualifies under this exception, it need not be further discussed.

(3) Exception three goes to the nature and value of legal services rendered in the case. Wattanasin urges that all of Kassenoff's testimony qualifies under this exception. Fujikawa respectfully submits that this quite simply not the case. The only legal services rendered by Kassenoff in the case discussed in the Kassenoff Declaration appear at pages 229 and 230 of the Wattanasin Record. On page 229, Kassenoff indicates:

> It is my best recollection that in February of 1988, I was in communication with Dr. Wattanasin concerning information which was needed by the patent department in order to prepare an application based on PD 299/84.

Later on, on page 230, Kassenoff indicates:

> These notes further indicate that I spoke with Sompong Wattanasin ("S.W.") on February 12, 1988 concerning his quinoline compounds and requested that he provide me with certain information.

Although other portions of the Kassenoff Declaration refer to materials received by Mr. Kassenoff, and Mr. Kassenoff's activities and services in connection with <u>other</u> cases, nothing else relates to Kassenoff's activities involved in the case at bar. Accordingly, as this exception applies only to the portions quoted above, these portions may be included without censure or sanction, but the remaining should be suppressed or otherwise treated as requested in the Fujikawa Motion for Sanctions.

Beginning at page 9 of the Wattanasin Opposition, Wattanasin stresses that the Kassenoff testimony should fall within exception three because it would appear to fall within the exception carved out for a registered patent practitioner to testify concerning attorney diligence. This is fine, except that Kassenoff's

testimony was not presented for the purpose of establishing attorney diligence. Kassenoff's testimony was presented solely with respect to the issue of abandonment, suppression or concealment, not diligence. Indeed, if Kassenoff's testimony is relevant to, or presented with respect to the issue of diligence, it is untimely and improper, as it should have presented in connection with Wattanasin's case-in-chief. Thus, the Kassenoff testimony simply does not fit the exception Wattanasin seeks to rely on. The case citation to Wilder v. Snyder, 201 USPQ 927 (POBI 1977) seems clearly inappropriate, as therein Fujikawa cites the exact language on which it relies to advance the sanction that the Kassenoff testimony be discounted. Wattanasin having presented absolutely no testimony with regard to diligence, except perhaps that of attorney Geisser, who, no longer employed by Sandoz, does not fit the proscription of 37 CFR §10.63(a), the Kassenoff testimony is simply not applicable to the exception in question.

(4) Without proof of fact, or even offer of proof, Wattanasin goes on to argue that Kassenoff is so exceptional and uniquely valuable that prohibiting Kassenoff from working on the case would have worked a "substantial hardship on the client because of the distinctive value of the practitioner". While Wattanasin asserts this exception applies, Wattanasin identifies no expertise offered

by Kassenoff, nor any activity, save testifying on behalf of Wattanasin, that Kassenoff has been involved in that could not have been don by anybody within the Patent Department. Initially, the Wattanasin Opposition indicates that:

> Kassenoff's role as an attorney in these Interferences has been primarily as a consultant or "sounding board," providing occasional advice on procedural and scientific issues.

Moreover, Wattanasin urges that:

> Mr. Kassenoff has not been an active participant in these Interferences (particularly following his changed responsibilities as of January 1993, referred to above); rather, he has served as a consultant on an intermittent basis concerning technical or PTO procedural matters. Page 20 of the Wattanasin Opposition.

This is not the stuff of an indispensable individual. It is of significance that Wattanasin cannot point to a single piece of advice, consultation or instruction that Kassenoff has provided in this case, nor offers a single declaration in support of its position that Kassenoff has lent valuable expertise to the proceedings. Without such evidence, Mr. Kassenoff simply has not been established as an individual meeting the omnibus "expertise exception" of 37 CFR §10.62(b)(4). In particular, it is not clear what "scientific matters" Kassenoff was consulted with respect to, or what procedural issues remain that would require Kassenoff's comment. Indeed, procedural fencing is almost at an end, it is time for filing the Briefs. Quite simply, Wattanasin fails to establish even one activity contributed by Kassenoff since his presentation of testimony that could not have been effectively done by somebody else in the Sandoz Patent Department.

Sandoz repeatedly casts dispersions on undersigned Counsel, and Fujikawa, for attempting to "discredit" someone who has submitted to rigorous cross-examination. As the cases all uniformly confirm, it is not Fujikawa, or undersigned Counsel, but rather Kassenoff himself who has caused his discredit.

> The giving of material testimony by an attorney for his own client is generally considered to be a breach of professional ethics....

Weinsteins Evidence, Competency, Section 601[4] (1993 Supplement).

Waltzer v. Transidyne General Corporation, 697 F.2d 130, 134-135 (Sixth Cir. 1983).

Wattanasin's desire to have its cake (or Kassenoff) and eat it too, prescribes a diet far too rich in ethical violations to be tolerated. The sanctions requested by Fujikawa, in the alternative, should be imposed.

III. THE FUJIKAWA MOTION IS TIMELY AND SUPPORTED BY PRECEDENT

The Fujikawa Opposition provides a discussion of the case law, in which it relies on the Wilder decision discussed above, and the decision in Wick v. Zindler, 230 USPQ 241 (POBI 1984). Oddly, Fujikawa's presentation of extensive and relevant cases is brushed

aside as either dicta or limited to the specific facts presented. Oddly enough, Wilder is a case in which the entire discussion of ethics was in the part indicated by the Board to be dicta, and presented only in the interests of completeness. The only other case cited by Wattanasin, Wick v. Zindler, 230 USPQ 241 (POBI 1984) is necessarily further removed from the facts than those discussed in the Fujikawa Motion. Specifically, Zindler is confined to the situation wherein the attorney confirms that corroborating evidence was in fact received on a specific date. Clearly, even a barely credible witness can testify as to such matters. It would take a greater degree of credibility, one that cannot be granted to Kassenoff, to admit testimony on reasons why attorneys could not have done the work assigned in a timely fashion, something Kassenoff attempts to explain.

Page 18 of the Wattanasin Opposition is dedicated to the inventive argument that Fujikawa's Motion was belated. Wattanasin urges that having been advised that Kassenoff was considered "deputy counsel" for the Interferences, a term no where defined in the Rules, Fujikawa should have objected to Kassenoff's testimony. This is utter nonsense. Until Kassenoff's Declaration was received, Fujikawa had no reason to believe that anybody in the Sandoz Patent Department would testify in this matter. Indeed, the

Fujikawa Motion makes it clear that it proceeds principally under 37 CFR §10.63.

Once it was determined that Kassenoff should act as a witness, his activity as Counsel should have ended. See Waltzer, supra. Fujikawa has no objection to any of the activities undertaken by Kassenoff in connection with this Interference prior to his offering of testimony. It is his action subsequent that violate the Code of Ethics and specific regulations provided. Inasmuch as Kassenoff's activity was to be triggered in this Interference, according to the notice of "deputy counsel", only in the absence of lead counsel Furman, and lead counsel Furman has never been absent from these proceedings, it is hard to see how Fujikawa should have been apprised of Kassenoff's silent, secretive activities as Counsel, until the appearance of his name on the Record. It was Kassenoff, and the Sandoz Patent Department, as discussed below, that took deliberate measures to sustain this clear violation of the Rules, not belatedness on the part of Fujikawa.

IV. THE OPPOSITION CONCEDES, BY ITS SILENCE, A VIOLATION OF 37 CFR §10.110

The Fujikawa Motion makes it clear that Fujikawa's Motion

proceeds not only under 37 CFR §10.63, but 37 CFR §10.110 as well. This regulation, Canon 9, which precludes a practitioner engaging even in the appearance of professional impropriety is discussed beginning on page 11 of the Fujikawa Motion. Conspicuous, by its absence, in the Wattanasin Opposition is <u>any</u> discussion of the appearance of impropriety created by maintaining Kassenoff's activities as Counsel, without disclosing them to Fujikawa or the EIC, even <u>after</u> it became apparent that Kassenoff would have to testify in this matter. If Kassenoff was really indispensable, or otherwise critical to the maintenance of the Wattanasin interests in this Interference, or Wattanasin otherwise earnestly believed that the Kassenoff testimony fell within one or more of the exceptions to 37 CFR §10.62 and §10.63, the proper course for Wattanasin to follow would be to have advised the EIC and Fujikawa of the need to preserve Kassenoff as Counsel for Wattanasin and as a witness on behalf of Wattanasin, presented sufficient facts so as to establish the merits of the arguments, and proceed accordingly. Instead, with full knowledge of the Rules (Kassenoff is held out in the Wattanasin Opposition as having particular and detailed knowledge of the Rules), Wattanasin continued in a course of action which at least, on its face, and without the necessary supporting facts, is in violation of those Rules. At a minimum, this creates

the appearance of impropriety. As noted in the Fujikawa Motion, it is this appearance of impropriety, and the failure to advise the EIC and Fujikawa of the practice undertaken by Wattanasin and Kassenoff, that supports the requested sanction of disqualification. Fujikawa does not urge that Kassenoff is incompetent, alone, to testify, Federal Rules of Evidence 601. Rather, Fujikawa submits that in suppressing the obvious and clear issue raised by Kassenoff's simultaneous representation and testimony, Wattanasin frustrated the intent, spirit and letter of the Rules, and should be sanctioned on that ground.

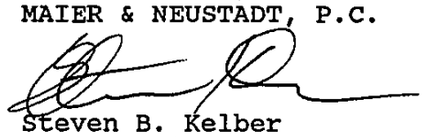
If Wattanasin had anything to say with respect to its appearance of impropriety, it certainly would have presented it in its Opposition. Having failed to do so, the conclusion that Wattanasin deliberately engaged in a course of conduct it knew, on its face, was impermissible, is driven home.

The Kassenoff testimony does not meet the exceptions one-four of Rule 10.62. Kassenoff, Wattanasin and the Patent Department at Sandoz has clearly engaged in activity that raises the appearance of impropriety, even if it could have been excused on a timely and complete explanation of the situation. On that basis alone, the sanctions requested by Fujikawa, in the alternative, should be

entered.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.



Steven B. Kelber
Registration No.: 30,073
Attorney for Fujikawa et al

CERTIFICATE OF SERVICE

I hereby certify that true copies of:

1. **FUJIKAWA REPLY TO THE WATTANASIN OPPOSITION TO THE MOTION FOR SANCTIONS**

2. **CERTIFICATE OF SERVICE**

were served upon Counsel for Wattanasin as follows:

Diane E. Furman
SANDOZ CORP.
59 Route 10
E. Hanover, New Jersey 07936

via FACSIMILE and FEDERAL EXPRESS, this 21ST day of JUNE, 1993.

STEVEN B. KELBER

Interference 102,648
Interference 102,975

Paper No. 102

All communications respecting this case should identify it by number and names of parties.

U.S. DEPARTMENT OF COMMERCE
Patent and Trademark Office

Address: BOX INTERFERENCE
Commissioner of Patents and Trademarks
Washington, D.C. 20231

Telephone: (703)557-4007
Facsimile: (703)557-8642

Interference No. 102,648

Wattanasin et al.

v.

Fujikawa et al.

Receipt is acknowledged of the motion for sanctions under 37 CFR 1.616, filed on May 26, 1993 by Fujikawa (Paper No. 95). An opposition (Paper No. 100) and a reply thereto (Paper No. 101) have been filed.

The motion requests that the following sanctions be entered against Wattanasin:

> 1. Disqualification of all members of the Sandoz Patent and Trademark Department from further participation in the interferences,
>
> 2. Precluding Sandoz from relying on the testimony of Mr. Melvyn Kassenoff, or
>
> 3. To the extent that Sandoz is permitted to rely upon Mr. Kassenoff's testimony, the testimony should be severely discounted.

The motion urges that sanctions are in order against the party Wattanasin for "deliberate and knowing violation of 37 CFR § 10.62(b) and § 10.63(a)." According to the motion, Wattanasin introduced and relied on the testimony of Mr. Kassenoff, a "crucial witness" with respect to the issues of abandonment, suppression and concealment, while at the same time listing him as "Of Counsel" on the record and

refusing to exclude him from participation in the preparation of the Wattanasin's brief and reply brief and for final hearing. Also the motion urges that to the extent that Mr. Kassenoff acted as a counsel in an advisory capacity, this action further aggravates the violations of § 10.62.

The opposition indicates that Mr. Kassenoff has been a member of the Sandoz Patent and Trademark Department for about 20 years and that his testimony became necessary in this case because Fujikawa filed a notice (Paper No. 69) under 37 CFR 1.632 raising the issue of suppression and concealment. Based on the filing of the notice, the party Wattanasin successfully moved to reopen its testimony period for purposes of introducing evidence to rebut any inference of suppression or concealment. See the order of February 5, 1993 (Paper No. 77), reopening testimony. According to the opposition, Mr. Kassenoff had relevant testimony which goes to the period between the last documented laboratory work and the filing of the Wattanasin application.

Insofar as the motion requests that disqualification of all members of the Sandoz Patent and Trademark Department from further participation in the interferences, the motion is denied. The movant acknowledges on page 4 of his reply (Paper No. 101) that some of the testimony taken by Mr. Kassenoff falls within the exception of § 10.62(b)(3), i.e., Mr. Kassenoff testified as to the nature of the legal services rendered by him. Under these circumstances, the

requested disqualification of the entire Sandoz legal department is not considered an appropriate, where one attorney of the department testifies as a witness in an interference within the exception of § 10.62(b)(3).

Insofar as the motion requests that Sandoz be precluded from relying on the testimony of Mr. Melvyn Kassenoff, the motion is denied. Since the movant acknowledges on page 4 of his reply (Paper No. 101) that some of the testimony taken by Mr. Kassenoff falls within the exception of § 10.62(b)(3), it would not be appropriate to preclude Sandoz from relying upon the testimony in question.

Insofar as the motion requests that the testimony of Mr. Kassenoff be "severely discounted", presumably be given little or no weight, consideration of the motion is deferred to final hearing provided that Fujikawa raises the matter in his brief. Matters not raised in the brief are ordinarily regarded as abandoned. Photis v. Lunkenheimer, 225 USPQ 948 (Bd.Pat.Int. 1984).

The times remain as set in Paper No. 99.

Michael Sofocleous
Examiner-in-Chief
(703) 557-4066

#103

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES FYI

JUL 19 1993
RECEIVED IN BOX INTERFERENCE

WATTANASIN

v. Interference No. 102,648

FUJIKAWA et al. Examiner-in-Chief: M. Sofocleous

APPROVED
JUL 22 1993
Examiner-in-Chief

MOTION FOR EXTENSION OF TIME

Petition is made for an extension of time of one day from July 15 to July 16, 1993, to file the Wattanasin Opening Brief in the above interference, since binding cannot otherwise be performed in time.

A telephone conference call was held today with EIC Sofocleous and opposing counsel, Steven B. Kelber, at which the requested extension of time was indicated to be acceptable to the EIC and opposing party [The Wattanasin Opening Brief (without binding) is today being served on counsel Kelber, as agreed.]

Respectfully submitted,

Diane Furman

Diane E. Furman
Attorney for the Party Wattanasin
Registration No. 31,104
201-503-7332

SANDOZ CORPORATION
59 Route 10
E. Hanover, NJ 07936

July 15, 1993

Encl.: As noted

DEF:rmf

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231, on July 15, 1993
(Date of Deposit)
Diane E. Furman
Name of applicant, assignee, or Registered Representative
Diane Furman
Signature
July 15, 1993
Date of Signature

CERTIFICATE OF SERVICE

It is hereby certified that a true copy of the paper entitled:

MOTION FOR EXTENSION OF TIME

was served on counsel for the party Fujikawa et al., this 15th day of July, 1993, by postage prepaid first-class mail addressed to the following:

Oblon, Spivak, McClelland, Maier &
Neustadt P.C.
Attn.: Steven B. Kelber, Esq.
1755 South Jefferson Davis Highway
Crystal Square 5, Ste. 400
Arlington, VA 22202

Diane Furman

Diane E. Furman

[redacted] [redacted] #104

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES FYI

WATTANASIN

v. Interference No. 102,648

FUJIKAWA et al. Examiner-in-Chief: M. Sofocleous

JUL 19 1993
RECEIVED IN BOX INTERFERENCE

APPROVED
JUL 22 1993
Examiner-in-Chief

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MAILED
JUL 23 1993
PAT. & T.M. OFFICE
BOARD OF PATENT APPEALS
AND INTERFERENCES

Respectfully submitted,

Diane Furman

Diane E. Furman
Attorney for the Party Wattanasin
Registration No. 31,104
201-503-7332

SANDOZ CORPORATION
59 Route 10
E. Hanover, NJ 07936

July 15, 1993

Encl.: As noted

DEF:rmf

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(Date of Deposit)
Diane E. Furman
Name of applicant, assignee, or Registered Representative
Diane Furman
Signature
July 15 1993
Date of Signature

#105

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

JUL 19 1993

RECEIVED IN
BOX INTERFERENCE

WATTANASIN v. FUJIKAWA ET AL.

INTERFERENCE NO. 102,648

BRIEF OF THE JUNIOR PARTY, WATTANASIN

FOR FINAL HEARING

Diane E. Furman
Sandoz Corporation
Patent and Trademark Department
Building 418
59 Route 10
E. Hanover, NJ 07936-1080
(201) 503-7332
Attorney for the party WATTANASIN

Of Counsel
Richard E. Vila
Melvyn M. Kassenoff
Sandoz Corporation
Patent and Trademark Department
Building 418
59 Route 10
E. Hanover, NJ 07936-1080
(201) 503-7852

July 15, 1993

7/16/93

"RIBBON COPY FOR PARTY" Wattanasin

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Wattanasin v. Fujikawa et al.
Interference No. 102,648

BRIEF OF THE JUNIOR PARTY, WATTANASIN FOR FINAL HEARING

TABLE OF CONTENTS

I. TABLE OF CASES

TABLE OF CASES (Cont.)

II. STATEMENT OF THE ISSUES

PRINCIPAL ISSUES

1. Whether the junior party Wattanasin has established by a preponderance of the evidence conception and reduction to practice prior to the Fujikawa effective date; and/or diligence from a time prior to such date through to a reduction to practice.

a. Whether Wattanasin has demonstrated conception and synthesis of at least one species of the count in an initial activity phase prior to May 17, 1985, and whether Wattanasin abandoned, suppressed or concealed his invention in the period prior to the second activity phase in early 1987.

b. Whether, in the second activity phase commencing in early 1987, Wattanasin synthesized at least one species of the count; and whether testing of the species prior to August 20, 1987 was necessary for reduction to practice since the practical utility of the compounds was clear and certain.

2. If the Board finds that testing is required for the compounds made in 1987, whether Wattanasin has demonstrated diligence from a time prior to the Fujikawa filing date of August 20, 1987 until such testing and reductins to practice were completed by and on behalf of Wattanasin.

3. Whether any abandonment of the invention by Wattanasin is indicated or proved because of apparent or alleged delay in filing the Wattanasin application after the 1987 reductions to practice.

ADDITIONAL ISSUES

4. Whether the Wattanasin biological testing satisfies the utility requirement of the count:

a. whether the Wattanasin *in vitro* testing meets the utility requirement;

b. whether the Wattanasin *in vivo* testing satisfies the requirement;

c. whether the Wattanasin *in vivo* testing is competent to show the efficacy of the Wattanasin compounds of the count in inhibiting cholesterol biosynthesis in a patient in need of said treatment when administered in combination with a pharmaceutically acceptable carrier.

III. INTRODUCTION AND BACKGROUND

The involvement of Sandoz Pharmaceuticals Corp., the Wattanasin real party in interest, in the field of cholesterol lowering and, more specifically, HMG-CoA reductase inhibition, is a story which began to unfold in 1979 (WR at 136).

A comprehensive survey of Sandoz' and other companies' activities in the field over the prior decade, is contained in the 1991 review article of record[1] by Dr. Faizulla Kathawala, formerly Director of Medicinal Chemistry -- Lipoprotein Metabolism, at the Sandoz Research Institute (SRI).

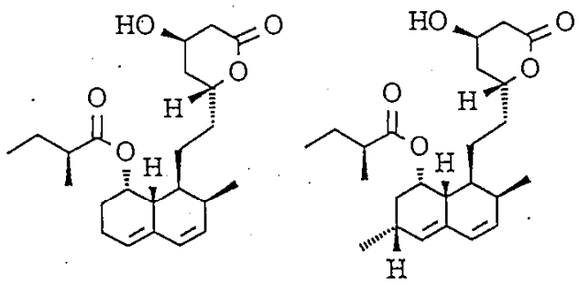
As the article indicates, and as Dr. Kathawala has himself testified in this interference, interest in the pharmaceutical industry early on focused on the enzyme, β-hydroxy-β-methyl-glutaryl-CoA reductase (HMG-CoA reductase), which controls a key step in the biosynthesis of cholesterol by catalyzing the conversion of the substrate HMG-CoA to mevalonate, an intermediate of cholesterol (WR at 471, 482)[2]. Inhibition of this enzyme has the potential to provide an effective treatment of hypercholesterolemia and atherosclerosis (WR at 136, 471), and this potential had been proved and recognized prior to 1985.

---

1. Medicinal Research Reviews, 11, No. 2, 121-146 (1991), WR at 470-495. (This article was in fact introduced as part of the Fujikawa rebuttal testimony of record.)

2. "WR" refers to the Wattanasin record; "WX" to the Wattanasin Exhibits.

Dr. Kathawala in his article describes the industry standards in the HMG-CoA reductase area prior to the entry of Sandoz. These comprised compounds such as compactin (tradename, "Mevastatin") and mevinolin (tradename, "Lovastatin"), having the following structures:



Mevastatin (Compactin) Lovastatin (Mevinolin)

WR at 472.

As is apparent from the structures above, both compounds are hydrogenated naphthyl derivatives of mevalonolactone.

The above compounds, while active as HMG-COA reductase inhibitors, could only be obtained from fungal broths (WR at 472).

Accordingly, Sandoz embarked on a major research program to develop synthetic heterocyclic derivatives of mevalonolactone which could also show activity as HMG-CoA reductase inhibitors (WR at 477-79; 486-87).

For over a decade Sandoz has been involved in an intense organized effort to discover such synthetic heterocyclic HMG-CoA reductase inhibiting compounds. The Sandoz research team grew to comprise five laboratory units each headed by a Ph.D. and also staffed by 12-15 other scientists (WR at 136), all dedicated to the synthesis of HMG-CoA reductase inhibitors.

Dr. Kathawala has testified in this interference that Sompong Wattanasin, Ph.D. joined the Sandoz project in 1982 as a Post-Doctoral level scientist working under Dr. Kathawala's supervision, and was later appointed as head of a laboratory unit (WR at 136).

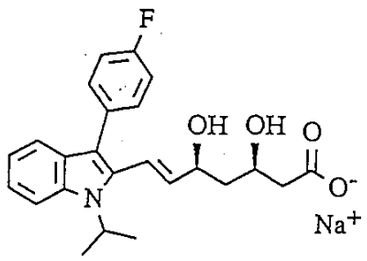
The Sandoz labs were involved not only in the synthesis of the quinoline compounds which are the subject of this interference, but also "chemically equivalent" analogs of mevalonolactone in other heterocyclic series such as the pyrazole, pyrimidine, indene, pyrrole, naphthalene, and indole systems (testimony of Kathawala, WR at 137).

Dr. Wattanasin has testified that during the period of July 1985 to July 1987, for example, his laboratory alone prepared 60 such compounds to be later tested for biological activity as HMG-CoA reductase inhibitors (WR at 63).

Since 1980, the extensive testing of biological activity of the compounds synthesized at Sandoz was conducted independently by Terence J. Scallen, M.D., Ph.D., Professor of Biochemistry in the Department of Biochemistry at the School of Medicine, University of New Mexico (testimony of Scallen, WR at 187).

Just an example of the various types of heterocyclic series being tested in the laboratory of Dr. Scallen at the University of New Mexico is evident from the pages of WX E-5 bearing a selection of Dr. Scallen's biological testing results with the structures of the corresponding compounds filled in by Dr. Robert Damon of Sandoz (testimony of Scallen, WR at 192; testimony of Damon, WR at 197). These results were repeatedly confirmed at Sandoz in in vivo assays in rats before and after 1985.

Early on, the Sandoz research program yielded the compound "fluvastatin" (XU 62-320), which is an indole analog of the open chain form of mevalonolactone, the indole ring also bearing a 4-fluorophenyl group and an isopropyl group, as follows:



Fluvastatin (XU 62-320)

WR at 472.

The Kathawala article of record indicates that the Sandoz compound fluvastatin had an IC_{50} of 0.0069 μM vs. an IC_{50} for the industry standard, compactin, of 1.011 μM, indicating that fluvastatin had a relative potency 146.1 times greater than that of compactin (WR at 483).[3]

3. IC_{50}: As explained in the Kathawala article (WR at 482), the potency of a therapeutic compound in an in vitro microsomal assay is typically expressed as an IC_{50} value (in μmoles), which is the concentration which inhibits, to

Likewise, the ED_{50} for fluvastatin is indicated by Kathawala (WR at 485) to be 0.093 mg/kg, while the ED_{50} for compactin was measured at 3.5 mg/kg; and thus, fluvastatin would be 40-fold more potent than compactin, according to Kathawala (WR at 485).[4]

An NDA filing on fluvastatin was completed by Sandoz in 1992 (WR at 62).

Of course, it is standard Sandoz policy, in order to preserve foreign patent rights, that publication of Sandoz inventions could not be released until a patent application was on file (testimony of Kassenoff, WR at 305-306). However, at least the indole series of heterocyclics was published out by Sandoz and available to the art as early as 1984 (see cover page of U.S. Patent No. 4,739,073 describing a genus of indole analogs of mevalonolactone including fluvastatin (WX-Z), which descends from a grandparent U.S. application filed on November 22, 1982, as well as footnote 10 (a) of the above-mentioned Kathawala article, which refers to a 1984 PCT application). [Other Sandoz filings between 1982 and 1991 in the HMG-CoA reductase area are summarized in the affidavit of patent attorney Melvyn M. Kassenoff, Director of the Sandoz Patent

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(Footnote 3 continued from previous page)
the extent of 50%, conversion of the substrate HMG-CoA to mevalonate. Obviously, the lower the IC_{50}, the more active the compound in an in vitro assay.

4. ED_{50}: In vivo activity of a compound is expressed as ED_{50} (mg/kg), which is a measure of the effective concentration which inhibits, to the extent of 50%, incorporation of C^{14} acetate into sterols when the formulated drug substance is administered in an appropriate dosage, as compared to controls receiving the drug vehicle alone. Thus, the lower the ED_{50}, the more active the compound in vivo.

Department (WR at 228-29)].

Thus Sandoz was involved in a substantial program to synthesize and identify an HMG-CoA reductase inhibitor to compete with the industry standards, mevinolin or compactin; and the Sandoz concept of a nitrogen-containing heterocyclic analog of mevalonolactone and its straight chain derivatives was published out in the art by Sandoz as early as 1984 if not earlier.

The multitude of subsequent filings by Sandoz as well as other companies in the pharmaceutical industry, on other heterocyclic series having corresponding ring substituents, is well-documented in the Kathawala article of record (WR at 490-92).

Among these filings in the HMG-CoA reductase area is the Fujikawa et al. involved U.S. patent application directed to quinoline analogs of mevalonolactone and the open chain forms thereof, which now stands in conflict with the involved Sandoz patent application.

IV. STATEMENT OF THE PARTIES AND THEIR FILING DATES

This interference is between an application Serial No. 07/498,301 of Wattanasin (junior party) assigned to Sandoz Pharmaceuticals Corporation, having an effective filing date of March 3, 1989[5], and an application Serial No. 07/233,752 of Fujikawa et al., (senior party) assigned to Nissan Chemical Industries Inc., having an uncontested Japanese priority date of August 20, 1987[6].

V. THE COUNT

The sole count in this interference comprises count 3, a copy of which is located at pages 17 to 20 of the Wattanasin Record (hereinafter "WR"). A copy of count 3 is also contained in the Appendix hereto.

VI. BURDEN OF PROOF

The junior party Wattanasin has the burden of proving prior invention over the senior party Fujikawa et al. application by a preponderance of the evidence, Holmwood v. Sugavanam, 948 F.2d 1236, 20 USPQ2d 1712, 1714 (Fed. Cir. 1991).

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5. The involved Wattanasin application is a Rule 60 continuation of Serial No. 07/318,773 filed March 3, 1989.

6. Two subsequent Japanese priority applications were filed on January 26, 1988 and August 3, 1988.

VII. SYNOPSIS OF WATTANASIN TESTIMONY

To sustain its burden, Wattanasin relies on the affidavit testimony of record of 16 witnesses, beginning with Dr, Sompong Wattanasin, the sole inventor on the junior party application; together with 51 exhibits. A list of the Wattanasin witnesses is provided at pages 1-2 of the Wattanasin record. Cross-examination depositions of four of the Wattanasin witnesses were taken by Fujikawa[7], and are also in the Wattanasin record following the affidavit of each respective witness. A list of the Wattanasin exhibits is provided at pages 3-10 of the Wattanasin Record.

The interrelationship of the various witnesses for Wattanasin, and the substance, in brief, of their testimony, is shown in tabular form below:

DR. SOMPONG WATTANASIN'S RESEARCH GROUP:

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1. The sole inventor (junior party), Sompong Wattanasin, Ph.D.

In brief, Dr. Wattanasin testifies by declaration and at deposition that he conceived of and synthesized at least three species of the count (Compound Nos. 63-366, 63-548

7. Melvyn M. Kassenoff, Esq., who was questioned before the other witnesses; Dr. Sompong Wattanasin; Mrs. Linda Rothwell; and Joanne M. Giesser, Esq.

and 63-549) by no later than May 17, 1985; that, given the high level of activity in his lab between mid-1985 and 1987, and the manpower shortage which developed, he was not able to complete the quinoline series of compounds until January 1987, when Ms. Rajeshvari Patel was retained in his lab for that express purpose; and that by March of 1987, when he was confident the remaining (four) compounds in the series (64-933, 64-934/NA, 64-935 and 64-936/NA) could be synthesized, he submitted his Patent Disclosure No. 299/84, on which the involved Wattanasin application is based, to the Sandoz Patent Committee. Dr. Wattanasin also testifies concerning his activities in relation to the filing of (the Rule 60 parent of) the involved Wattanasin patent application. Dr. Wattanasin's declaration and deposition testimony are at WR 21-135.

Supporting Exhibits for Wattanasin testimony:

The Sompong Wattanasin testimony is supported by at least the following Wattanasin exhibits: **A-1**, **A-2** (conception documents), **A-3** (Wattanasin Patent Disclosure 200/84); **B-1**, **B-2** (comprising pages from Dr. Wattanasin's Laboratory Notebook Nos. 1149, 1179); **O**; **P-1**, **P-2**, **P-3**; **Y-1**.

Corroboration of Sompong Wattanasin, sole inventor

Corroboration of Dr. Wattanasin's testimony going to his reductions to practice is provided by the testimony of the following individuals:

(i) **Dr. Faizulla G. Kathawala**, Director of Medicinal Chemistry -- Lipoprotein Metabolism during the time period covered by this interference, who supervised the Sandoz HMG-CoA reductase project, including the lab of

Dr. Wattanasin (WR at 136), and testifies concerning conception and reduction to practice (WR at 136-141);

(ii) Nicholas A. Paolella, Senior Scientist at Sandoz, who testifies concerning his witnessing of Dr. Wattanasin's laboratory notebooks (WR at 142-143);

(iii) Prasad Kapa, chemist in the Process Research and Development Group at Sandoz, who testifies that he provided Dr. Wattanasin with an intermediate used in the synthesis of one or more of the Wattanasin compounds (WR at 144-145).

Additional corroboration of Dr. Wattanasin's testimony going to a reduction to practice is provided by the testimony of **Drs. Patel, Barcza, Weinstein, Scallen, Damon, Engstrom, and Rodney Slaughter,** (described below), together with their supporting exhibits.

Additional corroboration of Dr. Wattanasin's testimony going to the filing of a patent application is provided by the testimony of Sandoz patent attorneys **Melvyn M. Kassenoff** and **Joanne M. Giesser;** as well as Patent Department docket clerk **Linda Rothwell** and **Lorraine M. Chesley,** secretary to Ms. Giesser (as described in brief below), and their supporting exhibits.

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2. Ms. Rajeshvari Patel, chemist who assisted Dr. Wattanasin in his laboratory

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In brief, Patel testifies that between March of 1987 and September of 1987 she synthesized at least four more species of the count (64-933, 64-934/NA, 64-935 and 64-936/NA), to complete the quinoline series of compounds.

Patel testifies about each of the synthesis steps leading to the end product in her declarations at WR 146-167.

Patel Supporting Documents

The Patel testimony is supported by Wattanasin exhibits **F-1** and **L-1** comprising pages of her Laboratory Notebook No. 1206. The Patel testimony is further supported by the declaration of Lawrence Perez, Ph.D., an Associate Fellow at Sandoz, who testifies concerning his witnessing of her laboratory notebook. (Certain pages in Exhibit F-1 were also witnessed by Dr. Wattanasin.)

Additional support for Ms. Patel's testimony is provided by the testimony of Drs. Patel, Barcza, Weinstein, Scallen, Damon, Engstrom, and Rodney Slaughter (see below), and their supporting exhibits.

DR. SANDOR BARCZA'S ANALYTICAL GROUP:

Dr. Sandor Barcza, Director of the Sandoz Department of Physical Organic Chemistry in the relevant time period, was responsible for supervising the personnel who performed the spectral and microanalyses of compound samples routinely sent by Sandoz chemists to the Department for characterization or confirmation of purification (WR at 172-182).

In brief, Dr. Barcza testifies as to his Department's procedure for logging in samples for IR, NMR or microanalysis. Dr. Barcza also testifies that individuals working under his direction initialed and dated the pages of the IR and NMR spectra which they personally recorded; and that WX

B-1, B-2 and F-1 contain copies of the spectra generated by his Department under his supervision. Further detail concerning the routine procedures of his laboratory is provided in his declaration of record.

Support for Barcza testimony

Support is found in WX C-1, C-2, C-3; D-1, D-2; G-1, G-2; H-1, and in the spectra enclosed in Exhibits B-1, B-2, F-1 and L-1 following each notebook page on which the characterized compound was synthesized.

DR. DAVID WEINSTEIN'S BIOLOGICAL TESTING GROUP:

Dr. David Weinstein, head of the Department of Lipid and Lipoprotein Metabolism, was in charge of the "Drug Room" at Sandoz, the facility where samples of compounds produced by Sandoz chemists are sent to be logged in for testing of biological activity. In brief, Dr. Weinstein testifies how, consistent with the routine procedure of his Department, a sample of a Sandoz compound with its official Sandoz number would be sent to Drug Room personnel, and the compound and date of its receipt by the Drug Room would be recorded in the Drug Room computer database. Dr. Weinstein testifies, in particular, that once logged into the Drug Room, Dr. Wattanasin's quinoline compounds were mailed according to routine procedure to Dr. Scallen at the University of New Mexico for biological testing. Dr. Weinstein's testimony is located at WR 183-186.

Support for Weinstein testimony

Dr. Weinstein's tesitmony is supported by WX H-1, I-1.

DR. TERENCE SCALLEN'S BIOLOGICAL TESTING LABORATORY AT THE UNIVERSITY OF NEW MEXICO

Dr. Scallen testifies by declaration in detail as to the in vitro microsomal assay he used to test Sandoz compounds synthesized in its HMG-CoA reductase program. He also testifies that he dated his laboratory records on the date he performed the testing, and therafter communicated the results containing the raw activity data to Dr. Damon of Sandoz, who used the data to calculate an IC_{50} for the tested compound (WR at 187-95).

Scallen's testimony is supported by WX E-1 to E-5; H-1 and I-1.

DR. ROBERT DAMON, CALCULATED IC_{50} VALUES

Dr. Damon of Sandoz testifies by declaration that under his direction, samples of Sandoz compounds were sent to the Drug Room for shipment to Dr. Scallen; that after Dr. Scallen performed an in vitro assay on Sandoz compounds he sent the raw data to Dr. Damon; and that on receiving the reports Dr. Damon would initial and date-stamp them, and write the structures and compute the IC_{50} values for the compounds tested on the reports. Dr. Damon testifies that within three or four days of receiving a report from Dr. Scallen, he would send the report, bearing his handwritten structures and IC_{50} data, to Dr. Wattanasin. Dr. Scallen also testifies that he recorded the IC_{50} data in his laboratory notebooks by affixing to a notebook page,

a form containing the structural formula of the compound retrieved from the Sandoz database, on which he wrote the IC_{50} data and the date on which Dr. Scallen tested the compound. Dr. Damon's testimony is at WR 196-202.

Support for Damon Testimony

Dr. Damon's testimony is supported by Wattanasin exhibits E-1 to E-5; J-1.

ROBERT G. ENGSTROM - IN VIVO TESTING

Robert G. Engstrom of the Sandoz Lipid Metabolism Department testifies by declaration that his laboratory conducted in vivo screening in rats of three of the Wattanasin quinoline compounds of the count, 64-933, 64-935 and 64-936/NA. The assay used by Engstrom, which is based on the conversion of ^{14}C-acetate to ^{14}C-cholesterol, is described in detail at WR 204. The counts of the precipitated sterols were entered by his lab assistant, Rodney Slaughter, into a computer program, which converted them to nano Curies (nCI) of sterol found per 100 ml. of serum at 4 hours after injection of ^{14}C-acetate.

Engstrom further testifies that he then entered this raw data into a separate computer program which calculates the ED_{50} of a compound from the data and compiles it in the Sandoz database of IC_{50} and ED_{50} values for compounds synthesized at Sandoz (WR at 205). Engstrom further testifies as to Biological Activity Data Reports which he generated for the Patent Department (WR at 207). Engstrom's testimony is located at WR 203-208.

Support for Engstrom

Support is found in the testimony of his lab assistant, Rodney Slaughter at WR 209-212, and in WX K-1 and Q.

SANDOZ PATENT DEPARTMENT:

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(1) **Melvyn M. Kassenoff, Esq.**, Director of the Sandoz Patent Department, testifies by declaration and at deposition as to Patent Department policies, and his role in gathering information for the involved Wattanasin application (WR 227-318);

(2) **Joanne M. Giesser, Esq.**, testifies by declaration and at deposition as to the events surrounding the drafting of the involved Wattanasin patent application (WR 319-467);

(3) **Mrs. Linda Rothwell**, the Patent Department docket clerk; testifies by declaration and at deposition as to the procedures of the Sandoz Patent Committee and the rating of Wattanasin Patent Disclosure 299/84 (WR 213-226);

(4) **Ms. Lorraine Chesley**, secretary to Ms. Giesser, testifies by declaration as to the date she started typing Giesser's handwritten draft of the involved Wattanasin application (WR 468-69).

Supporting Exhibits

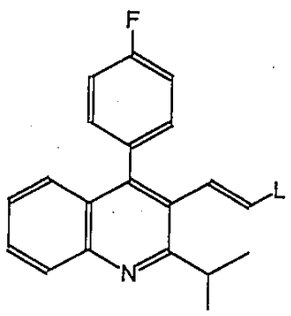
The above testimony is supported by Wattanasin exhibits M-1, M-2, M-3, M-4 and M-5; N; O; P; Q; R; S; T; U-1; U-2; V-1; V-2; W; X; Y-1; Y-2; Z; S-1; S-2; S-3, S-4

VIII. STATEMENT OF THE FACTS

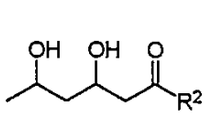
Conception

The Wattanasin conception of at least one species of the count goes back to November 28, 1983. It is Dr. Wattanasin's testimony, corroborated by Dr. Kathawala, his supervisor, that on or before this date he disclosed his proposal for 1984 research to Dr. Kathawala (WR at 23,138; WX A-1).

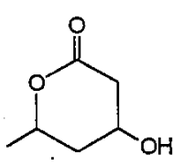
The 1984 Research Proposal contains the following structure of the count:



Wattanasin testified that "L" signified either a lactone or an open chain substituent, as follows:



and



where R^2 is an acid, salt or ester (WR at 23, WX A-1).

The 1984 research proposal concludes with the following forecast by Dr. Wattanasin of his progress in the succeeding year:

> It is unrealistic to expect all of these goals to be accomplished during the next year period, but we certainly expect to complete the indene analogue, the restricted rotation indole analogue, the optical synthesis of an aza analogue of compactin, to complete general study of Diels-Alder reaction of Z azatriene, and to make a substantial progress into the synthesis of other analogues.

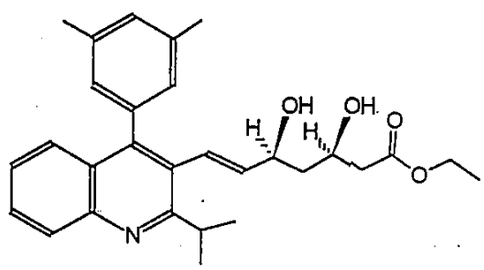
WX A-1 at 115[8].

First Activity Phase

Initial Reduction to Practice

By May 31, 1984, Dr. Wattanasin managed to begin to synthesize his first compound in the quinoline series of mevalonolactone analogs and straight chain derivatives.

Said compound 63-366 has the following structural formula of the count:



63-366

8. For convenience, where reference is made to a specific page of an exhibit, the handwritten page number at the upper right hand corner is used.

The synthesis was completed on or before November 26, 1984. Each of the 14 steps leading from commercially available starting materials to the end product 1079-111-19, designated 63-366, is described in detail in the Wattanasin declaration of record (WR at 30-44, WX B-1). (It will be noted that the predecessor intermediate of 63-366 is a keto-hydroxy compound which also is within the count.)

Support for sole inventor Wattanasin's testimony concerning compound 63-366 is found on the pages of Wattansin Laboratory Notebook Nos. 1149 and 1179 which comprise WX B-1, on which Wattanasin recorded contemporaneously the steps which he carried out to prepare end product 63-366 from commercially available or synthesized intermediates.

Corroboration of the Wattanasin testimony is provided by:

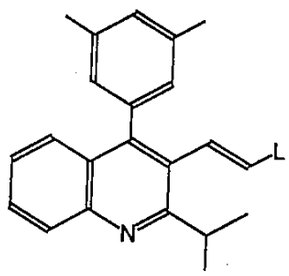
(1) the testimony of Nicholas Paolella, who witnessed the Wattanasin notebook pages (WR at 142). Specifically, Paolella testified that he himself had been involved in the synthesis of HMG-CoA reductase inhibitors, and that he had read and understood the pages of Dr. Wattanasin's notebook, which he recalled signing prior to August 20, 1987 (WR at 142);

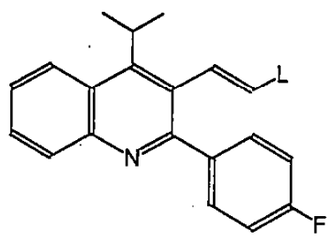
(2) the NMR and IR spectra and/or microanalyses taken by Dr. Barcza's Analytical Laboratory for the final compound, 63-366, and each of its intermediates (WR at 175-58; WX C-2, C-3, G-1, G-2), which are of record following each relevant laboratory notebook page.

(3) the further activities described below in connection with the biological testing of 63-366 by Dr. Scallen.

Just as he was completing the synthesis of 63-366, Dr. Wattanasin authored and sent to Dr. Kathawala (WR at 138) another annual research proposal dated November 19, 1984 in which he listed his research activities for the upcoming year of 1985 (WX A-2).

This document expressly discloses a number of additional species of the count (including the 4-fluorinated, isopropyl-substituted species originally disclosed in the prior year's proposal), as follows:





("L" having the significance previously indicated (WR at 24).

Note that the report contains the following statement of objectives for the year 1985:

> Complete the project on Quinoline system. If one of the quinoline proved to be very active, all of these three quinolines and a few new modifications might need to be prepared, because of their apparent ease of synthesis.

[emphasis supplied] WX A-2 at 121

At the same time, however, the research proposal for 1985 also indicated that Dr. Wattanasin intended to at least complete a parallel project in the indene system WX A-2 at 121).

Meanwhile, compound 63-366 was being characterized by the Sandoz Department of Physical Chemistry under Dr. Barcza and entered into the Sandoz database of compounds; then provided by Dr. Damon to the Sandoz Drug Room; from which it was shipped for biological testing to Terence Scallen, M.D., Ph.D., Professor of Biochemistry at the University of New Mexico (WR at 175, 184, 189-190).

Dr. Scallen was retained by Sandoz to conduct biological testing of the large numbers of compounds coming out of its HMG-CoA reductase research program (Scallen testimony, WR at 187). Dr. Scallen carefully developed an in vitro rat liver microsomal assay for this purpose based on information in the literature.

Dr. Scallen followed an "established protocol" for assaying the samples which he received, which for each assay carried out is described in detail on the first page of each of Exhibits E-1 to E-4 and is also described in detail in his declaration at WR 188-189. Dr. Scallen's assay was an in vitro assay using rat liver microsomes which served as the source of HMG-CoA reductase enzyme. From this assay, Prof. Scallen generated raw data concerning the HMG-CoA reductase inhibitory activity of a tested compound at different concentrations. From the raw data obtained by Scallen, an IC_{50} value was calculated by Dr. Damon, which could be evaluated relative to the IC_{50} of an industry standard in the HMG-CoA field, usually compactin (IC_{50} of 1.011 μM), or even the Sandoz compound fluvastatin (XU-62-320) (IC_{50} of 0.0069 μM) (See p 9 herein).

Dr. Scallen indicated that on or before December 13, 1984 he performed the assay; and on or before December 20, 1984, Dr. Damon testified he was in possession of the data (WR at 190).

The IC50 for 63-366 was computed by Dr. Damon to be as follows:

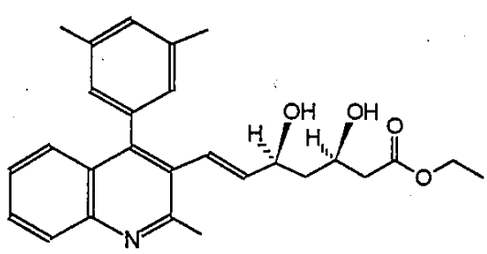
Compound	IC_{50} (μM)
63-366	1.58

WR at 199; WX E-1, E-5.

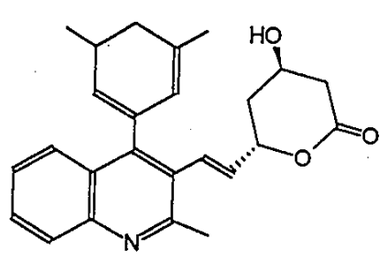
Note that the above activity level is fairly comparable to that of the industry standard, Compactin (IC_{50} of 1.011 μM).

Additional Wattanasin Reductions to Practice

Over the next six months, Dr. Wattanasin managed, as planned, to synthesize two more compounds of the quinoline series: 63-548 and its lactone, 63-549 (WR at 48-53; WX B-2). These compounds have the following structural formulae which place them within the count:



63-548



63-549

More particularly, Dr. Wattanasin testified that he commenced synthesis of 63-548 and 63-549 on or before May 2, 1985; and he would have completed the syntheses no later than May 17, 1985, i.e. no later than when the compounds were shipped to Dr. Scallen. Dr. Wattanasin's declaration provides a detailed step-by-step description of synthetic steps leading from commercially available starting materials to the compounds 63-548 and 63-549, which he recorded contemporaneously in his Laboratory Notebook No. 1179 (WR at 53; WX B-2).

Corroboration of record of inventor Wattanasin's testimony as to these additional syntheses consists of the following:

(a) the testimony of Nicholas Paolella, who witnessed the Wattanasin notebook pages, as above;

(b) the NMR, IR and/or UV spectra taken by the Sandoz Analytical Laboratory for the final compounds 63-548 and 63-549 and each of their intermediates which are included in WX B-2 following the relevant laboratory notebook page.

(c) the further activities by Drs. Scallen and Damon in connection with the biological testing of compounds 63-548 and 63-549.

Dr. Scallen testified that on or prior to June 13, 1985, he conducted biological testing of compounds 63-548 and 63-549; and Dr. Damon had the data on or before June 30, 1985 (WR at 190; E-2, E-5).

Dr. Damon calculated the IC_{50} values to be as follows:

Compound	IC_{50} (μM)
63-548	3.775
63-549	7.3100

(WR at 197-98; WX E-2, E-5)

Thus by mid-1985, Dr. Wattanasin was in possession of the first three compounds of his quinoline series and of the count: 63-366, 63-548 and 63-549. However, at least one compound depicted on the 1983-dated research proposal (WX A-1), bearing 4-fluorophenyl and isopropyl substituents, 64-935 (i.e. analogous in structure to the highly active Sandoz fluvastatin compound referred to above), remained to be synthesized.

Nonetheless, Dr. Wattanasin's lab was also committed to fulfilling his 1985 research objectives involving a substantial synthesis program to make heterocyclics for testing as HMG-CoA reductase inhibition. As he testified in his declaration:

> My laboratory was only one of six laboratories devoted virtually exclusively to the synthesis of HMG-CoA reductase inhibitors. By way of illustration of the large number of HMG-CoA compounds being synthesized at Sandoz, I note that during the period of July 1985 to July 1987, my laboratory alone prepared 60 such compounds. This is evidence of Sandoz' high level of interest in the project and intention since 1981, and including the period

of July 1985 to July 1987, to pursue its basic research project in the HMG-CoA reductase area and the inventive concept behind it.

WR at 104.

and again in deposition:

> Actually, at that time, actually 1985 because we are dealing with different classes of HMG-CoA reductase inhibitor compound, quinoline is not the only compound we are making. We are making other, different kind of heterocyclics, as well.

WR at 106.

Dr. Wattanasin's lab was the only one at Sandoz synthesizing quinoline HMG-CoA reductase compounds (WR at 106).

Dr. Wattanasin testified that "sometime in 1985" (WR at 107), it became apparent that he was facing a a manpower shortage in his lab which if left unfilled would prevent him from completing the quinoline series.

> "*** we are not complete the whole set of this compound yet *** because of a lack of manpower at that time because I'm the only one working at that time on the HMG-CoA reductase in this lab."

> "*** at that time with additional manpower, I felt that we should be able to complete the whole set of this quinoline case, that's why I file patent disclosure at that time."

WR at 106-110.

By the "whole set" of quinoline compounds, Dr. Wattanasin would have been referring at least to compound 64-933 and its sodium salt, 64-934/NA; and, in particular,

compound 64-935, as well as its sodium salt, 64-936/NA, which remained to be synthesized and tested.

Dr. Wattanasin initiated a request for an additional person, but he soon found that action on this request would take time:

> Normally to get someone, you have got to have approval from your boss and then subsequently, you have got to get approval by your department head and then it also depends on whether or not the opening is available at that time and when you got the actual head count, the opening, then you have got to get approval from your boss, from your department head and then from the head of -- from the president of SRI. And then you have to recruit the person. It takes a long time, actually *** In this case, a whole year.

WR at 197-198.

That person was Ms. Rajeshvari Patel, who in January 1987 joined the Wattanasin lab, and "from the start" was assigned to complete the quinoline series (WR at 104-110).

Confident by March of 1987 that he had the manpower to complete the quinoline series (WR at 106-110), Dr. Wattanasin went ahead and on March 16, 1987 executed, and had witnessed by Dr. Kathawala, Patent Disclosure No. 299/84[9], which he sent to the Patent Department for consideration in due course by the Sandoz Patent Committee (WR at 24-25).

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9. As Dr. Wattanasin testified, he received a blank disclosure form from the Patent Department in late 1983 with the number 299/84 appearing at the top. He held on to this disclosure form until March 1987, when he returned it completed to the Sandoz Patent Department (WR at 102-103).

However, as Dr. Wattansin has pointed out:

> *** if I did have the manpower before 1987, some key compounds should have been synthesized before that date, before March 3[sic], 1987.

WR at 109, 128-129.

Second Activity Phase

Wattanasin Resumed Activity for the Count

From no later than early March 1987 into September 1987, Rajeshvari Patel went on to synthesize the four more compounds in the quinoline series: 64-933 (an ethyl ester), and its sodium salt, 64-934/NA; and 64-935 (an ethyl ester), and its sodium salt, 64-936/NA.

In fact, by no later than mid-April of 1987, Ms. Patel was involved with preparing the necessary starting materials to synthesize the above quinoline compounds (see discussion below).

Contemporaneously, on April 29, 1987, the Sandoz Patent Committee met in regular fashion and took up for consideration Dr. Wattanasin's Patent Disclosure 299/84.

The Sandoz Patent Committee is comprised of the head and assistant heads of the Patent Department and members representing Chemistry, Biology, Pharmacy and possibly some other groups in Pharmaceutical Research (testimony of Kassenoff, WR at 294).

The Committee meets monthly to review patent disclosures submitted by research, and bestows one of 5

letter ratings on a disclosure, as follows:

"A" signifies that a patent disclosure is ripe for filing and should be filed on;

"B" indicates that a decision whether or not to file on the patent disclosure is deferred by the Patent Committee for three months' time, usually because there is "ongoing work" involved, such that the disclosure is deemed not ripe for filing (testimony of Kassenoff, WR at 238-39).

"C" means that decision on whether or not to file is deferred for six months, for the reasons stated above;

"X" is given when the people whose input is required before the disclosure is rated "A" are not at the meeting, or additional work is still on going and the results are expected within one month, such that is is anticipated that a decision will be made at the next regular monthly Patent Committee Meeting (testimony of Kassenoff, WR at 286).

"D" means that a decision is made not to file a patent application.

It was not within an attorney's jurisdiction to rate patent disclosures (testimony of Giesser, WR at 381).

Minutes of each meeting are distributed to all attorneys in the Sandoz Patent Department from within a few days to a week or two after a meeting (testimony of Kassenoff, WR at 244; testimony of Giesser, WR at 381).

No action on the part of the patent attorney to file a patent application is required in response to an "X", "B"

or "C" rating. Of course, a "D" rating means that no application will be filed.

At the Patent Committee meeting (PCM) of April 29, 1987, it was decided evidently in view of the ongoing work to complete the series, to rate the Wattanasin PD 299/84 "B", for reconsideration at the regular PCM in three months' time (testimony of Rothwell, WR 214; WX M-1).

During the ensuing period, the party Wattanasin's resumed work in the field continued, as Rajeshvari Patel diligently worked to synthesize additional compounds in the quinoline series.

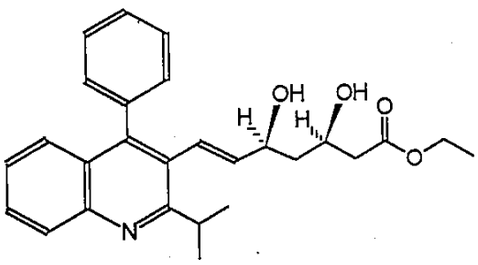
Patel testified in her declaration as to each synthesis step which she performed. Ms. Patel has testified that she kept Laboratory Notebook 1206 and that she dated each laboratory notebook page on the day she commenced the work reported on that page (WR at 147, 164).

Patel's testimony is supported by WX F-1 and L-1, which both comprise pages from her Laboratory Notebook No. 1206.

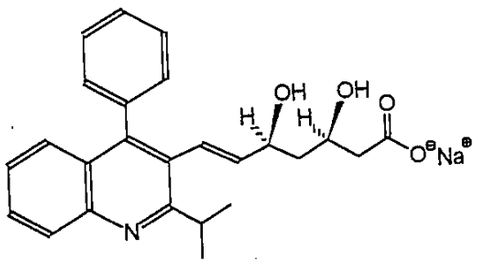
The pages of WX F-1 and L-1 can be re-ordered as follows to better view the synthesis steps in consecutive order:

L-1 Laboratory Notebook Pages: 86, 103, 199 (and spectra)
F-1 Laboratory Notebook Pages: 124, 130 (and spectra)
L-1 Laboratory Notebook Pages: 137, 145-end of L-1 (and spectra)
F-1 Laboratory Notebook Pages: 190, 201 (and spectra)

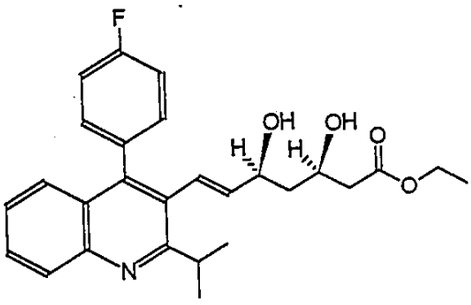
The structures of compounds 64-933, 64-933/NA, 64-935 and 64-936/NA are shown below as being of the count:



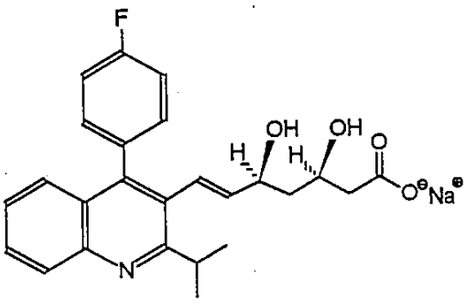
64-933



64-934/Na



64-935



64-936/Na

It is noted that the precedecessor intermediates of 64-933 and 64-935, respectively, comprising keto-hydroxy compounds [which are reduced by a triethylborane/sodium borohydride stereoselective reduction step to yield the predominantly erythro dihydroxy product (WX F-1, L-1)], are within the count as well.

Patel laboratory Notebook No. 1206 (WX L-1) shows that no later than April 13, 1987, Patel was involved with preparing the intermediates needed in the synthesis of 64-935 and 64-936/NA. Contemporaneously, she began the synthesis of 64-933 and 64-934/NA. Activity was recorded out on at least April 13-14 (WR at 165, WX L-1 at 341), April 21, 28, and May 4, 5, 8 and 11 (WR at 165, WX L-1 at 341-343), and May 20, 22 and 26 (WR at 165, WX L-1 at 344-345).

For convenience, the TABLE below is provided to summarize the dates, as of June 1, 1987, of the synthesis steps carried out by Ms. Patel; the dates on which the Analytical Laboratory logged in the compounds; and the dates on which spectra were taken and/or microanalyses performed on the end products and their intermediates.

The Table serves to condense Wattanasin Exhibits F-1 and L-1 (i.e. Patel Lab Notebook 1206), as well as WX C-3, G-1, G-2 and H-1.

TABLE

Relevant Testimony (WR)	Relevant Wattanasin Exhibit Page or Entry No.	Date	Description
		JUNE 1987	
PATEL	F-1 263	6/1/87	Commence synth. 1206-130-27
BARCZA	C-3 #3256	6/5/87	NMR lab receives 1206-130-27
	G-1 # 899	6/5/87	IR lab receives 1206-130-27
	F-1 264	6/5/78	IR of 1206-130-27 taken
	F-1 265	6/8/87	NMR of 1206-130-27 taken
	F-1 266	6/9/87	Commence synth. 1206-137-31
	C-3 #3326	6/12/87	NMR lab receives 1206-137-31
	F-1 268	6/12/87	NMR of 1206-137-31 taken
	G-1 # 922	6/12/87	IR lab receives 1206-137-31
	F-1 267	6/12/87	IR of 1206-137-31 taken
	F-1 269	6/17/87	Commence synth. 1206-145-25
	C-3 #3450	6/19/87	NMR lab receives 1206-145-25
	C-3 #3451	6/19/87	NMR lab receives 1206-145-26
	F-1 270	6/22/87	NMR of 1206-145-25 taken
	F-1 271	6/22/87	NMR of 1206-145-26 taken
	F-1 272	6/30/87	Commence synth. 1206-153-34
			(continued)
		JULY 1987	
	F-1 272	7/1/87	purif. 1206-153-41
	F-1 272	7/2/87	purif. 1206-153-41
	F-1 266	7/2/87	Patel signs p. 137
	C-3 #3596	7/2/87	NMR lab receives 1206-153-31
		7/2-7/3	(weekend)
	G-1 #900	7/6/87	1206-124-26 sub't to Analytical
	F-1 272	7/6/87	Patel signs p. 153
	F-1 274	7/6/87	NMR of 1206-153-31 taken
	C-3 # 315	7/7/87	NMR lab receives 1206-153-37
			(continued)

TABLE (continued)

Relevant Testimony (WR)	Relevant Wattanasin Exhibit	Page or Entry No.	Date	Description
PATEL BARCZA	F-1	275	7/7/87	NMR of 1206-153-37 taken
	F-1	158	7/7/87	Commence synth. 1206-158-41
	F-1	276	7/8/87	purif. 1206-158-41
	F-1	272	7/9/87	m.p. taken (1206-153-31)
	G-2	# 518	7/9/87	Micro lab receives 1206-153-31
	C-3	#3677	7/10/87	NMR lab receives 1206-158-41
	F-1	278	7/10/87	NMR of 1206-158-41 taken
	G-2	# 524	7/15/87	Micro lab receives 1206-158-41
	F-1	279	7/15/87	Commence synth. 1206-166-30
	L-1	346	7/15/87	synth. 1206-167-41
	F-1	273	7/15/87	IR of 1206-153-34 taken
	C-3	#3793	7/16/87	NMR lab receives 1206-166-30
	F-1	281	7/16/87	NMR of 1206-166-30 taken
	G-1	#1007	7/16/87	IR lab receives 1206-153-34
	F-1	276	7/17/87	Patel signs p. 158
	L-1	346	7/17/87	purif. 1206-167-41
			7/18-7/19	(weekend)
	F-1	282	7/20/87	Commence synth. 1206-175-4 = intermediate within count
	L-1	346	7/20/87	purif. 1206-167-41
	F-1	282	7/21/87	Patel signs p. 282
	G-1	#1037	7/21/87	IR lab receives 1206-158-41
	F-1	277	7/21/87	IR of 1206-158-41 taken
	F-1	283	7/22/87	synth. 1206-175-4

(continued)

TABLE (continued)

Relevant Testimony (WR)	Relevant Wattanasin Exhibit	Page or Entry No.	Date	Description
PATEL BARCZA	L-1	347	7/22/87	Commence synth. 1206-173-39
	C-3	#3874	7/22/87	NMR lab receives 1206-175-4
	L-1	347	7/23/87	Flash chromatography to give 1206-173-39
	G-2	# 545	7/23/87	Micro lab receives 1206-175-4
	G-1	#1052	7/23/87	IR lab receives 1206-175-4
	F-1	284	7/23/87	IR spectra of 1206-175-4 taken
	F-1	285	7/23/87	NMR spectra of 1206-175-4 taken
	F-1	286	**7/23/87**	**Commence synth. of final product 1206-176-41 (64-933) and 1206-176-43 from 1206-175-4**
	G-1	#1059	7/24/87	IR lab receives 1206-173-39
	G-2	#552	7/24/87	Micro lab receives 1206-173-39
	L-1	348	7/24/87	Commence synth. 1206-177-33
			7/25-7/26	(weekend)
	L-1	350	7/27/87	Repeat synthesis of p. 177
	G-1	#1093	7/27/87	IR lab receives 64-933
	C-3	#3934	7/27/87	NMR lab receives 64-933
	F-1	287	**7/27/87**	**NMR of 64-933**
	C-3	#3933	7/27/87	NMR lab receives 1206-176-43
	F-1	291	7/27/87	NMR of 1206-176-43 taken
	F-1	290	7/27/87	IR of 1206-176-43 taken
	G-2	#558	7/28/87	Micro lab receives 1206-177-33
	L-1	349	7/28/87	Commence synth. 1206-180-39
	L-1	350	7/28/87	purif. 1206-178-39
	F-1	293	**7/28/87**	**Commence synth. of final product 1206-179-30 (64-934/NA)**
	F-1	279	7/28/87	micro 1206-166-30 entered
	G-2	#560	7/28/87	Micro lab receives 1206-166-30
	F-1	288	**7/29/87**	**IR of 64-933**
	F-1	289	7/29/87	NMR of 64-933
	F-1	296	**7/29/87**	**NMR of 64-934/NA**
	G-2	#563	7/29/87	Micro lab receives 64-934/NA
	G-2	#565	7/29/87	Micro lab receives 1206-180-39
	L-1	351	7/29/87	Repeat synthesis shown on page 180 to prepare 1206-181-26

(continued)

Just as compounds 64-933 and 64-934/NA were being logged in and characterized by Dr. Barcza's Physical Chemistry Department in the context of additional ongoing preparations, the Wattanasin Patent Disclosure No. 299/84 came up for reconsideration at the regular meeting of the Sandoz Patent Committee on Wednesday, July 29, 1987. Presumably in light of the in vitro testing which was to follow, Wattanasin PD 299/84 was re-rated "B", for re-consideration in three months' time, i.e. at the October PCM (testimony of Rothwell, WR at 215; WX M-2).

Meanwhile, Patel's synthesis work, and the accompanying characterization of intermediates and end products, continued, as follows:

TABLE (continued)

Relevant Testimony (WR)	Wattanasin Exhibit Page or Entry No.		Date	Description
PATEL BARCZA	G-1	#1084	7/30/87	IR lab receives 1206-166-30
	F-1	280	7/30/87	IR of 1206-166-30 taken
	F-1	166	7/30/87	mass taken 1206-166-30
	F-1	292	7/30/87	NMR of 1206-176-43
	F-1	294	7/31/87	IR of 64-934/NA
	F-1	295	7/30/87	IR of 64-934/NA
	G-1	#1093	7/31/87	IR lab receives 1206-179-30
			AUGUST 1987	
			8/1-8/2	(weekend)
	L-1	352	8/3/87	Commence synth. 1206-183-31
	L-1	353	8/4/87	Commence synth. 1206-185-31
	F-1	283	8/5/87	Patel signs p. 175,177,179,186
	G-2	586	8/5/87	Micro lab receives 1206-185-31

(continued)

TABLE (continued)

Relevant Testimony (WR)	Wattanasin Exhibit Page or Entry No.	Date	Description
PATEL BARCZA	L-1 354	8/5/87	Commence synth. 1206-187-15 (and 1206-187-18), an intermediate within count; sign pages 177-186
	L-1 353	8/5/87	m.p. 1206-185-31
	L-1 355	8/5/87	synth. 1206-187-15
	L-1 352	8/6/87	take mass 1206-183-31
		8/8-8/9	(weekend)
	G-2 591	8/10/87	Micro receives 1206-187-15
	F-1 297	8/10/87	Commence red. of 1206-187-18 to 1206-190-38
	F-1 297	8/11/87	Obtain product from reaction mixture
	F-1 297	8/12/87	Purif. 1206-190-38
		8/15-8/16	(weekend)
	F-1 297	8/20/87	IR of 1206-190-38 taken
		8/22-8/23	(weekend)
	F-1 297	8/25/87	Convert 1206-190-41 (64-935) to its sodium salt, 1206-201-30 (64-936/NA)
	G-2 #634	8/26/87	Micro lab receives 64-936/NA
	F-1 301	8/27/87	NMR of 64-936/NA
	F-1 300	8/28/87	spectra of 64-936/NA
		8/29-8/30	(weekend)

Specifically in regard to the time period overlapping the senior party effective date, it is noted that by August 10, Ms. Patel had compound "449" on page 190 of her Laboratory Notebook 1206, the intermediate which immediately precedes the final product, and which is within the scope of the count. In a final sodium borohydride/ triethylborane reduction step commenced on August 10, 1987, Ms. Patel reduced said compound "449" to its dihydroxy product, i.e. compound 64-935, also of the count. Laboratory page 190 (WX L-1 at 297) shows that on August 11, 1987, the reaction system was quenched and washed with

methanol, to give a yellow oil, 1206-190-35). Flash chromatography followed to give a yellow-orange oil, namely 1206-190-38, product "(a)". 1206-190-38 was dried "over high vac" to give 1206-190-41, which was later denominated 64-935. Thus 1206-190-38 is the material of 1206-190-41 prior to drying. The spectrum of 1206-190-38 was taken on August 20, 1987 (WX L-1 at 298). Three working days later, i.e. on August 25,1987, compound 64-935, which is an ethyl ester compound, was converted to its salt, 64-936/NA (Notebook page 201, WX F-1 at 299).

Dr. Wattanasin has testified that during the synthesis, purification and characterization of the above compounds 64-933, 64-934/NA, 64-935 and 64-936/NA, he went to a meeting in New Orleans for over a week (WR at 118), and when he came back, he found out that the next scheduled shipment out of the Sandoz drug room to Dr. Scallen would be on October 2, so that even though the compounds were made before October 2,

> A. *** I would like all of these compounds to ship for testing together so I can have a better comparison of the potency in the same study.
> Q. When you say all of these compounds, you are referring to which ones?
> A. 64-933, 64-934 and 64-935 and 64-936, as well.

WR at 119, 188.

Meanwhile, as Patel finished off her laboratory work by signing her notebooks, compounds 64-933, 64-934/NA, 64-935 and 64-936/NA were on their way to the Sandoz Drug Room:

TABLE (continued)

Relevant Testimony (WR)	Relevant Wattanasin Exhibit Page or Entry No.	Date	Description
		SEPTEMBER 1987	
PATEL WEINSTEIN	F-1,L-1	9/1/87	Pages 187,201 of Notebook 1206 signed by Patel
		9/5-9/7	(Labor Day weekend)
	H-1	9/21/87	64-933, 64-934/NA and 64-935 received in Sandoz Drug Room
	H-1	9/22/87	64-936/NA received in Sandoz Drug Room
		9/26-9/27	(weekend)

Biological Testing of 64-933, 64-934/NA, 64-935 and 64-836/NA in in vitro rat microsomal assay

Thus compounds 64-933, 64-934/NA, 64-935 and 64-936/NA were shipped overnight on October 2, 1987 to Scallen (WX I-1 at 325-326). October 3 and 4, 1987 fell on the weekend. Meanwhile, Patel Notebook No. 1206 bears a notation dated October 6, 1987, that compound 1206-201-30 (64-936/NA) was being submitted for a solubility study (WX L-1). The Patel Notebook also bears a notation dated October 7, 1987, of a solubility value of .0958 mg/ml for (WX L-1 at). That same week, on October 8, 1987, Dr. Scallen tested compounds 64-933, 64-934/NA and 64-935 for biological activity in vitro (WR at 191, WX E-3). October 10 and 11 fell on the weekend. On October 13, 1987, 64-936/NA was also tested by Dr. Scallen (WR at 191, E-4 at 236). October 17 and 18, 1987 fell on a weekend.

Dr. Scallen reported the raw data for 64-933, 64-934/NA and 64-935, together with the data for 64-936/NA

to Damon on or before October 20, 1987 (WR at 191, WX E-3, E-4, E-5). Dr. Damon calculated the IC_{50} values and entered them into his notebook (WR at 199-200; WX E-3, E-5). These data are as follows:

Compound	IC_{50} (μM)
64-633	2.3700
64-934/NA	2.6100
64-935	0.4130
64-936/NA	0.5300

Hence, the preparation of the four "second activity phase" compounds and their in vitro testing was completed by October 13, 1987 as a result of continuous, uninterrupted activity and diligence by or on behalf of Wattanasin from a time in 1987 well before the August 20, 1987 Fujikawa filing date, as clearly shown by the evidence of record and the time/activity summaries provided hereinabove.

Biological Testing of 64-933, 64-935 and 64-836/NA in vivo

Once the in vitro results were received, the Sandoz Lipid Metabolism Department "HMGR Screening Unit" commenced in vivo rat studies of certain of the compounds.

Robert Engstrom of that Department has testified that the study of compound 64-936/NA was carried out on or before October 22, 1987, i.e. only two days after the Scallen in vitro report for that compound were received by Damon (WR at 205) (Exhibit K-1).

October 24 and 25, 1987 fell on a weekend.

On Wednesday, October 28, 1987, the Patent Committee had its regular meeting. At this meeting, PD 299/84 was rated "X" for the first time, meaning that it would be reconsidered in one month's time, at the next regular meeting in November (Testimony of Linda Rothwell, WR at 215, WX M-4).

The next day, October 29, 1987, (testimony of Engstrom at 205; testimony of Slaughter at 209; WX K-1 at 334, 336), compounds 64-933 and 64-935 were tested in vivo, generating raw activity data for those compounds at dosages of 0.1, 0.3 and 1.0 mg/kg (WX K-1 at 337-339).

However, the raw data had to be entered into the separate Sandoz database which calculated ED_{50} values. This additional activity for the count was performed by Engstrom by December 9, 1987. It was as of that date the ED_{50} data was available in the Sandoz database of ED_{50} values for compounds (WR at 205-206, WX K-1).

Thus at the Wednesay, November 25, 1987 meeting of the Sandoz Patent Committee, the Wattanasin Patent Disclosure 299/84 again earned a rating of "X", setting it up for reconsideration at the January 1988 PCM (Rothwell testimony, WR at 375; WX M-4) (no meeting ordinarily being held in the month of December (Kassenoff testimony).

By December 9, 1987, the ED_{50} of the three compounds, 64-933, 64-935 and 64-936/NA were computed and came on line in the Sandoz database. They are as follows:

COMPOUND	ED_{50} (mg/kg)[10]
64-933	>1 or 2.40
64-935	0.49
64-936	>1

WX Q at 418.

As is obvious from the IC50 and ID50 data reported on the above pages, compound 64-935 did prove to be the most active compound of the quinoline series prepared by Wattanasin.

It is noted that the involved Wattanasin application also contains the IC_{50} and ED_{50} data for compounds 64-935 and 64-936/NA.

At the January 27, 1988 meeting of the Sandoz Patent Committee, Wattanasin Disclosure 299/84 was rated "A" for filing. The patent disclosure, previously assigned to Fred Weinfeldt, was reassigned in his absence on disability leave, to Joanne M. Giesser, Esq., a junior attorney in the Sandoz Patent Department who had joined out of the Patent and Trademark Office a few months before, i.e. in August of 1987 (testimony of Giesser, WR at 319).

10. see Engstrom Declaration, WR at 206. Note that there is an inadvertent typographical error in the Engstrom Declaration consisting in the "switching" of ED_{50} data for compound 64-935 with one of the other compounds. This error was acknolwedged and corrected in the Engstrom Supplemental Declaration (WR at 207). Also, WX Q contains an additional ED_{50} point for compound 64-933, i.e. 2.40.

Mrs. Giesser would have received the minutes of the meeting shortly after the meeting (WR at 332).

Filing of the (Rule 60 parent of the) involved Wattanasin patent application (Sandoz Case 600-7101)

On the one hand, Giesser would have had no reason to pick up the disclosure prior to its being rated "A" for filing (WR at 423). By the same token, once assigned an "A"-rated disclosure, Giesser fully understood that she had "no choice" but to proceed with the filing of a patent application (WR at 382).

And given the general policy of the Sandoz Patent Department against hiring outside counsel for routine pharmaceutical patent application writing or prosecution (WR at 242-243), there could be no question of "farming out" the work to an outside firm.

The fact is, the "A"-rating of January 27, 1988 stood as a command imperative to file a patent application. This instruction could only be inactivated by taking the disclosure back to the Patent Committee for a re-rating from "A" down to either "B", "C", "D" or "X", "D" meaning drop and "X", "C" and "B" being various categories requiring reconsideration.[11]

11. If a Patent Disclosure were re-rated or even considered for re-rating, the re-rating would have become known through publication of the Minutes which were routinely circulated to the attorneys in the Sandoz Patent Deparment (Kassenoff testimony, WR at 295). In this case no such action was ever taken (WR at 381-82, 387).

Given the subject matter, this case fell within the supervisory jurisdiction of Melvyn M. Kassenoff, a senior patent attorney employed for some 15 years in the Sandoz Patent Department (WR at 227). Mrs. Giesser was being supervised in this area by Kassenoff.

Also, a backlog had developed in the department since the departure of Fred Weinfeldt, which Kassenoff now had to supervise (testimony of Kassenoff, WR at 245-56).

After the "A" rating, Kassenoff testified that notwithstanding that the patent disclosure had been assigned to Ms. Giesser, he himself went ahead and helped with some of "the initial spadework" for the case (WR at 257).

In fact, the record indicates that Mr. Kassenoff wrote a handwritten checklist for an application on 299/84 and also spoke with Dr. Wattanasin on February 12, 1988 (WR at 230, 255; WX N).

In response, Dr. Wattanasin sent to Kassenoff on or about February 29, 1988, a reaction scheme and other notes relating to PD 299/84 (testimony of Wattanasin, WR at 64; WX-O), which Kassenoff corroborated receiving on or about March 1, 1988 (WR at 230).

It is noted that, consistent with the patent disclosure, this material describes 2 synthetic routes to obtain the compounds of the disclosure. Scheme I" is a multi-step procedure of some 10 steps. "Scheme II' comprises some 6 steps. These documents originated what became the 58-page involved Wattanasin patent application.

Kassenoff testified that this material was "only partially" responsive to his requests for information (WR at 262).

Kassenoff further testified that he also placed a request with the Sandoz Biology Department for the IC_{50} and ED_{50} values for compounds of 299/84 he was planning to cover in a patent application and any other biological data needed (WR at 231).

In connection with these activities, Kassenoff testified as follows about the filing of a patent application:

> I assume that it was in the back of our minds that there was a possibility that I might do it ** if I had the available time because that's the only way I could explain the fact that I did request Dr. Wattanasin to send me ** the information required from the chemical side and I did request Biology to send me their input for the application.

WR at 293.

For Giesser, the "A" rating of the Wattanasin patent disclosure in effect marked the beginning of what was recalled in testimony, with perhaps some understatement, as being "a rather hectic time" (WR at 375-376).

First, Giesser had a rather extensive schedule of required business travel arising primarily out of her primary responsibility to handle the patent work for Zoecon (Palo Alto), Sandoz' agricultural research affiliate, and the Sandoz seed company affiliates, Northrup King (Minneapolis) and Rogers Brothers (Boise, Idaho), WR at 388. (Ms. Giesser had a Masters degree in Agronomy from

Clemson University, with a specialization in plant genetics, WR at 387). She testified that she compiled approximately 75,000 miles in air travel between February 1, 1988 and March 3, 1989 (WR at 321). She testified in this regard as follows:

> At that time I spend a large amount of time working for the seed companies, and it involved a large amount of travel. In fact, the most travel I've done in my career so far basically took place during approximately this year [i.e. 1988], and so I was out of the office a lot and had to do a lot of preparation for these various trips I was making in relation with the seed companies. So, therefore, it would have taken an extra long time for patent applications to be filed just because of the circumstances of being out of the office so much."

WR at 353-54.

For example, Giesser testified that in February of 1988, she was away an entire week on a business trip to, successively, Minneapolis, Boise and Palo Alto (WR at 388). On March 1, 1988, she attended a business meeting in Washington, D.C. Over March to April 1988, she made separate trips to Boston and Palo Alto (WR at 389), totaling seven days' actual out of office time, as well as additional preparation time. In April of 1988, she was in Des Plaines, Illinois attending a patent meeting for three days. May and June, 1988 required one and three days out of the office, respectively, to IBA meetings and Palo Alto. In July of 1988, she returned to Des Plaines for two days. In August of 1988, she was at Palo Alto on a 4-day trip. In September of 1988, four days were spent in Basle, Switzerland for a patent policy (seed) meeting. In October - November of 1988, there was a 3-day trip to Palo Alto; a

3-day trip to Wisconsin, and 2 days in Boulder, Colorado. December 1988 brought 2 days in Chicago, where she delivered a patent lecture to a Northrup King group. January 1989 occasioned 4 days divided between Minneapolis and Palo Alto; and February 1989, 3 days in Boise (WR at 388-391).

In the midst of this travel activity, Giesser was under pressure to file patent applications in the seed area. She testified that there were six cases in the seed area which had 102(b) on sale/public use bars coming up in March of 1989 (WR at 395), some of them actually falling on March 3, 1989, the filing date of the involved application (WR at 375-76):

> Q. So after you had begun drafting the application in question, was it necessary to put -- to interrupt that drafting in order to attend to the seed cases?
>
> A. I'm not sure whether I was -- I actually stopped working on it or whether I was working on it contemporaneously. The filing of the seed cases were in response to a policy change, and some of the discussions on the policy change were at the meeting in Basle in September, so the decision to file on these would have been after that.

WR at 439.

Even in the HMG-CoA reductase area, Mrs. Giesser was also under pressure to file a CIP on case 600-7025/CIP (WR at 398-401; WX S-3) and at the same time assist Basle in preparing a foreign text for filing under a deadline of October (WR at 454-55). The U.S. CIP would have also had to be on file by November 11, 1988 in order to avoid filing a continuation application. (WR at 400-401; WX S-3).

Of this case she testified:

> A. Well, the amount of material that was added, as I recall, was a lot. It wasn't just one extra example or something which you might put into a CIP. The amount of work involved was the equivalent to writing a new case, in my estimation.
>
> Q. Would that be the same material that you needed to provide to Basle for the foreign text?
>
> A. It would have involved the same material, yes.

WR at 462.

Other cases also involved a time pressure. In Case 600-7044/CONT, a Notice of Allowance was received which required payment of the issue fee by April 3, 1989. Ms. Giesser had to file a CIP on this case, and was under pressure to file it prior to the issue fee date. (WR at 403-404; WX S-4).

Another case, a "process" case was worked on concurrently with 600-7101 (WR at 349).

In sum, Giesser testified that between February 1988 and February 1989, she filed "close to 15" patent applications (WR at 338).

Giesser's task in relation to the Wattanasin application was made all the more difficult by the fact that prior to February 1, 1988, Mrs. Giesser had not filed any patent applications in the HMG-CoA reductase field (WR at 341, 373). In fact, prior to February 1, 1988, she had

not prepared for filing any application in the field of pharmaceuticals (WR at 346). This is understandable given that Ms. Giesser had joined Sandoz only a few months before, out of the Patent and Trademark Office (WR at 380).

She testified in the following exchange:

> Q. How would you rate the difficulty of case 600-7101, let's say on a scale of one to ten?
> A. With ten being hard?
> Q. Correct.
> A. Ten.
> Q. Why would you say that?
> A. It was a multi-step procedure. There were -- it was a long reaction. It's a very complex compound; it has ring substituents as well as side chain substituents, and the stereochemistry is important and is involved.

WR at 379.

However, Giesser's consistent testimony has been that all through this period, the "A" rating of the Wattanasin patent disclosure placed a continuing obligation on her to get the case on file.

Kassenoff lent a hand by directing Engstrom to "spool", i.e. download, the IC_{50} and ED_{50} data for compounds of PD 299/84, as well as for compactin and mevinolin, from the Sandoz database on May 23, 1984. This collection of data were sent with a covering memo to Kassenoff on or about May 24, 1988 (WR at 207, WX-Q).

Then, on August 2, 1988, Warner-Lambert issued out their U.S. Patent No. 4,761,419 (Picard et al.) directed to compounds of the count of this interference. (Warner-Lambert, an original party in interest in this interference took a default judgment and is no longer an involved

party.)

Ms. Giesser has testified while she could not have an exact recollection of when the Warner-Lambert patent issued, she was already involved in drafting the application prior to learning of it (WR at 411).

Giesser said either she or Kassenoff became aware of the Warner-Lambert patent "within a week or two after publication in the OG (WR at 427, 429).

Ms. Giesser's steadfast testimony concerning the Warner-Lambert patent has been that she was involved in preparing the application prior to finding out about it. More particularly, her testimony is that even in August of 1987, she had been at work on the Wattanasin application (WR at 433).

Ms. Giesser stood by her testimony under persistent cross-examination:

> Q. Isn't it correct, Ms. Giesser, that in fact the existence of the third-party patent application was brought to your attention before preparation of the draft of the Wattanasin application?
> A. No, that's not how I recall it.
> Q. So you recall preparing the draft and then becoming aware of the third-party case?
> A. I recall being involved in preparing the draft. It wasn't finished at the time when I learned about the third-party one.
> Q. Was the initial -- do you have a recollection was the initial draft prepared before learning of it?
> A. No, I was in the process of preparing it.

WR at 330-31.

Giesser testified that in view of her travel and other obligations as described above, just getting up the complete handwritten draft to give to her secretary, Lorraine Chesley, by November 3, 1988 would have meant that it would have been started a substantial amount of time before that date (WR at 352, 408). For one thing, "the attorneys at that time didn't have individual work stations. The secretaries had a word processor, so you would have to basically write the application in longhand and give it to the secretary to type" (WR at 408).

She further testified:

> *** I remember that when it came to light that Warner-Lambert had a patent application issued to the same subject matter -- or when their patent issued, I was in the process of writing this at that time."

WR at 411.

And further:

> Q. Did you focus more attention on the application after you learned of the Warner-Lambert patent?
> A. Not any more than I had been -- I mean, I didn't treat it any differently after I found out than before I found out.
> Q. Well, according to the best of your recollection, the best of your recollection tells you that you began drafting no later than September of 1988; is that correct?
> A. No, I believe the best of my recollection is that it would have been earlier than that.
> Q. August?
> A. I would say yes, because I recall that I was working on it when I heard of the Warner-Lambert patent.
> Q. July?
> A. I don't know exactly.
> Q. So the Warner-Lambert patent issuance really fixes in you mind the knowledge that

you were working on the application?
A. Yes.
Q. That was an important event for you in connection with the application?
A. Yes.
Q. So the best information that you have is sometime before the issuance of the Warner-Lambert application you began working?
A. Yes.

WR at 433-34.

What with Ms. Giesser's travel commitments to the managements of her various seed company clients taking up time in August, September and October of 1988 (particularly the trips to Madisdon and Boulder in October) (WR at 424-25), and the competing demands of ongoing projects, it is highly credible that the handwritten draft of an application amounting in typed form to close to 60 pages, would have to be prepared over an extended period of time prior to the November 3, 1988 date on which Ms. Giesser passed it to her secretary, Lorraine Chesley, for typing (WR at 408; WX Q):

Q. Do you recall how much of the *** draft application you had written before October of '88?

A. I would imagine it would have been relatively close to what I had given Lorraine on November 3rd, because I really wasn't in the office a whole lot or working on -- I was working on other projects for a large part of October."

WR at 438.

This is entirely consistent with her initial recollection earlier in time, in her declaration of February 19, 1993, that "no later than October 1988," she would have started working on the application (WR at 321,

449).

On December 14, 1988, Giesser sent Wattanasin the draft of his patent application, Case 600-7101.

Parallel to the Giesser activity, Engstrom on November 1, 1988, downloaded from the Sandoz computer database the structures of the compounds for the Wattanasin disclosure. This report was sent, via Wattanasin, to Kassenoff on January 4, 1988 (WR at 231; WX Y-2). Kassenoff made handwritten notations on this exhibit, including the handwritten date of January 11, 1989.

While Ms. Giesser concedes that the preparation of Case 600-7101 took somewhat longer (WR at 382), than her other patent applications, in fact, during the time between its "A"-rating and the filing of the involved Wattanasin application, Giesser regarded it as her continuing obligation to file a patent application on the Wattanasin disclosure. Certainly, she never received an instruction from research to drop the work (WR at 387, ll. 8-11). Giesser testified that, in fact, her obligation was only fulfilled "on the date I filed the application" (WR at 385-86).

On March 3, 1989, the (R60 parent of) the involved Wattanasin application was placed on file.

In regard to publication of the Wattanasin invention, it is noted that given the realities of international practice involving the filing of patent applications in "absolute novelty" countries, it was against Sandoz policy to publish prior to the filing a patent application on subject matter in which Sandoz had an interest (Kassenoff testimony, WR at 305).

It is noteworthy that soon after the involved Wattanasin application was on file, i.e. as early as March 30, 1989, and again on May 17, 1989, Dr. Wattanasin took action to publish out his results on the quinolines. Exhibit S-2 hereto contains copies of Dr. Wattanasin's publication requests and the underlying publications which disclose his quinoline HMG-CoA reductase species, which Wattanasin placed in the record in response to a discovery request by Fujikawa (WR at 130).

IX. THE REBUTTAL TESTIMONY

Dr. Terence Scallen, M.D., Ph.D., Department of Biochemistry University of New Mexico Alburquerque, New Mexico, conducted in vitro assays on the Sandoz HMG-CoA reductase inhibitors. The Kathawala article of record states that the success of the Sandoz work "is, in a large part due to our collaboration with Prof. T. Scallen, who has carried out all the in vitro studies" (WR at 494). Robert Engstrom, also acknowledge by Kathawala at WR 494, carried out the in vivo studies.

Fujikawa brought on for rebuttal testimony one Dr. Chester H. Holmlund, a purported "expert" in the field of HMG-CoA reductase inhibitors.

Dr. Holmlund has a lengthy resume of publications accumulated in a career spanning 50 years. However, it emerged on cross-examination that the closest Dr. Holmlund has ever come to an HMG-CoA reductase compound in the course of his research, was an in vitro assay of the industry standard, compactin, which was done "a number of years ago," not by himself, but by "someone in his lab"; and in fact his knowledge in the precise field of HMG-CoA reductase inhibitors appears to be limited.

Dr. Holmlund's relevant expertise was apparently restricted to the fine points of calculating ED_{50} values from raw data produced in the Engstrom in vivo assays (WX K-1). Dr. Holmlund's main purpose in appearing for Fujikawa was to criticize the computer determination of a

precise *in vivo* ED_{50} value of *0.49* for compound *64-935* based on the *in vivo* raw data of record (WX K-1). This criticism is judged *de minimus* at best, and especially since Dr. Homlund acknowledged that compound *64-935* exhibited significant activity in the low dose testing which was involved.

X. SUMMARY OF ARGUMENT

Fujikawa took no direct testimony, and is therefore restricted to its uncontested benefit date under 35 USC §119, based on its earliest Japanese priority application filed on August 20, 1987.

1. The junior party Wattanasin has established by a preponderance of the evidence conception and reduction to practice prior to the Fujikawa effective date.

a. Wattanasin has demonstrated conception and synthesis of at least one species of the count in an initial activity phase by May 17, 1985, and did not abandon, suppress or conceal his invention in the period prior to the second activity phase in early 1987, or otherwise.

b. In the second activity phase commencing in early 1987, Wattanasin synthesized at least one species of the count prior to the Fujikawa filing date, but testing was not completed until after August 20, 1987. However, testing of the compounds prior to August 20, 1987 was not necessary for reduction to practice since their practical utility was clear and certain. Hence the invention was reduced to practice on July 28, 1987 and July 29, 1987, the respective dates of completion of preparation of 64-933 and 64-934/NA.

2. If the Board finds that testing is required for the compounds made in 1987, Wattanasin has clearly demonstrated

diligence from a time prior to the Fujikawa filing date of August 20, 1987 until such testing and reductions to practice were completed by and on behalf of Wattanasin. The in vitro testing was completed by October 20, 1987 for all 1987 compounds. The in vivo testing was completed by October 29, 1987.

3. No abandonment of the invention by Wattanasin is indicated or proved because of apparent or alleged delay in filing the Wattanasin application after the 1987 reductions to practice.

4. The Wattanasin biological testing satisfies the utility requirement of the count.

a. The Wattanasin in vitro assays meet the utility requirement of the count;

b. The Wattanasin in vivo testing also satisfies the requirement of practical utility of the count.

c. The Wattanasin in vivo testing is competent to show the efficacy of the Wattanasin compounds of the count in inhibiting cholesterol biosynthesis in a patient in need of said treatment when administered in combination with a pharmaceutically acceptable carrier.

XI. ARGUMENT

Fujikawa took no direct testimony, and is therefore restricted to its uncontested benefit date under 35 USC §119, based on its earliest Japanese priority application filed on August 20, 1987.

1. **The junior party Wattanasin has established by a preponderance of the evidence conception and reduction to practice prior to the Fujikawa effective date.**

a. **Wattanasin has demonstrated conception and synthesis of at least one species of the count (in fact, three species) in an initial activity phase by May 17, 1985, and did not abandon, suppress or conceal his invention in the period prior to the second activity phase in early 1987, or otherwise.**

(i) The junior party Wattanasin respectfully submits it has established by a preponderance of the evidence that the junior party sole inventor, Sompong Wattanasin, conceived and reduced to practice the count of this interference prior to the senior party Fujikawa effective filing date of August 20, 1987.

(ii) The above description of facts, together with the testimony and exhibits A-1 and A-2 of record, establish that Sompong Wattanasin, the junior party sole inventor, conceived a genus of quinoline compounds having a

pharmacological use as HMG-CoA reductase inhibitors on or prior to November 31, 1984, and even on or prior to November 28, 1983.

(iii) The Statment of Facts and the testimony and exhibit B-1 of record, establish that in a first activity phase in 1984-1985, Dr. Wattanasin synthesized at least one species of the count, i.e. Sandoz compound 63-366, no later than December 31, 1984. The testimony of Wattanasin and exhibit B-2 demonstrate that Dr. Wattanasin also synthesized at least two additional species of the count no later than May 17, 1985. All three such compounds were tested and found active as discussed above and summarized herinafter.

(iv) The junior party Wattanasin submits that the record meets the legal requirement of corroboration. The testimony of sole inventor, Sompong Wattanasin, is well-corroborated by witness testimony as well as by independent circumstantial evidence in the Wattanasin record. The Wattanasin testimony as to conception is supported by conception documents WX A-1 and A-2; and is corroborated by the testimony of Dr. Kathawala, to whom Dr. Wattanasin disclosed this information orally and/or by providing copies of the conception documents. The Wattanasin testimony as to synthesis of compounds is corroborated by the testimony of Kathawala and Paoella, who witnessed his notebook pages. Compound numbers assigned by Wattanasin in all syntheses followed those compounds into the hands of others and the records they created.

(v) The biological testing of at least one species of the count constituted an actual reduction to practice in 1984-85 prior to the senior party benefit date.

As reviewed in the Statement of Facts section above, compound 63-366 was tested in an in vitro rat microsomal assay conducted by Terence Scallen, M.D. Ph.D., of the University of New Mexico, on or before December 13, 1984. The raw data was available no later than December 20, 1984 to Dr. Damon of Sandoz, who calculated the IC_{50} of 63-366 to be 1.58 µmolar.

Since the value of 1.58 µmolar for compound 63-366 established that the compound was active in an in vitro microsomal assay for HMG-CoA reductase inhibition, the count was first reduced to practice by Wattanasin no later than December 31, 1984.

(vi) Additional biological testing constituting further reductions to practice of species of the count took place no later than June 28, 1985, when the raw data from Dr. Scallen's testing was available to Dr. Damon, who calculated the IC_{50} for compound 63-548 to be 3.775 µmolar, and the IC_{50} for compound 63-549 to be 7.31 µmolar.

(vii) The demonstration of in vitro activity for the compounds prepared in 1984-85 was adequate to establish utility and a reduction to practice given the substantial prior history of the in vitro assay with numerous other similar type HMG-CoA reductase inhibitors and the recognized ability of the assay to equate with in vivo and clinical activity.

(viii) With respect to the evidence of record regarding conception and reduction to practice, the "rule of reason" applies in determining whether the requirement of corroboration has been met.

Rule of Reason: The Board of Patent Appeals and Interferences has consistently taken the view that the "proper approach" to evaluating evidence bearing on a reduction to practice involves "a reasoned examination, analysis and evaluation of all pertinent evidence," Halbert v. Schuurs, 220 USPQ 558, 563 (Bd. Pat. Int. 1983). That is, the Board must take into account "circumstantial evidence of an independent nature" to satisfy the corroboration rule, Donohue v. Baudry, 223 USPQ 823, 826 (Bd. Pat. Int. 1984).

A "rule of reason" standard has also been adopted by the CAFC and its predecessor court, the CCPA, Holmwood v. Sugavanam, 20 USPQ2d 1712, 1714 (Fed. Cir. 1991). See also Price v. Symsek, 26 USPQ2d 1031 (Fed. Cir. 1993); Smith v. Crivello, 215 USPQ at 450 (Fed. Cir.); Berges v. Gottstein, 618 F.2d 771, 205 USPQ 691 (CCPA 1980).

In Holmwood, the CAFC reiterated that the rule of reason requires the Board "to examine, analyze and evaluate reasonably all pertinent evidence when weighing the credibility of an inventor's story", and with full cognizance of "the realities of technical operations in modern day research laboratories", supra at 1714. On this rationale, for example, the Board may rely for corroboration even on a trained supervisor's testimony as to certain scientific methods or results performed or obtained by junior technicians working under him, Holmwood, supra at 1714.

Particularly in the context of an organized research program, a combination of corroborating testimony and independent circumstantial evidence is "more than adequate" to prove acts constituting actual reduction to practice by a preponderance of the evidence, Lacotte v. Thomas, 225 USPQ 633 (Fed. Cir. 1985).

In the instant case, Dr. Wattanasin was engaged in an organized, large-scale program of research directed to synthesizing and identifying candidate compounds for pharmacological use as HMG-CoA reductase inhibitors. Routine procedures were implemented as part of this program to effectuate the charcterization and biological testing of these compounds.

Dr. Wattanasin's synthesis work was recorded contemporaneously in a laboratory notebook maintained in the ordinary course of research. Not only were his Notebook Nos. 1149 and 1179 witnessed by scientists Kathawala and Paoella, but the whole accumulated weight of the circumstantial evidence surrounding his work also corroborates that the compounds were actually synthesized by the dates that he alleges. This associated evidence includes the logging in of the compounds in Dr. Barcza's analytical laboratory; the ensuing physical characterization which generated spectra in essence constituting distinctive fingerprints for each chemical compound; the routing of the compounds to the Sandoz Drug Room and their documented shipment out to Dr. Scallen for in vitro testing; and the return receipt of raw data from the testing to Dr. Damon at Sandoz, who calculated IC_{50} values for the compounds and informed the inventor, Sompong Wattanasin, of the results. Each step in the foregoing "information circuit" is carefully documented and testified to in the Wattanasin record.

On this basis, it is submitted that the Wattanasin record contains sufficient direct and circumstantial evidence of an independent nature within the meaning of Berges v. Gottstein, 618 F.2d 771, 205 USPQ 691 (CCPA 1980) to satisfy the corroboration rule.

(ix) Accordingly, since reduction to practice of a single species within the count is sufficient as a reduction to practice of the count, Mikus v. Wachtel, 183 USPQ 752 (CCPA 1974), it is respectfully submitted Wattanasin initially reduced to practice the count of this interference prior to the senior party effective date.

b. In the second activity phase commencing in early 1987, Wattanasin synthesized at least one species of the count (in fact, at least two, i.e. 64-933 and 64-934/NA) prior to the Fujikawa filing date, but testing was not completed until after August 20, 1987. However, testing of these compounds prior to August 20, 1987 was not necessary for reduction to practice since their utility was clear and certain. Hence the invention was reduced to practice on July 28, 1987 and July 29, 1987, the respective dates of completion of preparation of 64-933 and 64-934/NA.

(i) Abandonment, supression or concealment did not occur between July 1985 and January 1987.

Dr. Kathawala testified that prior to and contemporaneously as the Wattanasin invention in the quinoline series, he and/or other scientists in his department and under his direction had synthesized other HMG-CoA reductase inhibitors which were "chemically analogous" to the quinolines, i.e. comprising analogs of mevalonolactone, except that the quinoline moiety was replaced by another moiety.

Dr. Wattanasin also testified that in the period from mid-July to March of 1987 alone, he synthesized some 60 other HMG-CoA reductase inhibitor compounds, but none

within the scope of the count.

The activity of Wattanasin in synthesizing other heterocyclics within the generic Sandoz concept of a heterocyclic analog of mevalonolactone should not result in a conclusion of abandonment without clear confirming evidence of such intention. No such evidence was produced or existed. Rather the circumstances in this case do not show abandonment because of a clear intention to complete additional synthesis within the count, and a manpower shortage in view of other general HMG-CoA reductase project obligations which interrupted Wattanasin's efforts. Confirmation thereof is provided by the evidence of record that additional synthesis work in the count commenced promptly after the new hire (Patel) was obtained. In any case, resumed work for the count prior to the senior party entry into the field should be credited to Wattanasin, Paulik v. Rizkalla, 760 F.2d 1270, 226 USPQ 224 (Fed. Cir. 1985).

(ii) The record establishes that by March of 1987, Patel was already involved in the synthesis of the following compounds within the count: 64-933 (ethyl ester) and its sodium salt, 64-934/NA; and 64-935 (ethyl ester) and its sodium salt, 64-936/NA.

(iii) Patel's work prior to the senior party entry into the field completed the synthesis of compounds 64-933 and 64-934/NA, both within the count. The synthesis by Patel and characterization of the two additional compounds 64-935 and 64-936/NA, within the count, continued after the senior party effective date, but with clear diligence to these reductions of the count to practice from a time prior to the senior party's date. No corroboration is even needed for Patel's testimony, De Solms v. Schoenwald, 15

USPQ2d 1507, 1509 (BPAI 1990); however, the associated IR and NMR spectra performed by Dr. Barcza's Physical Chemistry Department; and the testing performed by Dr. Scallen and Robert Engstrom, serve to substantiate the synthesis activities of Patel, Lacotte v. Thomas, supra.

(iv) Testing of all four "second activity phase" compounds took place after the senior party date but is submitted to have been unnecessary in this case to complete a reduction to practice.

Whether a composition must be tested in order to establish a reduction to practice must be decided on a case-by-case basis, Blicke v. Treves, 44 CCPA 753, 241 F.2d 718, 112 USPQ 472 (1957).

The CAFC has indicated in Cross v. Iizuka, 753, F.2d 1040, 224 USPQ2d 739, 746 (Fed. Cir. 1985), that a particular pharmacological activity identified with prior art compounds may have probative value in relation to whether the compound of the count possesses the same pharmacological activity where there is a structural similarity between the prior art compounds and the compound of the count, supra at 746. (The Court went on to state that "[v]ariation in potency, moreover, is a matter of degree of activity*** but is still indicative of activity. There is no requirement that the compounds have the same degree of activity." (supra at fn. 17)).

Prior to August 20, 1987, Wattanasin had every reason to know with certainty that the compounds synthesized in 1987 would be useful and would be active not only in vitro but also in vivo. (See testimony of Wattanasin, WR at 45-47; 114-116; testimony of Kathawala WR at 140-41; testimony of Scallen, WR at 193-95; testimony of Damon, WR

at 201).

Prior to August 20, 1987, Wattanasin and the Sandoz Project groups had had substantial background and experience in totally analogous heterocyclic HMG-CoA reductase compounds synthesize at Sandoz, one of them being fluvastatin (XU 63-320), an indole analog of mevalonlactone bearing a 4-fluorophenyl and an isopropyl substituent, similar to Wattanasin compound 63-935. Fluvastatin had been found to be highly active relative to the industry standard, compactin, as stated on the record by Kathawala.

Moreover, Wattanasin himself had already prepared and found clearly active in 1984-1985 three other quinoline compounds within the scope of the count. In fact, as concerns the two second activity phase compounds whose preparation was fully completed prior to August 20, 1987, the relationship to the prior most active 1984-85 compound of the count was a simple homologous relationship, i.e. unsubstituted phenyl vs. dimethylphenyl. Hence, Wattanasin had every right to know, as he testified, that all four second phase compounds would be active (the other two second phase compounds whose synthesis was completed just after the Fujikawa filing date had a monofluorophenyl vs. dimethylphenyl relationship to the most active compound of the count that was tested in the first activity phase in 1984-85. In short, actual testing of none of the second phase compounds would have been necessary to recognize their utility.

C. If the Board finds that testing is required for the compounds made in 1987, Wattanasin has clearly demonstrated diligence from a time prior to the Fujikawa filing date of August 20, 1987 until such testing and reductions to

practice were completed by and on behalf of Wattanasin.

(i) If testing of at least one of the four second activity phase compounds will be required for reduction to practice, Wattanasin submits that such testing concluded following continuously diligent activity from a time prior to the senior party's date.

(ii) The record shows clearly continuous activity of the junior party in the field leading up to the senior party effective filing date of August 20, 1987 (see Statement of Facts). As shown supra, these activities were virtually day-to-day, with only a small and excusable waiting period while the compounds awaited the next scheduled delivery to Dr. Scallen. It is noted that Wattanasin wanted all four second activity phase compounds tested by Dr. Scallen at the same time, a legitimate scientific procedure. Hence, testing of the early synthesized compounds awaited completion of the second pair, and all four were then promptly sent to Dr. Scallen (and promptly tested by Dr. Scallen). The in vitro testing was completed by October 20, 1987 and the in vivo testing was completed by October 29, 1987.

3. No abandonment of the invention by Wattanasin is indicated or proved because of apparent or alleged delay in filing the Wattanasin application after the 1987 reductions to practice.

(i) The period of fifteen months between the last activity for the count, i.e. on December 9, 1987 (when Engstrom entered the ED_{50} data for 64-933, 64-935 and 64-936/NA into the computer database), and the filing of

the involved Wattanasin application on March 3, 1989, is not such as would be per se reasonable, or even raise an inference of abandonment, supression or conceal- ment.

(ii) Secondly, the documented activities on the part of the Sandoz Patent Committee in rating the Wattanasin disclosure; by Wattanasin in providing information to the Patent Department over the timer period in question; and by patent attorneys Giesser and Kassenoff, in developing a patent application over this period, certainly disprove any issue of abandonment.

(iii) The "A" rating of the Wattanasin patent disclosure in January 1988 imposed a continuating obligation to file a patent application on the Wattanasin invention. This obligation was not discharged until the application was filed.

(iv) Far from being spurred into activity by the Warner-Lambert publication, Ms. Giesser's testimony in her declaration and under cross-examination and the other evidence of record suggests that she was at work on the draft before Warner-Lambert entered the field. The fact is, Kassenoff was obtaining information for case by late February and into March of 1988; Engstrom was also involved in providing Wattanasin and Kassenoff biological data for compounds of the count on May 23, 1988, roughly two months prior to the Warner-Lambert date. The evidence of record suggests that there was activity toward filing an application throughout the relevant period. Additionally, the fact that Ms. Giesser was able to provide to her secretary, by November 3, 1988, a substanti- ally complete hand-written draft of the application, viewed against the background of her extensive travel and other activities in September through October of 1989, strongly suggests that

she would have been working even in August or earlier to get the application on file.

(v) The "A"-rating of the Wattanasin patent disclosure as of January 27, 1988 stood as a command imperative to file a patent application even before Warner-Lambert ever appeared on the scene; and there could heardly be an inference of abandonment between that date and the Warner-Lambert publication date of August 2, 1988, in view of the Wattanasin activities of record during this time period. The activities of record confirm that Ms. Giesser acted with reasonable diligence in filing the Wattanasin application under the circumstances of her job duties in 1988-89.

4. The Wattanasin biological testing satisfies the utility requirement of the count.

(i) The in vitro testing carried out by Dr. Scallen on compounds 63-366, 63-548, 63-549, 64-933, 64-934/NA, 64-935 and 64-936/NA is believed to satisfy the requirement of practice utility.

(ii) The Wattanasin record makes clear that Prof. Terence Scallen was involved in a large scale testing program of synthesized Sandoz compounds to identify biological activity against a known enzyme in an in vitro rat microsomal assay. The testing procedures of Dr. Scallen included the administration of standard tests in a highly organized program designed by Dr. Scallen to specifically test chemical compounds for HMG-CoA reductase inhibition.

(iii) A standard in vitro test may be sufficient to

demonstrate pharmacological activity of a compound, i.e., "practical utility", provided there is "a resonable correlation between the two". Nelson v. Bowler, 262 F.2d 853, 206 USPQ 881 (CCPA 1980); Bigham v. Godtfredsen, 222 USPQ 632 (Pat. Bd. Int. 1984); Cross v. Iiuka, 224 USPQ 739 (Fed. Cir. 1985).

(iv) The IC_{50} values for the Wattanasin compounds were found to be as follows:

COMPOUND	IC_{50} (μM)
63-366	1.58
63-548	3.775
63-549	7.3100
64-633	2.3700
64-934/NA	2.6100
64-935	0.4130
64-936/NA	0.5300

Background assays of compactin and fluvastatin are also evident on the Scallen data of record, WX E-1 to E-5.

(v) It is clear from Dr. Scallen's testimony that these tests established at the time in question that the test compounds had HMG-CoA reductase activity, particularly since the activity of the test compound was compared with that of compactin and the Sandoz developmental compound, fluvastatin.

(vi) It is submitted that the program of in vitro reductase inhibition testing carried out by Dr. Scallen, and the activity data generated for the Wattanasin compounds of the count, in the context of side-by-side controls comprising known industry standards such as compactin and fluvastatin (see Scallen laboratory reports

at WX E-1 to E-5), provides the basis for a conclusion of phamacological utility as to the Wattanasin compounds of the count, i.e. both the earlier synthesized compounds 63-366, 63-548 and 63-549, and the other four compounds of the count: 64-933, 64-933/NA; 64-935 and 64-936/NA.

(vii) The above is borne out by the actual testing results of record. Compounds 64-935 and 64-936/NA, which are structurally cloest of the Wattanasin compounds to fluvastatin, registered most active on the Scallen assays of record.

(viii) The decisional authority supports the competency of in vitro testing to satisfy the utility requirement in circumstances such as this. See Cross, supra at 747.

c. **The in vivo testing satisfies the requirement of practical utility of the count, and is also competent to show the efficacy of the Wattanasin compounds of the count in inhibiting cholesterol biosynthesis in a patient in need of said treatment when administered in combination with a pharmaceutically acceptable carrier.**

(i) The Engstrom in vivo testing in rats is submitted to be competent to confirm practical utility. Exhibit K-1 corroborates the extensiveness of Engstrom's program of testing of Sandoz HMG-CoA compounds for HMG-CoA reductase, and hence, cholesterol inhibition, activity.

(ii) Like Scallen's program, Engstrom's was based on a routine protocol employed in connection with large numbers of compounds, against a background of comparative results for known industry standards.

(iii) ED_{50}'s of the tested Wattanasin compounds are as follows:

COMPOUND	ED_{50} (mg/kg)
64-933	>1 or 2.40
64-935	0.49
64-936	>1

WX K-1, Q at 418.

Compound 64-935, in particular, had a demonstrable in vivo activity in the assays of record.

The results of both IC50 and ED50 testing suggest a reliable correlation between in vitro and in vivo activity for the tested Wattanasin compounds, particularly in the case of compound 63-935.

The pharmacological activity of a compound of the Wattanasin invention having a known IC_{50} or ED_{50} could be predicted with reasonable assurance based on the demonstrated activities of compactin or fluvastatin in inhibiting cholesterol.

XI. CONCLUSION

Accordingly, it is submitted that Wattanasin is entitled to prevail on the sole count of this interference.

XII. APPENDIX

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

WATTANASIN

v.

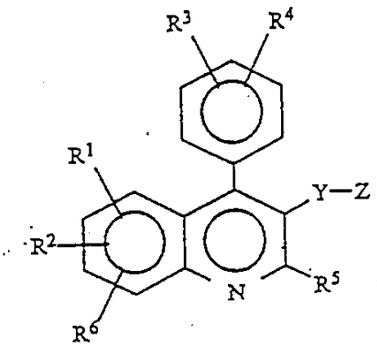
FUJIKAWA et al.

Interference No. 102,648
Examiner-in-Chief: M. Sofocleous

COUNT

[Count 3]

A method of inhibiting cholesterol biosynthesis in a patient in need of said treatment comprising administering a cholesterol synthesis inhibiting amount of a compound of the formula:



wherein R^1, R^2, R^3, R^4 and R^6 are independently
hydrogen,
C_{1-6} alkyl,
C_{1-6} cycloalkyl,

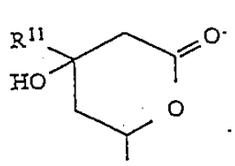
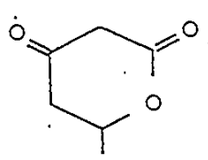
C_{1-3} alkoxy,
n-butoxy,
i-butoxy,
sec-butoxy,
R^7R^8N- (wherein R^7 and R^8 are independently hydrogen or C_{1-3} alkyl),
trifluoromethyl,
trifluoromethoxy,
difluoromethoxy,
fluoro,
chloro,
bromo,
phenyl,
phenoxy,
benzyloxy,
hydroxy,
hydroxymethyl,
$-O(CH_2)_\alpha OR^{19}$ (wherein R^{19} is hydrogen or C_{1-3}alkyl and α is 1, 2 or 3),
or when located at the ortho position to each other, R^3 and R^4 together optionally form $-CH=CH-CH=CH-$;

R^5 is hydrogen,
C_{1-6} alkyl,
C_{2-3} alkenyl,
C_{3-6} cycloalkyl,
phenyl substituted by R^9 (wherein R^9 is hydrogen, C_{1-4}alkyl, C_{1-3}alkoxy, fluoro, chloro, bromo or trifluoromethyl),
phenyl-$(CH_2)_m$- (wherein m is 1, 2 or 3), $-(CH_2)_nCH(CH_3)$-phenyl or phenyl-$(CH_2)_nCH(CH_3)$- (wherein n is 0, 1 or 2).

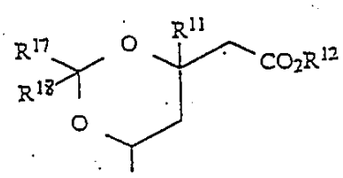
Y is

$-CH_2-$,
$-CH_2CH_2-$,
$-CH=CH-$,
$-CH_2-CH=CH-$, or
$-CH=CH-CH_2-$;

Z is

or



or $-Q-CH_2WCH_2-CO_2R^{12}$ (where R^{12} is hydrogen or R^{14});

Q is $-CH(OH)-$.
$-C(O)-$, or
$-C(OR^{13})_2-$;

W is $-C(R^{11})(OH)-$ (where R^{11} is hydrogen or C_{1-3} alkyl),
$-C(O)-$, or
$-C(OR^{13})_2-$;

the two R^{13} are independently primary or secondary C_{1-6} alkyl; or two R^{13} together form $-(CH_2)_2-$ or $-(CH_2)_3-$;

R^{14} is physiologically hydrolyzable alkyl or M (wherein M is NH_4, sodium, potassium, 1/2 calcium or a hydrate of lower alkylamine, di-lower alkylamine or tri-lower alkylamine); and

R^{17} and R^{18} are independently hydrogen or C_{1-3} alkyl;

as defined in combination with pharmaceutically acceptable carrier.

The claims of the party Wattanasin which correspond to count 3 are claims 8 and 9.

#105

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

FYI

WATTANASIN

JUL 19 1993

v. Interference No. 102,648

RECEIVED IN BOX INTERFERENCE

FUJIKAWA et al. Examiner-in-Chief: M. Sofocleous

TRANSMITTAL LETTER FOR WATTANASIN OPENING BRIEF

Dear Sir:

Enclosed please find four (4) copies of the opening brief of the junior party Wattanasin for the above-identified interference.

Also being filed concurrently herewith is a paper entitled "Junior Party Watttanasin Proposed Findings of Fact."

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231, on July 16, 1993
(Date of Deposit)
Diane E. Furman
Name of applicant, assignee, or Registered Representative
Diane Furman
Signature
July 16, 1993
Date of Signature

Respectfully submitted,

Diane Furman

Diane E. Furman
Attorney for the Party Wattanasin
Registration No. 31,104
201-503-7332

SANDOZ CORPORATION
59 Route 10
E. Hanover, NJ 07936

July 16, 1993

Enclosures: Wattanasin Opening Brief for Final Hearing
Junior Party Wattanasin Proposed Findings of Fact

DEF:rmf

Int. No. 102,648

CERTIFICATE OF SERVICE

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TRANSMITTAL LETTER FOR WATTANASIN OPENING BRIEF

and the Wattanasin OPENING BRIEF enclosed therewith were served on counsel for the party Fujikawa et al., this 16th day of July 1993, by postage prepaid first-class mail addressed to the following:

Oblon, Spivak, McClelland, Maier & Neustadt P.C.
Attn.: Steven B. Kelber, Esq.
1755 South Jefferson Davis Highway
Crystal Square 5, Ste. 400
Arlington, VA 22202

Diane Furman
Diane E. Furman

#106

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FYI

WATTANASIN

v. Interference No. 102,648

FUJIKAWA et al. Examiner-in-Chief: M. Sofocleous

JUNIOR PARTY WATTANASIN
PROPOSED FINDINGS OF FACT

Fujikawa took no direct testimony, and is therefore restricted to its uncontested benefit date under 35 USC §119, based on its earliest Japanese priority application filed on August 20, 1987.

1. The junior party Wattanasin has established by a preponderance of the evidence conception and reduction to practice prior to the Fujikawa effective date.

a. Wattanasin has demonstrated conception and synthesis of at least one species of the count in an initial activity phase by May 17, 1985, and did not abandon, suppress or conceal his invention in the period prior to the second activity phase in early 1987, or otherwise.

b. In the second activity phase commencing in early 1987, Wattanasin synthesized at least one species of the count prior to the Fujikawa filing date, but testing was not completed until after August 20, 1987. However, testing of the compounds prior to August 20, 1987 was not necessary for reduction to practice since their practical utility was clear and certain. Hence the invention was reduced to practice on July 28, 1987 and July 29, 1987, the respective dates of completion of preparation of 64-933 and 64-934/NA.

2. If the Board finds that testing is required for the compounds made in 1987, Wattanasin has clearly demonstrated diligence from a time prior to the Fujikawa filing date of August 20, 1987 until such testing and reductions to practice were completed by and on behalf of Wattanasin. The in vitro testing was completed by October 20, 1987 for all 1987 compounds. The in vivo testing was completed by October 29, 1987.

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Wattanasin
Int. No. 102,648
Prop. Findings Fact

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#107

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

WATTANASIN	:	INTERFERENCE NO.: 102,648
V.	:	EXAMINER-IN-CHIEF MICHAEL SOFOCLEOUS
FUJIKAWA ET AL	:	

BRIEF AT FINAL HEARING OF THE SENIOR PARTY FUJIKAWA ET AL

Steven B. Kelber
Registration No. 30,073
Attorney for the Party
Fujikawa et al

OBLON, SPIVAK, McCLELLAND, MAIER & NEUSTADT, P.C.
1755 Jefferson Davis Highway
Fourth Floor
Arlington, Virginia
(703) 413-3000

TABLE OF CONTENTS:

TABLE OF AUTHORITIES

Cases:

Rules:

Unpublished Decisions:

I. STATEMENT OF THE ISSUES PRESENTED FOR DECISION

Fujikawa et al (Fujikawa) is dissatisfied with the Statement of Issues presented for decision in the Brief of the Junior Party, Wattanasin Brief, pages 4-5 (hereinafter Wattanasin's Brief shall be referred to as WB, Wattanasin's Record referred to as WR, and Wattanasin's Exhibits referred to as WX, with page or exhibit designations following. Similarly, the Fujikawa Record shall be referred to as FR, with the page designation following). The Wattanasin Statement of Issues omits issues preserved for Final Hearing, and does not clearly delineate others. Accordingly, pursuant to 37 CFR §1.656(c)(1), Fujikawa identifies the following issues for decision.

1. Was the Decision of the EIC denying Fujikawa's Motion to add additional Counts to the Interference in error?

2. Has Wattanasin shouldered its burden of proof in demonstrating entitlement to priority?

   A. The burden of proof is clear and convincing evidence.

   B. Wattanasin has not demonstrated an actual reduction to practice of the Count prior to its constructive reduction to practice,

the filing of U.S. Application Serial No. 07/318,773, filed March 3, 1989.

C. Wattanasin ceased activity with respect to the invention after June 30, 1985, and did not resume activity until March, 1987.

D. Wattanasin did not proceed with diligence to its U.S. patent filing in 1989.

E. In the event the Record does reflect an actual reduction to practice on the part of Wattanasin, Wattanasin suppressed or concealed the invention from the date of invention to March 3, 1989.

3. The testimony of Melvyn Kassenoff should be discredited.

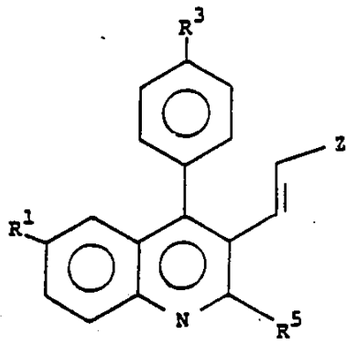
II. RELEVANT FACTS

The Wattanasin recitation of facts relevant to the Interference, WB 21-59 includes assertions not supported by the Record[1]. Additionally, the Wattanasin Statement of Facts omits important, relevant facts discussed hereinbelow, and any statement of the events in the Interference below necessary for consideration, which are presented after the Statement of the Facts drawn from the Record. The facts relevant to the Interference are these.

1. Methods of administration within the Count of the Interference wherein the formula is limited such that:

[1] As an example of unsupported assertion, see page 29, wherein Counsel for Wattanasin attempts to interpret what Wattanasin intended by "the whole set of this quinoline case", see in particular, the paragraph bridging pages 29 and 30. There is no evidence of record that this is what Wattanasin meant, and arguments of the attorney do not rise to the level of facts.

A compound of the formula:



wherein R^1 = H

R^3 = F

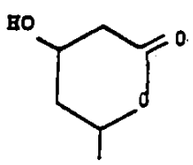
R^5 = cyclopropyl (c-Pr) and z is selected from the group consisting of:

$-CH(OH)-CH_2-CH(OH)-CH_2-COOH$

$-CH(OH)-CH_2-CH(OH)-CH_2-COONa$

$-CH(OH)-CH_2-CH(OH)-CH_2-COO1/2Ca$

$-CH(OH)-CH_2-CH(OH)-CH_2-COOR$, wherein R is C_{1-3}, alkyl and



lactone.

result in significant and unpredicted improvement in inhibition of cholesterol biosynthesis. FR 3. That superior activity could not have been predicted on the basis of chemical structure alone, by those of ordinary skill in the art. FR 4. Repeated discrete comparisons demonstrate persuasively, in side-by-side testing, superiority for the narrowed scope within the Count. Additional proof of the uniformity of this unobvious superiority appears at FR 11 and 13.

2. The application of Wattanasin involved herein specifically describes cyclopropyl as one of the identities for the substituent corresponding to R^5 in the formula of the Count of the Interference. Further, one of ordinary skill in the art would have recognized it as specifically identifying cyclopropyl as a possible substituent at that position. FR 116 -117. On questioning from his own Counsel, the inventor Wattanasin testified that

cyclopropyl is similar, structurally, to isopropyl. FR 138.

3. Subsequent to March, 1985, Wattanasin did not do any work on methods within the Count of the Interference, including the preparation of compounds therefor, due to the assignment of projects other than those involving the compounds embraced by the Count of the Interference which other projects were given a higher priority. WR 165-166.

4. Wattanasin was completely uncertain as to whether or not the compounds embraced by the Count of this Interference would prove to be active, WX A-2 at 121, and could not predict that activity with any certainty. FR 151-152.

5. The in vitro assays reflected in the Scallen Declaration, WR at 190, do not provide certainty that the compounds tested would be

useful in the method of the Count of this Interference. They may be indicative of such activity, but they may not be. FR 186.

6. The in vivo data reflected in the Engstrom Declaration does not demonstrate the method of administration of the Count of the Interference to be effective in inhibiting HMG Co-A activity or the biosynthesis of cholesterol. FR 194-195. The in vivo tests reflected in the Engstrom Declaration demonstrate the unreliability of the in vitro tests of the Scallen Declaration. FR 196.

7. The Wattanasin disclosure leading to the filing of the Wattanasin application was originally evaluated on April 29, 1987. The real party-in-interest for Wattanasin determined that a patent application should not be prepared on the disclosure, assigning it a rating of B, WR 214, and continuing to assign the disclosure a rating other than A,

rating preparation of a patent application, through the entirety of 1987, not rating the disclosure as appropriate for a patent application until January 27, 1988. WB 45. During that period, and until a patent application was filed, no publication of the invention addressed could be made. WB 56, WR 305.

8. The Sandoz attorney responsible for preparation of the Wattanasin application cannot fix a date in time with any surety earlier than October, 1988 as the date on which she began working on the application draft. FR 375. The Picard patent, which prompted the filing of the Wattanasin application, issued August 2, 1988.

9. Sandoz elected to file other cases, including the Sandoz case identified as 7025-CIP/CIP prior to the Wattanasin parent application, even though it was docketed after the

Wattanasin patent application, because the subject matter of the earlier-filed case was considered important. FR 390.

A. HISTORY OF THE CASE

This Interference was declared March 11, 1992 between U.S. Application Serial No. 07/498,301, the involved application of Wattanasin as Junior Party, U.S. Patent 4,761,419, Picard et al, as Junior Party, and U.S. Application Serial No. 07/233,752, the involved application of Fujikawa et al. The Wattanasin application was accorded benefit of its parent filing date, March 3, 1989, and the Fujikawa application was accorded benefit of its foreign priority documents, of August 20, 1987. The Interference was declared with two Counts, one directed to compounds per se, and the other directed to methods of administration. Ultimately, the compound Count was deleted from this Interference, leaving only a claim directed to methods of administration. Clearly, this Interference involves a United States Patent, and just as clearly, the victor in this Interference will be entitled to rights not dissimilar from those originally conveyed in U.S. Patent 4,761,419.

The patentee did not contest this Interference. In preliminary Motions, Fujikawa moved to add Counts 3 and 4 to the Interference, directed to a compound and method of administrating the same within the scope of the original Count, specifying particular substituents. Fujikawa also moved for benefit of an additional foreign priority document not previously granted, dated August 19, 1988. Fujikawa submitted evidence in support of its Motion to add Counts to the Interference, in the form of two Declarations.

Wattanasin moved pursuant to Rule 633(c)(1) and Rule 635 to substitute a Count and add a Patent. The Fujikawa Motion to add Counts, and the Wattanasin Motion to substitute Counts and add a Patent were opposed.

The parties agreed to designate Claim 1 of U.S. Patent 5,011,930 as corresponding to the compound Count of the Interference.

In the Decision on Motions, Paper No. 40, the EIC sua sponte redeclared the Interference with the sole current Count, the method of administration, declaring a second Interference, ultimately designated Interference 102,975, with the compound Count. U.S. Patent 5,011,930, Claim 1, is involved in Interference 102,975.

All Motions were denied or dismissed as moot. Fujikawa

requested reconsideration of the decision dismissing its Motion for Benefit, and the Motion to add Counts, which was denied on the grounds that the Wattanasin application lacked disclosure of the cyclopropyl moiety recited in the claims proposed by Fujikawa for Wattanasin as corresponding to the Count of the Interference. The Request for Reconsideration was granted as to the Motion for Benefit, and denied as to the Motion to add Counts.

Wattanasin presented priority testimony by Affidavit. Fujikawa requested cross-examination of declarant Wattanasin and filed a Notice of Intent to Argue Abandonment, Suppression or Concealment. In response to this Notice, Wattanasin was granted an additional testimony period in which to present evidence relevant to abandonment, suppression or concealment. Paper No. 72 Interference 102,648.

Wattanasin presented additional testimony tending to go to the issue of abandonment, suppression or concealment, together with a Declaration attempting to correct an earlier Declaration (Engstrom Supplemental Declaration). Fujikawa took cross-examination of declarants Wattanasin, Kassenoff, Rothwell and Giesser.

Fujikawa submitted rebuttal testimony on the issue of actual reduction to practice through the deposition of Chester A. Holmlund, offered by Fujikawa as an expert. Fujikawa submitted

evidence pursuant to Rule 682 and 672. No cross-examination was taken, nor objection filed.

III. ARGUMENT

SUMMARY OF THE ARGUMENT

The Fujikawa testimony demonstrates conclusively that the subject matter of the proposed counts of the Fujikawa Motion to Add Counts 3 and 4[2/] is unobviously superior to, in terms of HMG-CoA reductase inhibition activity, to compounds closely related thereto, within the scope of the Interference, but outside the proposed claims, i.e., wherein the substituent at the 2 position of the compound is isopropyl, as compared with the cyclopropyl of the proposed counts. Accordingly, this subject matter is patentably distinct from the subject matter of the Count of this Interference, and a separate Count directed thereto should be declared.

The Wattanasin application unquestionably has a written description of the subject matter of the proposed count. The sole point of dispute is with regard to the description of the

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[2/] Because of the redeclaration of interference, Count 4 falls within Count 3 of the interference, and proposed Count 3 falls within Count 1 of Interference 102,975. The Counts will be referred to generically, but where differences exist with regard to the law or the evidence, will be discussed in separate briefs.

substituent at the 2 position. The Wattanasin application describes the substituent as C3-7 cycloalkyl. Wattanasin, as well as the attorney preparing the application stated unequivocally that this meant cyclopropyl, and that those of ordinary skill in the art would recognize it as including and specifically describing cyclopropyl. The class of compounds embraced by the substituents is limited to five compounds, and the selection of cyclopropyl out of those five, for the purposes of written description, is not beyond the skill of the artisan in the field, without the exercise of inventive faculty. Clearly, the cyclopropyl substituent at the 2 position was within the invention described at the time of filing the Wattanasin application, as well as its parent application. Thus, the Wattanasin application supports Claims 11 and 12 suggested for it in the Fujikawa Motion as corresponding to proposed counts 3 and 4, and the Decision of the EIC denying that Motion should be reversed. As Wattanasin has not provided any evidence of conception, actual reduction to practice or diligence with respect to this subject matter before sometime in October of 1988, and no reduction to practice of the subject matter until the constructive reduction to practice of March 3, 1989, Fujikawa is necessarily entitled to priority as to this narrow Count.

The Wattanasin Record is devoid of evidence of an actual

reduction to practice of any of the subject matter within the Count of the Interference. The Count calls for administering a compound of the Count to a patient in need of cholesterol biosynthesis inhibition in a cholesterol biosynthesis inhibiting amount. The compound is to be combined with a pharmaceutically acceptable carrier. To establish an actual reduction to practice of this invention, evidence establishing that the method will work for its intended purpose, not the possibility that it will work for its intended purpose is required. No such evidence has been supplied by Wattanasin. Further, Wattanasin has supplied absolutely no evidence of any investigation or recognition of suitable pharmaceutically acceptable carriers prior to its constructive reduction to practice of March 3, 1989, nor has Wattanasin supplied any evidence of establishing cholesterol biosynthesis inhibiting amounts prior to its constructive reduction to practice of March 3, 1989. It should be noted that the applications of both parties in the Interference make it clear that the sole type of patient to be treated according to this method is a human. There is no apparent value or utility in inhibiting cholesterol biosynthesis in animals. The in vitro data relied on by Wattanasin is inadequate to prove an actual reduction to practice, and the in vivo data does not demonstrate activity of any type, much less a pharmaceutically or

cholesterol biosynthesis inhibiting amount.

To the extent that Wattanasin demonstrated an actual reduction to practice in its "original phase" of investigations concluding at the end of June, 1985, in the 45-month period between that reduction to practice and the filing of an application, Wattanasin both ceased activity with respect to the invention of the Count of this Interference until no earlier than March, 1987, and throughout the 45-month period suppressed and concealed the invention, filing only after it became aware of an issued patent directed to identical subject matter.

To the extent Wattanasin urges that it renewed its activity with respect to the invention as of March, 1987, it did not proceed with diligence to a reduction to practice, or to the filing of its application. Moreover, if in fact the October, 1987 tests conducted by Dr. Engstrom are indicative of an actual reduction to practice, Wattanasin suppressed or concealed the invention for more than 17 months prior to filing its application. Pursuant to the provisions of 35 USC §102(g), an award of priority adverse to Wattanasin must be issued, in light of its abandonment, suppression or concealment of any invention conceived and reduced to practice. The paucity of evidence presented by Wattanasin in this regard, not withstanding the volume of pages submitted, is further highlighted

by the fact that the burden Wattanasin must shoulder is one of clear and convincing evidence, not a mere preponderance of the evidence.

Wattanasin relies heavily on the testimony of Kassenoff to preclude an inference of suppression or concealment in the period of April, 1987 - October, 1988. This testimony can not be taken at face value, and should be discredited. Kassenoff appeared both as a fact witness in this case, and as an attorney. The same is prohibited by the provisions of 37 CFR §10.62 and §10.63, in particular, §10.63(a). The cases are uniform that violation of this prescription, unless the testimony is directed to the sole issue of what the attorney did in the intervening time period, is to be heavily discounted.

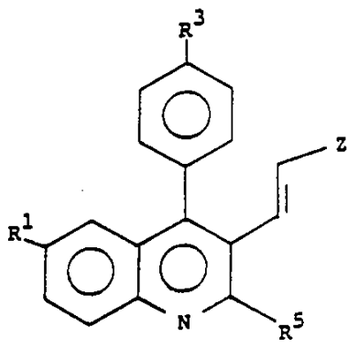
1. THE EXAMINER'S DECISION DENYING FUJIKAWA'S MOTION TO ADD COUNTS 3 AND 4 TO THIS INTERFERENCE WAS MANIFEST ERROR

Fujikawa's Motion to add proposed Counts 3 and 4 to this Interference is based on the proposition that the subject matter of this Interference, and that of Interference 102,975, when the compound of the formula recited is limited such that R^3 is F, R^5 is cyclopropyl, R^1, R^2, R^4 and R^6 are hydrogen, and Z is selected as indicated below, the resulting compounds show unexpected and

qualitatively different and superior activity, in the inhibition of cholesterol biosynthesis, and offer a superior means of inhibiting cholesterol biosynthesis in a patient in need of the same. For the convenience of the Board, Counts 3 and 4 are reproduced herein below.

Count 3

A compound of the formula:



wherein R^1 = H

R^3 = F

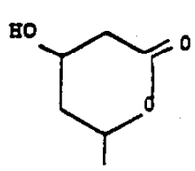
R^5 = cyclopropyl (c-Pr) and Z is selected from the group consisting of

-CH(OHO-CH_2-CH(OH)-CH_2-COOH

-CH(OHO-CH_2-CH(OH)-CH_2-COONa

-CH(OHO-CH_2-CH(OH)-CH_2C001/2Ca

-CH(OHO-CH_2-CH(OH)-CH_2.C00R, wherein R is C_{1-3}, alkyl and



lactone.

Count 4

A method of inhibiting cholesterol biosynthesis in a patient in need of said treatment comprising administering thereto a cholesterol synthesis inhibiting amount of a compound as defined by Count 3 in combination with a pharmaceutically acceptable carrier.

It is immediately clear the subgenus embraced by proposed counts 3 and 4 includes nine possible compounds (substituent R can be methyl, ethyl, n-propyl or isopropyl) each of which has been demonstrated to yield unpredictably, unobviously superior activity. Fujikawa's testimony in support of its position consists of the Declaration of Masaki Kitahara and Kitahara's Supplemental Declaration, FR 1-13. At FR 4, Kitahara states absolutely and without qualification that the superior activity of the compounds reflecting the cyclopropyl substituent at the 2 position discussed at FR 3-4 could not have been predicted by those of ordinary skill in the art, corresponding to a graduate chemist with several years of experience in the field. This is sine qua non of nonobviousness. Note that the subject matter of the proposed counts was compared not only as to the preferred isopropyl substituent at the 2 position of the Wattanasin application, but

the N-propyl substituent as well. This testing was extended in the activity reflected in the Supplemental Declaration, FR 10-13, leading Kitahara to conclude that

> all compounds within the scope of the formula[3/] set forth in paragraph 3 of my Declaration dated June 1, 1992, uniformly demonstrate unobvious superiority when R^5 is cyclopropyl, as opposed to closely related isomeric structures.

FR 11. Indeed, the Kitahara Declarations make it clear that the closest activity values within the current Count of the Interference to those of the proposed Counts is two and a half times inferior, that is, the IC_{50} value for the compounds of the current Count most closely related to those of the proposed Count are more than twice as high as those of the proposed Count. When the substituent at the 2 position is isopropyl, the IC_{50} values are about 2.5 times greater than that for cyclopropyl, and the IC_{50} value for N-propyl is 22 times greater than that of cyclopropyl (a lower IC_{50} value indicates greater activity). It is of particular importance that this is true of all the members of the sub-genus of the proposed count, whether tested in vitro or in vivo.

Subject matter of a sub-genus that is unobvious over the

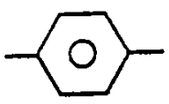
3/ Identical to the formula of proposed counts 3 and 4.

generic Count of an Interference is directed to a separate patentable invention than the generic Count of the Interference, 37 CFR §1.601(n) and should be the subject of a separate Count. M.P.E.P. 2309.01. One conventional method of demonstrating the unobvious nature, and patentability, of a sub-genus over an embracing genus can be by submission of proof demonstrating activity in the sub-genus that is unpredictably higher than that exhibited in the genus as a whole. Ex parte Ebata, 19 USPQ 2d 1952 (POBAI 1991).

As noted above, the Declarations of Kitahara, unchallenged and unrebutted by Wattanasin clearly demonstrate such unpredicted superior bioactivity. Thus, particularly in terms of the Count of this Interference, administration of the sub-genus of proposed count 4 (described by proposed count 3) results in superior cholesterol biosynthesis inhibition in the patients so treated. Advantageously, the administration of the compounds requires dramatically reduced dosages, or reduced administration periods, to achieve the same results as a method of administration embracing compounds within the current Count, but outside the proposed count of the Interference. The uncontested evidence demonstrating superior activity throughout the proposed counts unquestionably supports a finding of two separate patentable inventions residing

patents of the parties involved can present claims corresponding to the same, these should be separate inventions contested separately from the generic Count of this Interference.

Fujikawa's motion to add proposed counts 3 and 4 to this Interference was denied on the basis of the Examiner's conclusion that the Wattanasin application lacks support for the claims proposed by Fujikawa for the Wattanasin application, specifically on the grounds that the Wattanasin application lacked disclosure of the substituent at the 2 position being cyclopropyl. The proposed claims are set forth below.

Claim 11. The compound of claim 1, wherein R_1 and R_2 are hydrogen, R_5 is  F, X is -CH=CH-, R is cyclopropyl, Q is  R_6 is H, R_8 is an alkyl of 1-3 carbon atoms and M is sodium.

Claim 12. A method of inhibiting cholesterol biosynthesis in a patient in need of said treatment comprising administering a cholesterol biosynthesis inhibiting amount of the compound of Claim 11 in combination with a pharmaceutically acceptable carrier.

The sole issue raised with respect to the ability of Wattanasin to "make" these claims was the alleged lack of written description of the identity of the substituent at the 2 position as cyclopropyl. The Wattanasin application unquestionably describes just this substituent.

Fujikawa submits that the Wattanasin application involved herein contains express, ipsis verbis support and description of the genus wherein the substituent at the 2 position is cyclopropyl. At page 1, lines 3-4, the Wattanasin application identifies as appropriate substituents of the 2 position three different classes of moieties, including C_{1-6} alkyl, a ring compound referred to as Ring A, and in particular, C_{3-7} cycloalkyl. C_3 specifically identified as a suitable substituent, is cyclopropyl. The inventor Wattanasin, himself, testified that C_3 cycloalkyl was in fact cyclopropyl. From FR 116

Q. (C3-7) would be five compounds, actually, wouldn't it, Dr., independent of substitutions, that would be 5?

A. Yes.

Q. Can you name those compounds for me, what five basic compounds are encompassed by that group C3 to C7 cycloalkyl?

A. The name?

Q. The name of the compound.

A. It should be cyclopropane....

Wattanasin's attorney responsible for preparation of his application testified identically. At FR 294, Joanne M. Giesser testified.

Q. Certainly that phrase (C3-7 cycloalkyl) identified two possible compounds, one cycloalkyl compound with three carbon atoms and one with seven; is that correct?

A. Yes.

Q. If it had three carbon atoms, would that be cyclopropyl?

A. Yes.

Where literal support, of the type set forth above, appears in the specification, even in the absence of an example corresponding to the sample, the written description requirement of 35 USC §112, first paragraph, is satisfied, and no further inquiry need be made. Snitzer v. Etzel, 175 USPQ 108 (CCPA 1972).

Prior case law certainly agrees with the testimony of Wattanasin and Giesser herein, to the effect that the language

appearing in the Wattanasin application relied upon by Fujikawa is a description of cyclopropyl at the 2 position. See, In re Petering, 133 USPQ 275 (CCPA 1962), where the Court observed that a prior art patent, using the same sort of language, described to one of ordinary skill in the art, not only the broad class encompassed, but the individual members within that class. See page 280. See, to the same effect, In re Saviramakarshna, 213 USPQ 441, 442 (CCPA 1982).

This is not a case like Bigham v. Godtfredsen, 8 USPQ 2nd 1266 (Fed. Circuit 1988), which found a lack of disclosure of a constructive reduction to practice of the specific halogens, iodine and bromine, based on a disclosure that recited halogens and identified chlorine, where patentable distinction has been drawn between chlorine on the one hand and iodine and bromine on the other hand. In the current case, Wattanasin has specifically named cyclopropyl, and more is unnecessary for written description.

Above and beyond the literal description appearing in the Wattanasin application, however, Fujikawa submits that the Wattanasin application unquestionably meets the test of written description, that is, whether the application as originally filed would reasonably convey to those of skill in the art that the inventor had possession of the subject matter claimed at the time

of filing, in this case, had possession of the invention wherein the 2 position is substituted by a cyclopropyl group. It is this test, rather than the presence or absence of literal or exemplary support, that has been repeatedly applied by the Court of Appeals for the Federal Circuit. Vas-Cath, Inc. v. Mahurkar, 19 USPQ 2nd 1111, 1116 (Fed. Circuit 1991) and In re Kaslow, 217 USPQ 1089, 1096 (Fed. Circuit 1983). It is at least clear that the claim language need not be described in identical or literal correspondence in the specification, to satisfy the written description requirement, if those of ordinary skill in the art would understand the description to include the contested subject matter. Kennecott Corp. v. Kyocera International, Inc., 5 USPQ 2nd 1194, 1197 (Fed. Circuit 1987), cert. denied, 108 S.Ct. 1735 (1988). Certainly, Wattanasin testified that those of ordinary skill in the art would recognize that he intended to claim, and had possession of, compounds of Counts 3 and 4, wherein the substituent at the 2 position is cyclopropyl, as of the filing date. FR 117. Giesser testified to the same effect, FR 294.

> Q. Do you have an estimate of whether or not those of ordinary skill in the art of making HMG-CoA reductase field would have interpreted it similarly (to Giesser's

interpretation)?

A. I think they would.

Unquestionably, whether measured on the basis of literal support for the substitution at the 2 position being cyclopropyl, or what the application conveys to those of ordinary skill in the art at the time it was filed, the Wattanasin application has support for proposed Claims 11 and 12. As this is the sole grounds for denying the Fujikawa Motion to Add Counts 3 and 4, the Examiner's Decision denying that Motion is manifestly in error, and Counts 3 and 4 should be adopted.

With respect to Counts 3 and 4, Fujikawa is entitled to a filing date of August 20, 1987, Fujikawa having moved for benefit with respect thereto, that Motion being unopposed. Wattanasin has not offered a single shred of evidence with respect to the limited compounds and method of proposed Count 3 and 4, either with respect to conception or actual reduction to practice, prior to its actual filing date of March 3, 1989. On that basis, priority with respect to proposed Counts 3 and 4 must be awarded to Fujikawa.

2. WATTANASIN HAS NOT SHOULDERED ITS BURDEN OF PROOF IN DEMONSTRATING A DATE OF INVENTION PRIOR TO AUGUST 20, 1987

A. BURDEN OF PROOF

Wattanasin correctly observed that the burden of proof with respect to demonstration of priority rests on the Junior Party Wattanasin. WB 12. Wattanasin's assertion that the burden of proof is one of preponderance of the evidence is, however, incorrect. The appropriate burden of proof is clear and convincing evidence.

As previously noted, this Interference involves not only the two involved applications of Wattanasin and Fujikawa, but U.S. Patent 4,761,419 ('419). Indeed, the Wattanasin application was filed together with a Request for Interference with the '419 patent in an effort to remove the patent right granted therein. Similarly, Fujikawa had requested Interference with the '419 patent.[4/] It is therefore abundantly clear that this Interference

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[4/] Note, moreover, that Interference 102,975, the companion to the Interference also involves, at Wattanasin's insistence, U.S. Patent 5,011,930. Although Fujikawa does not believe all issues in the two Interferences to be identical, Wattanasin has filed identical Briefs in both Interferences. It is therefore clear that Wattanasin is expecting identical treatment, with respect to the

involves not only patent applications, but patents as well.

The appropriate standard of proof with respect to priority in an Interference involving an issued patent claim is clear and convincing evidence. Price v. Symsek, 26 USPQ 2d 1031 (Fed. Cir. 1993).[5/] It should be noted that this is not a new or novel requirement. It has long been the case that, where a party seeks to deprive a patentee of its monopoly through an Interference, such as when the party copies claims, proof of priority by clear and convincing evidence is required. In re Reuter, 210 USPQ 249, 255 (CCPA 1981). Although the 1985 Rules change instituting 37 CFR §1.601 et seq has removed the need to copy claims, Wattanasin did the "new Rule" equivalent of copying claims, in filing a patent application with claims which were indicated, at the time of filing, to be directly in Interference with the claims of U.S.

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burden of proof, in both Interferences. It would surely elevate form over substance to apply a lower burden of proof in this Interference than companion Interference 102,975.

[5/] This decision was followed with an unpublished decision, Larson v. Nurney, Appeal No. 93-1040, 1993 US App LEXIS 11738, May 17, 1993. While not directly citable as precedent, the Larson decision is continuing evidence of the Federal Circuit's determination to require proof that is clear and convincing with respect to priority, when a U.S. Patent claim is involved.

Patent 4,761,419. See the Wattanasin Request for Declaration of Interference filed March 3, 1989.

It is important to note that the difference between "preponderance of the evidence" and "clear and convincing evidence" is more than mere semantics. As the Court has observed in Price, supra, and Buildex, Inc. v. Kason Industries, Inc., 7 USPQ 2d 1325, 1327 (Fed. Cir. 1988), clear and convincing evidence has been described as evidence which produces, in the mind of this Board, "an abiding conviction that the truth of the factual contentions are highly probable", quoting Colorado v. New Mexico, 467 US 310, 316 (1983). Application of the clear and convincing standard herein is also appropriate, given the fact that the applicants are seeking more than monetary damages, they are seeking a monopoly or exclusionary right. The Supreme Court noted in Santosky v. Kramer, 455 US 745, 756 (1981) that the clear and convincing standard is appropriate in a civil case wherever the interest at stake is one that is "particularly important" and "more substantial than mere loss of money". The interest at stake herein is clearly more than a question of loss of money. The interest at stake is limited monopoly power over a pharmaceutical of widespread applicability. Congress and the Courts of this country have uniformly regarded monopoly power as an interest rising above issues of monetary

recovery. See, the Hearings before the Temporary National Economic Committee, 76th Congress, First Session, 839-840 (1939) as quoted in the dissenting opinion of Justice Burton in U.S. v. Line Material Company, 333 US 287 (1948). Accordingly, given the nature of the issues and interests at stake, and recent and consistent Federal Circuit precedent on the matter, the correct measure of proof is clear and convincing evidence. While it should be noted, as discussed, infra, that the Wattanasin evidence does not amount even to the standard of preponderance of the evidence, there surely is inadequate evidence to demonstrate that it is highly probable that Wattanasin completed its invention in advance of August 20, 1987, the uncontested priority date of Fujikawa.

B. WATTANASIN HAS NOT DEMONSTRATED AN ACTUAL REDUCTION TO PRACTICE OF THE COUNT OF THIS INTERFERENCE PRIOR TO ITS CONSTRUCTIVE REDUCTION TO PRACTICE, THE FILING OF U.S. APPLICATION SERIAL NO. 07/318,773, FILED MARCH 3, 1989

35 U.S.C. §102(g) provides that priority can be awarded to the inventor who is first to conceive the invention, and reduce it to practice, but also to the inventor who is first to conceive the invention and the last to reduce it to practice, proceeding with diligence from a time prior to conception of the other interfering

party. There is a requirement that the first inventor, de facto, not abandon, suppress or conceal the invention. Fujikawa's date of invention is fixed at August 20, 1987. For Wattanasin to prevail on priority, it must demonstrate either a conception and actual reduction to practice prior to that date, or a conception of the invention prior to August 20, 1987, followed with a reduction to practice diligently pursued from prior to August 20, 1987. Wattanasin urges these actual reductions to practice, first by reason of an in vitro assay, on December 31, 1984, followed by additional in vitro testing on June 28, 1985, as its first actual reduction to practice. WB 63-64. Wattanasin then urges that synthesis of two compounds, identified as 64-933 and 64-934/NA occurred, without the need for testing to establish an actual reduction to practice, on July 28 and 29, 1987. WB 67. Finally, Wattanasin urges a third date of actual reduction to practice of the invention based on in vitro testing of October 20, 1987 and in vivo testing of October 29, 1987. WB 71.

Fujikawa submits that none of the evidence provided establishes an actual reduction to practice of the Count of this Interference, which is directed not to a compound, per se, and any activity per se, but rather, a method of treating a patient in need of cholesterol biosynthesis inhibition, which comprises

administering a compound of the designated formula to that individual in a biocholesterol inhibiting amount. Thus, this is not a case where "any activity" will do, the Count of this Interference requires a proof of a very special and succinct utility. Note that the Wattanasin application specifically identifies humans as the target patient, page 35, and gives dosage values only for humans. There is no known value in reducing the cholesterol, or controlling blood cholesterol levels, in animals other than humans.

As a starting point, it should be noted that a reduction to practice, where the treatment of mammalian subjects is contemplated, generally requires in vivo testing. Bigham v. Gotfredson, 222 USPQ 632, 637 (POBI 1984). This is particularly in light of the fact that tests that fail to simulate the varying and multiple conditions of an invention's intended environment (the human body) do not serve to prove an actual reduction to practice. Kahl v. Scoville, 219 USPQ 725 (POBI 1982). Further, to prove an actual reduction to practice, it is necessary that the testing must demonstrate that the invention will work for its intended purpose. King Instruments v. Otari Corporation, 226 USPQ 402, 407 (Fed. Cir. 1988), cert. denied, 475 US 1016, cited in Symmes v. King, 21 USPQ

2d 1463 (Fed. Cir. 1991).[6/] In this regard, it should be noted that the test is not whether the subject matter invented might work for its intended purpose, but that it did actually work. Newkirk v. Lulejian, 3 USPQ 2d 1793 (Fed. Cir. 1987). Moreover, any actual reduction to practice must reflect each and every limitation of the Count at issue, and not only some of those limitations, or the limitations regarded by the inventor as critical. Newkirk at 1794, Alsenz v. Hargraves, 13 USPQ 2d 1371, 1375 (POBI 1989). Fujikawa respectfully submits that the Wattanasin evidence fails to make out an actual reduction to practice, under the standards enunciated by the cases cited above.

(i) As noted, Wattanasin urges this Board adopt the position its synthesis of compounds in 1984, followed by in vitro testing conducted by Dr. Scallen in 1985 is adequate to demonstrate an actual reduction to practice. This is surely not the case. Where an invention is intended for use with humans, as is the method of the Count herein, testing on humans or animals, or simulation thereof, in order to determine whether the invention will perform its intended function successfully under conditions of use is

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[6/] Symmes v. King is not directly citable as precedent, but is evidence of the continuing vitality of the decision in King Instruments.

required. Wilder v. Snyder, 201 USPQ 927, 934 (POBI 1977). Bigham v. Gotfredson, 222 USPQ 632, 637 (POBI 1984). The Declaration of Scallen, Wattanasin's in vitro investigator, confirms the fact that even Scallen acknowledged that he had no actual, first-hand knowledge of in vivo activity of any of the compounds in question, his entire familiarity being with other compounds based on secondhand knowledge obtained from individuals at Sandoz, WR 193-194, and that correlation between in vitro and in vivo results was, at best, only "typically highly correlatable", WR 193. Moreover, the Scallen testimony relied upon by Wattanasin to prove an actual reduction to practice does not reflect, in testing, any therapeutic or biocholesterol synthesis inhibiting amounts. The statement at WR 195 that the compounds would be active if administered to a human according to the dosage regiment recited in the Wattanasin specification is speculation, not actual testing, and as noted above, based on secondhand information, and not within the expertise of the investigator.

As rebuttal testimony, Fujikawa took the deposition of Chester E. Holmlund, an expert in the field of HMG-CoA reductase inhibition activity.[7/] Dr. Holmlund was first asked to review the Scallen

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[7/] Although the Wattanasin Brief contains certain unsupported "digs" at Holmlund's expertise, Wattanasin never established the standard for an expert herein, provided expert testimony in

Declaration and exhibits accompanying it, FR 184-185. Dr. Holmlund was familiar with the in vitro assays employed by Dr. Scallen. Dr. Holmlund was then asked to comment on the investigator's conclusion that the in vitro activity was a reliable predictor of in vivo activity.

> Q. Doctor, do you have sufficient knowledge, experience and expertise to have formed an opinion as to the validity of the conclusions set forth in paragraph 3 with respect to the second sentence of that paragraph; that is, the second sentence that reads "if a compound possesses this activity, it would be useful for lowering the blood cholesterol level in animals"?
>
> A. Short answer, yes.

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contrast thereto, or challenged Holmlund's expertise. Moreover, the Wattanasin derogatory assertion that "it emerged on cross-examination" that Dr. Holmlund lacked the necessary expertise and "in fact his knowledge in the precise field of HMG-CoA reductase inhibitors appears to be limited" is unsupported by any reference to the record. At a minimum, challenges to the reputation of a distinguished investigator in the field should be backed up by fact, not attorney assertion. Dr. Holmlund, at least recognized the importance of discretion when making such assertions, FR 228, lines 12-13.

Q. Can you give me that opinion, sir.

A. The problem that I have with that statement as it appears here is the declaration that such compounds would be useful. They may be, but they may not be.

Q. Can you tell me under what situations compounds exhibiting in vitro activity as referred to would not be useful?

A. Well, when a compound is administered to an intact animal, there are many other fates which can befall it before it interacts with its intended target, namely, HMG-CoA reductase in this case.

Q. Is it then your testimony that it is possible for a compound to exhibit in vitro activity pursuant to the type of assay in paragraph 4 and still not exhibit reductase inhibition in vivo?

A. Yes.

Clearly, the in vitro testing conducted by Scallen and Sandoz, for the benefit of Wattanasin in 1985 do not meet the standards prescribed for an actual reduction to practice. The standard is

not that they might work, but that the compounds would work. Note that Holmlund offered identical testimony with regard to the conclusory and penultimate paragraph of the Scallen Declaration.

Under cross-examination, Dr. Holmlund had the opportunity to expound on the reasons for his opinion. At FR 223-224, Holmlund testified that even if Scallen had experience beyond that reflected in his Declaration, it would still not be correct to conclude that the in vitro activity would indicate activity in vivo, in humans. Rather, Holmlund concluded:

> There is a reasonable element of doubt that some compounds may be encountered which are active in the in vitro assay, but yet inactive in the in vivo assay.

Dr. Holmlund noted, FR 233-234, that there are a large number of steps (between ten and twenty) in the synthesis that occurs in vivo, and that assessment of any particular activity in vitro would involve assessment of thirty or more enzymes, depending on the starting material. FR 235-236. Dr. Holmlund concluded:

> It is almost impossible to be assured, to set up an in vitro assay where you can be assured that all those necessary requirements are present.

FR 236.

It is a simple fact that the in vitro testing identifies neither therapeutic amounts for the compounds in question, as required by the Count of the Interference, nor does it reliably establish cholesterol biosynthesis inhibition in humans. The same is required by the law for an actual reduction to practice. The 1985 work by Wattanasin and Sandoz with respect to synthesis and in vitro testing does not establish an actual reduction to practice.

The references Fujikawa submitted pursuant to 37 CFR §1.682 as evidence of the understanding of those of skill in the art echo the lack of reliability of in vitro testing to predict in vivo activity. See, e.g., FR 455, which has a table comparing various in vitro activity for compounds corresponding to the compounds of the method of the Interference. Note that it was the conclusion of the authors that in only three of the ten cases studied were in vitro predictions accurate as to in vivo performance. Certain compounds defied explanation as to the difference between in vitro and in vivo activity observed. Even within the compounds relied upon as predictors, the authors concede that compound 11 was less potent in vivo than was predicted in vitro. Indeed, even between cells of different mammals, prediction is not accurate. FR 464. Moreover, at FR 465, the reference documents the fact, as testified

to by Dr. Holmlund, that a variety of events may occur in an intact animal that preclude obtaining the results reflected in in vitro assays, such as the poor bioavailability to the liver referred to in the reference. Finally, note that the article published by the Sandoz researcher supervising Wattanasin, Kathawala, concedes that it is not correct to conclude that in vitro microsomal activity against HMG-CoA reductase parallels in vivo activity in rates for all compounds of the class embraced by the Count herein. FR 486-487. Indeed, an examination of the document shows the reliability to be at best only slightly more than 50 percent of the compound studied. Clearly, the in vitro studies are recognized by those of skill in the art, including those at Sandoz, the real party-in-interest for Wattanasin, as not a sufficiently accurate predictor of in vivo activity to satisfy the requirements for an actual reduction to practice.

(ii) As an alternative grounds for finding an actual reduction to practice, Wattanasin urges at WB 67-70 that the synthesis of two compounds in 1987, without any testing at all, constitutes an actual reduction to practice. Wattanasin suggests that the law supports the conclusion that the utility of prior art compounds of the same general chemical class as those within the method of the Count is adequate to make out a reduction to

practice. The cases relied upon by Wattanasin are inapposite, and the factual record, including the statements of Sandoz researchers, including Wattanasin, clearly indicate Wattanasin's position to be unfounded.

Wattanasin relies heavily on the decision in Blicke v. Treves, 112 USPQ 472 (CCPA 1957) as supporting the proposition that testing is unnecessary to establish an actual reduction to practice in this case. This is a serious mischaracterization of the Blicke decision. Quoting from the decision at 112 USPQ 475, the Court specifically rejected the appellants' contention that proof of an actual reduction to practice could be made out, in a case involving pharmacological utilities, by reference to related compounds.

> In the instant case, both the application of appellant and the patents of appellee state that the compositions in issue are antispasmodic agents, and that is the only use set forth by appellant in his specifications. Appellant urges that such compositions are of a kind known to be antispasmodics and that, by analogy to Kyrides v. Bruson, 41 USPQ 107 (CCPA), it should be held that no tests were necessary. However, the utility which was held to be known or obvious in the Kyrides case was that of a plasticizer, which is quite different from an antispasmodic or other pharmacological material. That distinction was specifically made in the Kyrides decision, as shown by the following quotation, 41 USPQ at 109-110... (portion of the quote omitted). "This case is easily distinguishable for the reason that while the material was a new substance, it could not possibly be determined

> whether it would have any effect whatever on a hog until a test had been made." It is evident, that while the antispasmodic properties of a new material might be reasonably deduced from its similarity to known antispasmodics, they could not be foretold with certainty, and the fact is apparent from the record here which shows that appellant and his associates subjected the new material to very extensive tests.

Rather than supporting Wattanasin's position, Fujikawa respectfully submits that Blicke unquestionably supports the conclusion that synthesis of the compounds in question, without testing, is inadequate to make out an actual reduction to practice for the Count of this Interference.

Wattanasin himself wrote in 1984 that he could not predict the activity of the compounds in question. Quoting from WX A-2, and WB 24:

> If one of the quinoline prove to be very active, all of these three quinolines and few new modifications might need to be prepared, because of their apparent ease of synthesis. (Emphasis added).

Even the need for further synthesis, in Wattanasin's viewpoint, could not be predicted without activity testing. Moreover, Wattanasin testified that even within the group of compounds

confined to the Count of the Interference, compounds with worse activity were recovered, without being able to predict the same. FR 122. Wattanasin testified in response to questioning from his own attorney that he could not predict the activity of the compounds in question without testing. FR 151. It is clear beyond question that simple synthesis, without adequate testing to show pharmacological properties, is insufficient to make out an actual reduction to practice of the method of the Count of this Interference.

Wattanasin's reliance on the decision in Cross v. Iizuka, 224 USPQ 739, 746 (Fed. Cir. 1985) is equally misplaced. THE DECISION IN CROSS DOES NOT ADDRESS THE ISSUE OF PROOF OF AN ACTUAL REDUCTION TO PRACTICE AT ALL. The decision in Cross has to do with whether or not art recognition of a particular pharmacological activity exhibited by compounds related to those addressed in a Japanese priority document can be sufficient to satisfy the utility requirement under 35 U.S.C. §101, and 35 U.S.C. §112. The Court concluded that utility and enablement was made out by reliance on this prior art, in light of Declarations submitted establishing the close relation between the two. The Court did not consider an actual reduction to practice. It should be noted that, as discussed above, to demonstrate an actual reduction to practice, it

must be demonstrated that the invention did in fact work whereas, to satisfy the utility and enablement requirements of 35 U.S.C. §101, 35 U.S.C. §112, all that need be made out is a reasonable probability that those of ordinary skill in the art could make the invention work. There is a substantial chasm between the two standards, a chasm that the Wattanasin evidence cannot span.

In addition to controlling precedent, and the testimony of Wattanasin himself, the articles submitted by Fujikawa pursuant to 37 CFR §1.682 confirm the lack of reliability of related structures as a predictor of activity. Attention is directed, e.g., to FR 446, which reflects no less than twenty-two structurally related compounds similar to those embraced by the Count of this Interference, having similar activity in the inhibition of CoA reductase. Even though the structures are at least as similar, one to the other, as the structures that Wattanasin alleges, but points to no Record discussion, as being equivalent, activity values and relevant potency vary between the compounds by as much as three orders of magnitude. Clearly, structure, alone, is not a predictor of activity. Dr. Kathawala, Wattanasin's supervisor and a corroborating witness, confirmed the same in his article, FR 484, where he noted that the preparation of a homolog, exactly the type of compound Wattanasin seeks to rely on, WB 70, resulted in a

substantial loss of activity of the type addressed by the Count herein.

> Surprisingly, introduction of methyl group at C-3 in either syn- or anti- configuration was considerably less active (Table III).

Not even the real party-in-interest for Wattanasin believes that structure, alone, is an accurate predictor of HMG-CoA reductase inhibition in humans.

Sandoz further recognized that even between compounds having putative activity of this type, wide variations in activity (as measured by IC_{50} values from <u>in vitro</u> assays) would be expected. Thus, as reported at Table IV, V, X, XI and XIII of <u>Medicinal Research Reviews</u>, Vol. 11, No. 2, pp. 121-146(1991) FR 471-496, the difference between IC_{50} values for compounds as closely related as

(a) dimethylphenyl v. (b) unsubstituted phenyl

and

(c) dimethylphenyl v. (d) monofluorophenyl,

the very compounds Wattanasin urges as the basis for comparison, WB 70, can be as great as

a = 0.62 v. b = 28

c = 0.02 v. d = 7

In other words, a difference of two orders of magnitude. Clearly, structure does not predict activity. Synthesis, alone, cannot constitute an actual reduction to practice.

(iii) The third type of evidence Wattanasin seeks to rely on to prove an actual reduction to practice is the in vivo testing conducted by Dr. Engstrom. It should be noted that the in vivo testing occurred well after Fujikawa's own effective date of August 20, 1987, and accordingly, diligence is an issue, inquired into below. More importantly, however, Fujikawa respectfully submits that it is the unquestioned testimony of Dr. Holmlund, unrebutted by any evidence or questioning attempted by Wattanasin, that the reports of the in vivo activity in this particular case not only failed to demonstrate activity in the inhibition of cholesterol biosynthesis, but confirmed Dr. Holmlund's statement that in vitro activity could not be relied upon to prove in vivo activity, as Dr. Scallen concluded that there was in vitro activity, but Sandoz's own researcher, Dr. Engstrom, concluded that there was no in vivo activity in the tests conducted.

Dr. Engstrom's Declarations and the Exhibit Q thereto, have

been objected-to separately. Moreover, the Supplemental Declaration has been objected-to on additional grounds, in the Fujikawa Motion to Suppress. Nonetheless, the Declarations are treated in their entirety herein. Dr. Engstrom's testing relied upon by Wattanasin consisted of the in vivo testing of three compounds, designated 64-933, 64-935 and 64-936. With respect to two of these compounds, 64-935 and 64-936, Dr. Engstrom concluded that the ED_{50} value for compounds 64-935 and 64-936 was greater than 1.0 mg/kg in both cases. A ED_{50} value that is greater than a specified number is a meaningless value. Compounds having no activity at all have a ED_{50} of greater than 1.0. Dr. Holmlund so testified. From FR 193-194:

> Q. Let me ask you, Doctor, what is the meaning of an ED_{50} value?
>
> A. This is the effective dosage in an in vivo assay, in this case, which would reduce the rate of cholesterol biosynthesis by 50 percent.
>
> Q. What is the meaning, then, of an ED_{50}

value as being indicated as greater than 1.0?

A. Well, I can't attach any significance to that whatsoever. The implication is that there would be activity at a dose greater than 1 milligram per kilogram were used. But without any experimental data confirming, that deduction would seem to be meaningless.

Q. Let me direct your attention to the page of F-17 that bears the legend 110 in the top right-hand corner. Do you see, in about the middle of page there, two entries for ED_{50} values of greater than 1.0?

A. I do.

Q. Would your comments a moment ago with regard to the meaning of a ED_{50} value of greater than 1.0 apply?

A. They would.

Q. It is possible in the absence of

further information that a reductase inhibitor having a ED_{50} value of greater than 1.0 may have no inhibition activity at all.

A. Yes.

Clearly, for two of the compounds so tested, no activity was shown at all. Dr. Holmlund commented on this, noting that it was proof of his statement earlier that assays showing activity in vitro cannot predict activity in vivo. From FR 196-197:

Q. In light of your testimony regarding the in vivo testing that you have just provided and the meaning of an ED_{50} value of greater than 1.0, can you draw any correlation between the in vitro tests addressed in F 11, that's the Scallen declaration, and the in vivo test results reflected in F 17, the Engstrom declaration?

A. As I recall, in the Scallen declaration, all of these named compounds were described and shown to be active in the in vitro assay,

and the statement was made they would be active in vivo. Yet, the in vivo data here clearly indicate that that is certainly not the case for 64-933 and probably not the case for the other two compounds as well.

Q. And that is probably not the case because?

A. Because the data are so scattered for 64-935 and 64-936. There is no significant dose and activity relationship.

64-933 is reflected in the Engstrom Declaration, WR 206, as having a ED_{50} value of 0.49. Dr. Holmlund was asked for his opinion with regard to the data provided relevant to this compound as well. FR 195:

Q. Doctor, let me turn your attention to F-17 for a moment, and specifically the indication on the last page of that document that a ED_{50} value for compound 64-933 of 0.49. On the basis of the

information contained in K-1 alone, what, if any, is your opinion as to the validity of the assignment of a ED_{50} value of 0.49 for this compound?

A. Your question referred to K-1?

Q. I am sorry. F-18.

A. The data provided in F-18 with respect to compound 64-933 in no way can be used to provide a figure of 0.49, and a ED_{50} value of 0.49 for 64-933 as shown on page 110.

Q. Can any ED_{50} value be assigned to this compound, 64-933--

A. No. Excuse me.

Q. --On the basis of F-18 alone?

A. No.

It is demonstrably clear that none of the three compounds tested by Dr. Engstrom indicated any activity at all, and thus do not constitute an actual reduction to practice.

On cross-examination of Dr. Holmlund, Wattanasin attempted to rely on the Supplemental Declaration of Engstrom, which was objected-to by Fujikawa, which attempts to switch values assigned to compounds 933 and 935. Nonetheless, even if admitted, the

Supplemental Declaration fails to demonstrate activity for any of the compounds tested. Dr. Holmlund testified, repeatedly, that the numeric values, given for the compounds, including 64-936, did not exhibit significant reductions, according to the standards of the researcher. FR 205. At FR 206, Dr. Holmlund expanded on his testimony under cross-examination.

> Q. Yet I believe that you were saying that a result of -36.3 for the compound 64-933 on Record page 338 which differs only by 3 percent from the result for 936 is not a significant result?
>
> A. Yes. Again, based on the statistical data, and these differences, bring dramatically to light the kind of biological variation which occurs in biological experiments.

Later on, on page 206, Dr. Holmlund reiterated his testimony.

> Q. 64-933 on page 338 and 339, are any of these results showing an indication of activity which would

be statistically above the level of a zero control?

A. No.

On page 207, Dr. Holmlund testified that the value of 0.49 for the ED_{50} value of compound 64-935 could not obtained based on the data attached to the Engstrom Declaration, due to the absence of any reasonable dose response curve. At page 209, Dr. Holmlund testified:

Q. Is it your testimony this compound has a significant activity?

A. My testimony would be that it may have. Based on the data that are presented, I cannot make a final conclusion on it.

Again and again, throughout cross-examination, Dr. Holmlund drove home the point that according to the statistical assessment conducted by the Sandoz researcher himself, Dr. Engstrom, not one of the three compounds tested exhibited activity. The fact that higher values might be provable was irrelevant, as such higher values had not been tested.

There are other problems with both the Engstrom Declaration and Supplemental Declaration. The Declaration purports to test the

ED_{50} value of 64-936. Dr. Engstrom was provided 64-936 NA, the sodium salt. WR 205. See also, WB 43-44, which confirms that three compounds, 64-933, 64-935 and 64-936/NA, were forwarded to Engstrom for in vivo testing. Yet, the Engstrom Declaration does not assign a ED_{50} value to this compound, but rather to the free acid, 64-936. WR 206. Dr. Holmlund testified that in fact the variation between the compound forwarded to Engstrom and the compound addressed in his Declaration, can be of significance. This testimony appears at FR 188:

> Q. On the basis of your review of the documents provided, can you tell me the significance of the suffix "NA"?
>
> A. That is intended to indicate that it is the sodium salt of the compound that is being tested.
>
> Q. Doctor, on the basis of your knowledge, experience and expertise, can the in vivo activity shown by a sodium salt of a compound having reductase inhibition activity be different from the activity shown by the corresponding free acid?

A. It can.

Thus, the Engstrom Declaration is not reliable, in that it reflects a ED_{50} value for a compound never tested, 64-936, the basis for the assignment of that ED_{50} value appearing no where in the supporting documents. It is unclear, on the record presented, whether this discrepancy is due to attorney error, declarant mistake, or a fundamental error in preparation and testing. In the absence of a clear explanation, which is not present in the Record, the Engstrom Declaration must be severely discounted.

The in vitro and in vivo testing is further inadequate to prove an actual reduction to practice because the Count herein is a method of treating human patients. To demonstrate efficacy for that method, a demonstration of low toxicity and side effects would be necessary. See FR 218-219, where Dr. Holmlund testified that an active compound would not be useful to administer if the "possibility of toxicity associated with the compound" had not been ruled out. Even Counsel for Wattanasin agreed, "I can certainly give you that, Doctor." FR 219.

The Engstrom Declaration, and the results addressed therein, do not make out sufficient evidence of activity to establish an actual reduction to practice. At best, the Engstrom Declaration indicates that at dosage values higher than those actually tested,

activity might be indicated. This is not the standard for an actual reduction to practice, which requires proof that the invention did in fact work. That is, the method performed inhibited biosynthesis of cholesterol. The testimony of Holmlund is unrebutted in this regard, and the standard of the law clear. Wattanasin having failed to prove, by clear and convincing evidence, or even a preponderance of the evidence, that the subject matter of the method of the Count was ever reduced to practice by Wattanasin prior to its filing date, Wattanasin has, at best, a conception followed by a constructive reduction to practice as of March 3, 1989.

C. WATTANASIN CEASED ACTIVITY WITH RESPECT TO THE INVENTION AFTER ITS JUNE 20, 1985 ACTIVITY, AND DID NOT RESUME ACTIVITY UNTIL MARCH, 1987

As noted above, the Party Wattanasin has not made out evidence of an actual reduction to practice. Accordingly, in order to prevail in this Interference, Wattanasin must demonstrate, by clear and convincing evidence, that it had possession of a full conception of the invention prior to August 20, 1987, and proceeded with diligence to its constructive reduction to practice of March 3, 1989. Fujikawa respectfully submits that the earliest date of

conception on which Wattanasin can rely is its March, 1987 synthesis activity. Although Wattanasin did not proceed with diligence to its filing on March 3, 1989 from that synthesis activity, as discussed herein below, Wattanasin alleges a date of conception no later than June 30, 1985. Wattanasin cannot rely on this date, however, as there was absolutely no activity subsequent to that date for a period of 20 months, without excuse or evidence, a period of delay too long to be considered diligent activity.

The argument section of the Wattanasin brief, pages 62-76 is totally silent as to whatever diligence Wattanasin may have practiced with respect to the subject matter of this Count between the Scallen testing completed in June, 1985 and the resumption of activity in March, 1987. Although there is a section relating to abandonment, suppression or concealment between those dates, as noted above, there is no evidence of any actual reduction to practice prior to March of 1987. Accordingly, issues of abandonment, suppression or concealment are not reached. Peeler v. Miller, 190 USPQ 117 (CCPA 1976), Connin v. Andrews, 223 USPQ 243, 249 (POBI 1984). As proof necessary for diligence is quite different than that necessary to avoid the inference of abandonment, suppression or concealment, it is believed that Wattanasin has essentially conceded an absence of diligence between the end of June, 1985 and March, 1987. Nonetheless, discussed

below is the activity referred to during that period, the case law unquestionably indicating that the activity referred to is insufficient to establish diligence. At WB 67-68, Wattanasin attempts to rely on the activity of Wattanasin in synthesizing compounds outside the scope of the Count of this Interference as apparent evidence of continued work. It is to be noted that there is absolutely no record support for the allegation that the compounds testified to by Dr. Kathawala and referred to at WB 67 were "chemically analogous" to the subject matter of the count of the Interference. In any event, the case law establishes that this activity is insufficient to support diligence.

Diligence must ordinarily be directed to a reduction to practice of subject matter within the Count at issue. Naber v. Cricki, 196 USPQ 294 (CCPA 1977). Work performed on related products or methods outside the Count of the Interference is generally not acceptable as evidence of diligence. To qualify as evidence in support of diligence, the work performed must be described in the application involved in the Interference. Hoffman v. Schoenwald, 15 USPQ 2nd 1512 (BOPAI 1990), Ginos v. Nedlec, 220 USPQ 831 (POBA 1983). It is to be noted that even if the compounds Wattanasin worked on between July, 1985 and March, 1987 were "chemically analogous" or "related", Wattanasin cannot rely on that

activity if in fact it was directed to subject matter that constitutes an invention independent of this case. Smith v. Crivello, 215 USPQ 446, 453 (POBI 1982).

Wattanasin also attempts to attribute the absence of activity from July, 1985 to July, 1987 to a manpower shortage. This was a manpower shortage of Wattanasin's own election, and approved of by Sandoz, the real-party-in-interest. During the period in question, Wattanasin did not cease work, but rather, elected to pursue other compounds, presumably because they enjoyed a higher priority. WB 28-29. Moreover, Sandoz was satisfied with the manpower shortage, and believed that other efforts enjoyed a higher priority. From FR 165-166

Q. The very last answer you gave had to do with the manpower shortage and the priority being set on things. Did you set the priority with regard to the compounds in question that you just testified to?

A. The priority was set either by myself or my boss.

Q. In this particular case, do you recall who set the priority?

A. In this particular case, I think -- actually both,

I will say, both. You see, I mentioned before, this is not the only compound, only class of compound we are working with. We are working on different classes of compounds during the HMG-CoA reductase and probably as you have seen from the patent, as well, we have to key compounds, very important compounds, indole and indene.

Q. Did those projects receive a higher priority than the project in question?

A. Yes, according to my supervisor, yes.

Clearly, Wattanasin and Sandoz felt that other projects had a higher priority, and had set aside work on the subject matter of the Count at issue in favor of those other products. This is not diligence. See in particular, Monce v. Adams, 1872 CD 1, wherein, over 100 years ago, an 18-month delay in order to work on other related inventions that were being pursued commercially was sufficient to establish a lack of diligent work towards a reduction to practice. There is simply no evidence of any diligence at all with regard to the subject matter of the Count of this Interference between June 30, 1985 and March, 1987.

D. WATTANASIN DID NOT PROCEED WITH DILIGENCE FROM MARCH, 1987 TO ITS PATENT FILING IN MARCH, 1989

As Wattanasin notes, activity on the subject matter of the Count of the Interference, or rather synthesis of compounds embraced by the Count of the Interference, did not resume until March of 1987, when researcher Patel joined Wattanasin's group and began synthesis of the compounds. It is not clear that there is any evidence that the synthesis of the compounds was directed to establishing a method for treating patients in need of cholesterol biosynthesis inhibition. The Court's decision on appeal after remand in Paulik v. Rizkalla, 226 USPQ 224 (Fed. Circuit 1985) leaves open the question of whether or not Wattanasin is entitled to rely on whatever activity testing it conducted in 1985 to establish the conception for the invention, of which the March, 1987 synthesis was part of. In other words, it is not entirely clear from the opinion that Wattanasin can reach back and use the evidence of conception in 1985 to apply to its 1987 synthesis. The decision in Paulik does, however, make it clear that Wattanasin,

while not permitted to rely on the 1985 date, is in fact permitted to rely on the 1985 activity for some purposes. As Wattanasin did not proceed with diligence to a filing in March of 1989, this open issue need not be reached. For the purposes of this brief, therefore, it will be assumed, although there is no clear precedent thereon, that the March, 1987 synthesis can be considered as conducted in light of the conception of the invention that is the Count of this Interference.

Wattanasin did not even begin testing of the compounds synthesized beginning March, 1987 until after Fujikawa's filing date. WB 71. Since Wattanasin necessarily must rely on its earlier conception to establish a date of conception of March, 1987, from March until October, 1987, the sole activity of Wattanasin with respect to the subject matter of the Count was the synthesis of additional compounds, a synthesis that Wattanasin himself did not believe to be necessary for a patent application, i.e., a constructive reduction to practice, in light of the fact that Wattanasin himself prepared the patent disclosure on which the involved Wattanasin application is based on March 16, 1987 in advance of any renewed synthesis activity. WR 24-25, WB 30. Clearly then, Wattanasin already had established his conception of the invention, and for more than seven months did nothing in the

way to advance the subject matter to a constructive reduction to practice other than the synthesis of additional materials. Wattanasin himself testified, as noted above, that some of the compounds would be expected to be more active, and some of the compounds were expected to be less active. Certainly, mere continued synthesis of additional compounds within the scope of the Count of the Interference does not ordinarily demonstrate diligence. For continued testing to demonstrate diligence, it must be proven that the purpose of the testing was to improve the invention or obtain the best design. Brokaw v. Vogel, 166 USPQ 428, 431 (CCPA 1970), Dewey v. Lawton, 146 USPQ 187 (CCPA 1965), and Gallagher v. Smith, 99 USPQ 132 (CCPA 1953). There is absolutely no evidence of record which would suggest that Wattanasin expected the compounds synthesized between March and October, 1987 to be superior in any way to the compounds previously synthesized. The 7-month delay involved simply cannot constitute diligence.

Notwithstanding the absence of diligence from March to October, 1987, thus, a point well after Fujikawa's filing date, Fujikawa further submits that a most glaring example of an absence of diligence runs from October, 1987 until March, 1989, a 16-month delay. The only activity Wattanasin attempts to rely on during

this period is the activity of its Patent Department. Evidence of diligence is sorely lacking. Fujikawa starts with a proposition that the party charged with diligence must account for the entire period, and show diligence throughout, or provide acceptable reasons or excuse why no activity took place. Staehlin v. Secher, 24 USPQ 2nd 1513 (POBAI 1992). Quite simply, this Wattanasin has not done. The only activity reported between October, 1987 and the end of January, 1988, when the patent department met and rated the Wattanasin disclosure "A", that is ready for filing, was to rate the disclosure as not ready for filing, thus precluding any activity with respect to a reduction to practice thereof. WB 44. It is to be noted that Wattanasin concedes it had a policy against publication of subject matter that had been rated not ready for filing, and that no action on the part of a patent attorney is required in response to an "X" rating. WB 32-33.[8/]

As sparse as the record is with respect to activity between March, 1985 and January, 1988, the record deteriorates thereafter. From January until at least August 1988, neither Wattanasin, nor

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[8/] The "entering" of data previously obtained into the data base on December 9, 1987, WB 71-72 does not constitute an activity that would support diligence. This activity was simply for the convenience of Sandoz, the actual values having been obtained earlier.

the patent attorneys at Sandoz did anything with respect to the application in question. Note that the rating of the invention disclosure as "A", ready to file, is unavailing, Peeler v. Miller, 190 USPQ 117, 123 (CCPA 1976).

The Wattanasin application was assigned to Giesser. She had primary responsibility for the case. FR 262. Yet Giesser was reliably able to establish work in the application beginning no later than October, 1988. Rather, Giesser decided to pay attention to other cases she felt enjoyed a higher priority, although docketed well after the Wattanasin application for filing. From FR 263

> Q. Now, the other responsibilities that you had identified, and particularly the seed companies and RSRC, did you have any filing responsibilities for them that would take priority over the filing responsibility for 600-7101 (the Wattanasin case)?
>
> A. Yes.
>
> Q. Could you describe those responsibilities for me.
>
> A. As it turned out, there were a number of applications which, out of the seed companies,

although as of January 1988 had not been decided to be filed upon but later on as the year progressed were coming up against time bars.

Q. So as of January, those cases had not been assigned to you for preparation?

A. Right.

Q. Were they subsequently assigned to you for preparation?

A. Yes.

*** *** *** *** *** *** *** *** *** *** *** *** ***

Q. So these cases were designated A after, and by A, I mean intended for filing -- after 600-7101 but were intended for filing before 600-7101; is that correct?

A. Yes.

Q. And they took priority over 7101 because --

A. Well, certainly, at least as I recall, I think some of the crop protection cases had -- either the scientists had wanted to publish, or were scheduled to publish, so there were bars of that sort running

on them. (Emphasis added).

Although other examples abound in the testimony of Giesser, it is clear from the foregoing that Giesser, and the attorneys at the Sandoz Patent Department, failed to take up the Wattanasin application in the order they received it for filing. Such activity forecloses a finding of reasonable diligence. Mendenhall v. Astec Industries, Inc., 13 USPQ 2nd 1913 (DC Tenn. 1988) affd. 13 USPQ 2d 1956 (Fed. Cir. 1989). As the Board of Patent Interferences observed in Choi v. Godfrey, 212 USPQ 286, 290 (POBI 1990), when an attorney intentionally passes over a disclosure in favor of subsequent disclosures thought by the assignee to be more important, this, alone justifies an adverse award of priority. It is to be noted that the second element of Choi, spurring, is also present in the case, as discussed below.

Moreover, Giesser's work on other cases cannot be relied upon to prove diligence. Under certain circumstances, work on a group of cases may be relied on to prove diligence as to one particular case, where the work involved is clearly related, or similar in scope and requires similar starting materials. If the interfering party is to rely on the other cases prepared, the burden is on that party to show the order in which each case was docketed, the activity pertaining to each case during the time in question, and

why cases docketed later were worked on earlier. Bey v. Kollonitsch, 215 USPQ 455, 462 (POBI 1982). Wattanasin has failed to meet the specific guidelines of Bey. Note that Giesser could not even remember when the "seed cases" were assigned, FR 264, but in all likelihood, these cases directed to entirely different applications, were not assigned as early as June. FR 264. Accordingly, from January, 1988, when the Wattanasin application preparation was assigned to Giesser as having primary responsibility, to at least later than June of that year, Giesser did absolutely nothing with respect to the application in question. Yet, a CIP case, 7025/CIP/CIP was prepared after assignment of the Wattanasin application, and filed in advance thereof, October 6, 1988 for reasons that remain unclear. FR 266. In fact, Giesser prepared four different applications in the pharmaceutical area assigned to Giesser after the Wattanasin application, but filed in advance thereof. FR 274-279.

Wattanasin does try to justify Giesser's inattention to the Wattanasin application by discussing Giesser's travel schedule. Even taken at face value, Giesser's entire travel schedule amounts to no more than 38 days between January 27, 1988, and December, 1988. Thus, only 38 days out of more than 330 are accounted for. That travel, however, was largely scheduled at Sandoz's election,

and was not business that only Giesser could attend to. Dick Vila, of record in this Interference on behalf of Wattanasin, directed Giesser to undertake much of the travel, at the time he was aware of Giesser's responsibility for the Wattanasin application. FR 288. Moreover, one of the travel opportunities, to New York City, was not on behalf of Sandoz, but "was basically open to anyone in the Department", FR 291. Moreover, during the time that Giesser did spend travelling, she elected not to work on business matters, including the Wattanasin application, while travelling. FR 285.

Giesser testified, FR 350-351 that Vila could have represented the interests of Sandoz alone, but chose to have Giesser accompany him. It was clearly the policy of Sandoz to rate other work as having a priority over the Wattanasin application. This precludes a showing of diligence. The same thing is true with regard to the CIP application that took so much of Giesser's time, identified as 7025/CIP/CIP. Giesser had already been assigned an earlier priority of preparing the Wattanasin application. When she received 7025/CIP/CIP, rather than extending the time necessary for filing a continuation application or by taking the full time available in which to file the CIP, Giesser elected to file it early, FR 346. Again and again, Giesser took cases out of order, ahead of the Wattanasin application, because Sandoz had put a

higher priority on these later cases, or simply because Giesser preferred to do that.[2/] This cannot constitute diligence. The very end of the period in question, from January until March 1988 is devoid of any evidence with respect to Giesser's work on the Wattanasin application, or indeed, any work by Wattanasin or anybody at Sandoz with regard to this invention. On cross-examination, Giesser could not recall any activity she undertook with regard to the Wattanasin application between January 4, 1989 and March 3, 1989. Ms. Giesser so testified, FR 296

> Q. Ms. Giesser, can you recall any activity you undertook between January 4, 1989 and March 3, 1989 with regard to case 600-7101?
>
> A. I have no recollection.

This hiatus, alone, would be sufficient to destroy any claim to diligence. In Kondo v. Martel, 223 USPQ 528, 532 (POBI 1984), failure to conduct any work with the case for five weeks was fatal

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[2/] No criticism of Giesser is intended herein. She may well have taken these steps at the direction of her boss, Dick Vila. Giesser so testified. Additionally, Vila and Sandoz knew that Giesser was inexperienced in the pharmaceutical field. The decisions and judgment of Vila and Sandoz, however, adversely affect the Wattanasin position. He is bound by the activities of his assignee.

to diligence. The Board specifically noted that a heavy work load is not an excuse.

Even if the decision by the Sandoz Patent Department in January, 1988 to proceed with the filing of a patent application on subject matter it had earlier concealed from the public could be understood to be an activity counting towards diligence, of the more than 14 months between that decision and the filing of the Wattanasin application, no more than about two (October-December 1988) are accounted for. This cannot be diligence. Delays of far less have been held unreasonable. Shindelar v. Holdeman, 207 USPQ 112, (CCPA 1980) cert. denied 210 USPQ 776 (1981) concluding that 3-4 months would be reasonable for preparation of an application. An attorneys work load, the Court held, should not excuse further delay. See also, Willis v. Suppa v. Koehler, 209 USPQ 406, 418 (POBI 1980) where the Board found that only four months of unaccounted for attorney time demonstrated an absence of diligence, citing Emery v. Roden, 188 USPQ 264 (POBI 1974).

Wattanasin alleges a conception of the invention in 1985. Diligence must be demonstrated from 1985 until March, 1989. There are at least three interruptions during that period where no activity was undertaken, from June, 1985 to March, 1987, from October, 1987 to January, 1988, and from January, 1988 until March,

1989. Even assuming that Wattanasin need only prove diligence from March, 1987 to its filing date, the showing is inadequate. The only excuse Wattanasin offers is an exceptional attorney work load. The work load was not exceptional, and contrary to the testimony of Kassenoff, and the assertion of Wattanasin, the attorney responsible for the Wattanasin application had no backlog of work when the application was assigned.

> Q. As of February 1, 1988, do you recall whether you had a backlog of cases to prepare and file?
>
> A. I don't think I had a backlog, no.

FR 305. With no backlog, and no cases assigned to Giesser for filing in advance of the Wattanasin application, the Wattanasin application should not have taken 15 months to file. That in fact it did is a clear case of lack of diligence.

E. IF WATTANASIN HAS PROVED AN ACTUAL REDUCTION TO PRACTICE, THE WATTANASIN INVENTION WAS SUPPRESSED OR CONCEALED FROM ITS DATE OF INVENTION, OF ABOUT JUNE 30, 1985, UNTIL ITS FILING DATE OF MARCH 3, 1989

Wattanasin and its real-party-in-interest, Sandoz, took

deliberate steps to prevent publication of, or public access to, information regarding the invention, and at the same time took deliberate steps to delay preparation of a patent application directed thereto. Thus, for over 44 months, Wattanasin's invention was suppressed or concealed, Sandoz deliberately taking later cases and advancing them in front of the Wattanasin invention, and in fact, not pursuing any activity toward the actual preparation of an application until Sandoz became aware of the '419 Patent involved herein. It was awareness of the '419 Patent that finally spurred Sandoz into filing the Wattanasin application. This is a classic case of suppression and concealment.

The law of suppression and concealment dates as far back as 1872, where it was noted in the decision in Monce v. Adams, 1872 CD1, that where the de facto first inventer kept his invention secret for 18 months, while he pursued commercialization of other, related invention, and filed for an application only after being approached by Adams for a license, suppression and concealment forced an award of priority to Adams. The leading decision of the CCPA on suppression and concealment, Young v. Dworkin, 180 USPQ 388 (CCPA 1974) clearly establishes that matters of suppression and concealment are to be interpreted as concerned with that situation where the patent applicant or his assignee takes active measures to keep the subject matter from public knowledge. In Young two

elements were identified as contributing to a finding of suppression and concealment, the first being a deliberate delay in filing the application while preventing publication of the same, and the second, being spurred into the filing of an application by knowledge of another's entry into the field, e.g., by issuance of a patent. Only one element need be present for a finding of suppression or concealment, Choi v. Godfrey, 212 USPQ 290, (POBI 1980), and Fujikawa submits that both are present herein.

Wattanasin concedes that Sandoz deliberately kept secret the subject matter of the Wattanasin invention, suppressing any publication thereof until after a patent application was filed. WB 56, WR 305. Yet, when the Sandoz Patent Department learned of the invention, it elected, for 9 months, to keep the invention secret but not pursue a patent application. The patent disclosure was first reviewed April 29, 1987, and was not deemed of sufficient importance to reconsider until 3 months had passed. WB 33, WR 14. When the case did come up for reconsideration on July 29, 1987, the Patent Committee again determined not to file a patent application thereon, rating the application for reconsideration in another 3 months time, October. WB 39, WR 215. Again in October, the Patent Committee declined to give approval for filing a patent application on the Wattanasin disclosure, rating it "X" for reconsideration at

the next meeting. At that next meeting, November 25, 1987, the Patent Committee again decided to not initiate filing of a patent application, setting it for reconsideration in January, 1988. WB 44, WR 215 and 376. It was not until January 27, 1988, that the Patent Committee decided to rate the disclosure as ready for filing, WB 45, and assign the case to its most junior attorney, Joanne Giesser, WB 45. Thus, from June, 1985 until January 27, 1988, Sandoz took deliberate steps to prevent publication of the Wattanasin invention, and at the same time, knowingly, deliberately precluded the filing of a patent application. Delays of this magnitude have previously been held to be fatal to the de facto first inventor. Smith v. Crivello, 215 USPQ 446 (POBI 1982) (22 months), Connin v. Andrews, 223 USPQ 243 (3 years is unreasonably long), Young v. Dworkin, supra (27 month delay sufficient to demonstrate suppression or concealment). In any event, it is to be noted that the Doctrine of suppression and concealment is not to be confined to extreme cases, and should be invoked in the public interest wherever the facts warrant it. Brokaw v. Vogel, 166 USPQ 428, 431. While each case must be considered on its own facts, Myers v. Feigelman, 172 USPQ 580 (CCPA 1972), Fujikawa respectfully submits that the evidence is clear and overwhelming that Sandoz took deliberate, knowing measures to keep the Wattanasin disclosure

from the public, and prevent the filing of a patent application with respect thereto.

Subsequent to the decision of the Patent Committee in January, 1988 to initiate the filing of a patent application, Sandoz engaged in a further and deliberate attempt to suppress the invention. The Wattanasin invention was docketed for filing as a patent application 3 weeks after its "A" rating, or February, 1988. FR 99. In response to redirect questioning by Wattanasin's counsel, it was established that the regular procedure was to work on cases in the order that they were docketed.

> A. Theoretically, at least, the case that was rated "A" first should be acted on first by the person to whom it is assigned, but I would not guarantee that was followed by everybody at all times.

WR 276. The reason for the lack of a guarantee is clear. Instead of following established procedure, Giesser, the attorney responsible for the application in question again and again took cases assigned to her after the Wattanasin disclosure had been rated "A", and worked on those first. See the discussion above with respect to diligence. This was true even when there was no

bar or other immediate concern that required work on the cases Giesser elected to work on, instead of the Wattanasin application. Indeed, Giesser went on travel to various meetings of patent attorneys not specific to Sandoz, rather than working on the Wattanasin application. See, e.g., FR 316, with regard to the trip to Washington. This happened again and again.

In point of fact, absolutely no activity with regard to the Wattanasin application was undertaken, save for a request for information made by Kassenoff because he was working on a related case, WR 257-258 (note, Giesser could have done it, she didn't have a backlog in her work at the time). The first event connected the preparation of a patent application on the Wattanasin disclosure that is established by the record is the Sandoz recognition that the '419 Patent to Picard, on the exact same subject matter of the Wattanasin invention, had issued. The Picard '419 Patent issued August 2, 1988. Giesser testified that she would have learned of that within about a week or so. Kassenoff testified that such knowledge would have influenced his judgment in whether to pursue a patent application on a specific disclosure, WR 281. It is clear from the record that Giesser has no actual memory of working on the Wattanasin application, in any way, until after she learned of the issuance of the '419 Patent. Note, for example, Giesser's

confirmation that

Q. So the Warner-Lambert patent issuance really fixes in your mind the knowledge that you were working on the application?

A. Yes.

Q. That was an important event for you in connection with the application; is that correct?

A. Yes.

Q. Do you have any recollection as to whether you were working a long time on this application in terms of drafting before you learned of the Warner-Lambert application?

A. No, I don't have any recollection of that.

In fact, in Giesser's direct testimony, her Declaration, Giesser stated that she began work on the patent application as of October, 1988, well after she would have learned of the issuance of the '419 patent. Under prodding from Counsel, Giesser began to "push" the date she began work on the application earlier, first back in

September, and then back into August. Even under counsel's guidance, Giesser could not testify it was as early as July. Any assertion that in fact work began on the application by Giesser before October is unreliable, Giesser had no knowledge of any activity prior to October, and vacillated when she was asked to specify what work she did prior to October. See FR 368-371. See also the uncertainty at FR 375-377, Giesser being certain only of the fact that

No, I don't recall when I started to work on 600-7101.

FR 376-377.

Fujikawa respectfully submits that, looking at the record, the '419 Patent, claiming the subject matter of the Wattanasin disclosure issued, and the Sandoz Patent Department, including Giesser, knew of it, before the earliest provable date of work on the application of October, 1988. In view of Giesser's repeated work on cases docketed after the Wattanasin disclosure, before working on the Wattanasin disclosure, even if Giesser had begun work on the patent disclosure prior to that time, there is no reason to believe that the work would have been continuous or substantial. It is unquestionably the case Giesser, and Sandoz, were spurred into filing by knowledge of entry into the field by

Warner-Lambert, by reason of learning of the '419 Patent. Prior to that time, Sandoz had no expectation that Warner-Lambert or any other third party was in the field.

> Q. Did the issuance of the Warner-Lambert patent change the size of the fire, in your determination, with respect to 7101 (the Wattanasin application docket number)?
>
> A. It certainly caused a lot of concern, because we were not expecting to see a Warner-Lambert patent issued to the same subject matter -- we were not expecting any patent to be issued to the same subject matter (parenthetical added).

FR 374.

Where an assignee deliberately, with knowledge, passes over a disclosure, in favor of subsequent disclosures to work on, because the assignee found them to be more important, and where the assignee was spurred into filing because it became aware of an interfering patent, a classic case of suppression and concealment is made out. Young v. Dworkin, 180 USPQ 388 (CCPA 1974), Choi v. Godfrey, 212 USPQ 290. On similar facts, involving a similar

period of delay between invention date and filing date, and knowledge of entry by a third party into the field, suppression and concealment has consistently been found. Woofter v. Carlson, 151 USPQ 407 (CCPA 1966) cert. denied sub. nom., AMP, Inc. v. General Motors, Inc., 389 US 847 (1967), and Engelhardt v. Judd, 151 USPQ 732 (CCPA 1966). Note that this is not an ordinary case, such as Engelhardt, where the court observed that direct evidence of intention to suppress is difficult to find, and that intention must be inferred on the basis of delay. Wattanasin acknowledges, in its Brief, its deliberate intention to keep secret the Wattanasin application until after filing, repeatedly delayed even approval for filing, and once filing had been approved, repeatedly put the case aside in favor of later-docketed cases, and did not move expeditiously toward filing until after it became aware of the Warner-Lambert patent. Such is the measure of suppression and concealment.

To the extent Wattanasin reduced the invention to practice, the invention was deliberately, and with knowledge suppressed from public availability until Wattanasin and its real-party-in-interest were spurred into filing by the entry of a third party into the field, through issuance of the '419 Patent. Wattanasin suppressed and/or concealed its invention, and cannot be entitled to an award of priority.

3. THE TESTIMONY OF MELVYN KASSENOFF SHOULD BE DISCREDITED

Sandoz relies heavily on the testimony of Kassenoff to justify its delay of January-October 1988 in preparing a patent application with regard to the Wattanasin disclosure, relying on Kassenoff's testimony to indicate that the Sandoz Corporation always had an intention to file the application, pursued the application to the best of its ability, and did not otherwise suppress or conceal the invention. While Kassenoff's testimony may be used as an admission against Sandoz, supra, Fujikawa submits that the testimony relied upon by Sandoz must be heavily discounted, and is unreliable by reason of violation of 37 CFR § 10.63(a), which incorporates provisions of 37 CFR § 10.62(b).

When this Interference was declared, Diane Furman was designated Lead Counsel. Kassenoff was designated as counsel to go to in the absence of Furman. For all events in the Interference, Furman has not been absent. Accordingly, until submission of Kassenoff's testimony, in support of the Wattanasin position that it had not abandoned, suppressed or concealed the invention, Fujikawa and counsel had no reason to believe that Kassenoff was

involved, as counsel, in the Interference. Kassenoff's cross-examination was taken, along with that of other witnesses, including Wattanasin. During the Wattanasin cross-examination, Kassenoff attempted to ask a question, now not as a fact witness, but a lawyer. Counsel for Fujikawa indicated discomfort with the concept of a fact witness participating in the proceeding as a lawyer. FR 135. After cross-examination of Kassenoff, Kassenoff's name did not further appear in the Interference until the filing of the Wattanasin Record. Kassenoff's name does not appear, for example, as Of Counsel, or as Counsel, in any of the papers filed between Kassenoff's cross-examination and the filing of the Record, although numerous papers appear. Accordingly, Fujikawa had no knowledge that Kassenoff was continuing to participate as a lawyer on behalf of Wattanasin in this proceeding, until the Record was filed with Kassenoff's name as Of Counsel.

Fujikawa immediately objected to such presentation, urging that once it became clear that Kassenoff would have to testify with regard to abandonment, suppression or concealment, 37 CFR § 10.63(a) prohibited his further participation in the Interference as counsel. Wattanasin refused to agree to prevent Kassenoff from further activities on behalf of Wattanasin as counsel and accordingly, Fujikawa filed a Motion for Sanctions with respect

thereto, asking, inter alia that Kassenoff's testimony be heavily discounted. In the Decision of EIC, the issue of discounting Kassenoff's testimony, that is, giving it little or no weight, was deferred to final hearing. See page 3 of the decision on Motions dated June 23, 1993. Fujikawa respectfully submits that, having learned of the Fujikawa protest, having participated in the Interference as a fact witness, Kassenoff has no good reason to continue in the case as counsel, and no good reason has been established by any proper evidence. Accordingly, that testimony should be heavily discounted, as established by controlling precedent.

Kassenoff undertook very little work with respect to the Wattanasin invention, in fact, the only thing Kassenoff did was to request some information from Wattanasin. With respect to that, Kassenoff's testimony is admissible notwithstanding his participation as counsel, on the grounds that it goes only to the nature and value of his own work involved. With respect to this testimony, Fujikawa offers no argument. This testimony appears at WR 229-230.

In opposition to Fujikawa's Motion, Wattanasin urged that Kassenoff was essential to the Wattanasin effort in this Interference, and it would work a hardship to Sandoz to prevent his

further participation as counsel. No proof, or even offer of proof has been made by Wattanasin with regard to this point. Wattanasin has not identified any expertise offered by Kassenoff, nor any activity engaged in by Kassenoff, other than testifying, that could not have been undertaken by anybody within the Patent Department. Indeed, the Wattanasin Opposition to the Motion for Sanction, page 20, indicates that Kassenoff has not even been an active participant in the Interferences. Why then was it necessary to preserve his participation as counsel?

In any event, the giving of material testimony by an attorney, on behalf of his own client, is considered to be a breach of professional ethics, Weinsteins Evidence, Competency, §601[4](1993) and Waltzer v. Transidyne General Corp., 697 F.2nd 130, 134-135 (6th Cir. 1983).

Because such testimony cannot be prohibited, per se, as incompetent, the case law uniformly holds that such testimony should be heavily discounted. Universal Athletic Sales Co. v. American Gym, Recreational and Athletic Equipment Corp. Inc., 192 USPQ 193, 199 (3rd Cir. 1976) cert. denied, 193 USPQ 570 (1977), Lau Ah Tew v. Dulles, 257 F.2nd 744 (9th Cir. 1958), Wilder v. Snyder, 201 USPQ 927, 934 (POBI 1977) (The professional relationship of the witness effects his credibility). See also

Little Caesar Enterprises Inc., v. Dominoes Pizza, Inc., 11 USPQ 2nd 1233 (Comm. of Pat. 1989).

While Fujikawa urges that the activity testified to by Kassenoff, with respect to the intention of Sandoz to file a patent application, with respect to the backlog of cases in the Sandoz Patent Department, and its policies with respect to retaining outside counsel, are insufficient to avoid a holding of suppression or concealment, to the effect they are relied on at all, they must be heavily discounted.

V. PRECISE RELIEF REQUESTED

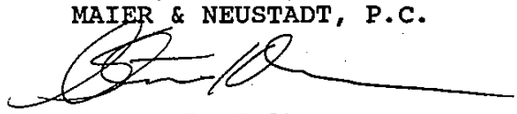
Fujikawa respectfully requests this Board hold:

A. The Decision of the EIC denying the Fujikawa Motion to add Counts 3 and 4 to Interference 102,648 as originally declared was in error, and those Counts should be added (it may be appropriate to add Count 4 to this Interference, and Count 3 to Interference 102,975, as the Counts pertain to process and product, respectively). As to those Counts, Fujikawa is entitled to priority.

B. Enter an award of priority adverse to Wattanasin. The Junior Party has not met its burden of proof in demonstrating a date of invention earlier than August 20, 1987, the uncontested Fujikawa date of invention.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.



Steven B. Kelber
Registration No.: 30,073
Attorney for the
Party Fujikawa et al

49-111-0

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

WATTANASIN	:	
	:	INTERFERENCE NO.: 102,648
V.	:	EXAMINER-IN-CHIEF:
FUJIKAWA ET AL	:	MICHAEL SOFOCLEOUS

SUBMISSION OF THE BRIEF AT FINAL HEARING FOR THE PARTY FUJIKAWA ET AL, 37 CFR § 1.656

HONORABLE COMMISSIONER OF PATENTS AND TRADEMARKS
WASHINGTON, D.C. 20231
BOX INTERFERENCE

SIR:

Pursuant to the provisions of the above-captioned rule, Fujikawa submits herewith its Brief at Final Hearing.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.

Steven B. Kelber
Registration No.: 30,073
Attorney for Fujikawa et al

CERTIFICATE OF SERVICE

I hereby certify that true copies of:

1. **SUBMISSION OF THE BRIEF AT FINAL HEARING FOR THE PARTY FUJIKAWA ET AL, 37 CFR § 1.656**

2. **FUJIKAWA OPPOSITION TO WATTANASIN'S PROPOSED FINDINGS OF FACT, 37 CFR 1.656(g)**

3. **FUJIKAWA ET AL MOTION TO SUPPRESS EVIDENCE,**

4. **CERTIFICATE OF SERVICE**

were served upon Counsel for Wattanasin as follows:

Diane E. Furman
SANDOZ CORP.
59 Route 10
E. Hanover, New Jersey 07936

via First Class Mail, postage prepaid, this 16th day of AUGUST, 1993.

STEVEN B. KELBER

Interference 102,648
Interference 102,975

#110

ERRATA SHEET FOR
BRIEF AT FINAL HEARING OF THE SENIOR PARTY
FUJIKAWA ET AL

PAGE NUMBER	LINE	CORRECTIONS TO BRIEF AT FINAL HEARING OF THE SENIOR PARTY FUJIKAWA ET AL
17	16-19	Change the formulations: $-CH(OHO-CH_2-CH(OH)-CH_2-COOH$ $-CH(OHO-CH_2-CH(OH)-CH_2-COONa$ $-CH(OHO-CH_2-CH(OH)-CH_2COO1/2Ca$ $-CH(OH-CH_2-CH(OH)-CH_2COOR,$ to: $-CH(OH)-CH_2-CH(OH)-CH_2-COOH$ $-CH(OH)-CH_2-CH(OH)-CH_2-COONa$ $-CH(OH)-CH_2-CH(OH)-CH_2COO1/2Ca$ $-CH(OH)-CH_2-CH(OH)-CH_2COOR,$
18	8	change "nine" to --eight--
20	22	after the last line on page 20, please insert the following text: --in the proposed Counts respectively, and, if the applications or--

#108

49-111-0

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

WATTANASIN	:	
	:	INTERFERENCE NO.: 102,648
V.	:	EXAMINER-IN-CHIEF:
FUJIKAWA ET AL	:	MICHAEL SOFOCLEOUS

FUJIKAWA OPPOSITION TO WATTANASIN'S PROPOSED FINDINGS OF FACT, 37 CFR § 1.656(g)

HONORABLE COMMISSIONER OF PATENTS AND TRADEMARKS
WASHINGTON, D.C. 20231
BOX INTERFERENCE

SIR:

Fujikawa hereby opposes the Wattanasin Proposed Findings of Fact. They are opposed on procedural and substantive grounds.

I. PROCEDURAL GROUNDS

37 CFR § 1.656(g) specifically requires that proposed findings of fact be supported by specific references to the Record. There is no reference to either the Wattanasin or Fujikawa Record in any

of the proposed findings of fact offered by Wattanasin. Neither Fujikawa or this Board, should be compelled to review the entire volume of the Record in this case to determine where, if any, support for the proposed findings of fact can be found.

It should be further noted that most of the "proposed findings of fact" are not factual findings at all, but rather proposed conclusions of law. For instance, proposed findings 1a and 1b propose that it be found that

> the junior party Wattanasin has established by a preponderance of the evidence conception and reduction to practice prior to the Fujikawa effective date.

Conclusions of conception and reduction to practice are conclusions of law, although the legal determinations are based on factual inquiries. Hybritech, Inc. v. Monoclonal Antibodies, Inc., 231 USPQ 81, 87 (Fed. Cir. 1986) cert. denied 480 US 947 (1987). It should be noted that if the Wattanasin proposals are to be considered proposed conclusions of law, rather than findings of fact, they are unsupported by citation to any authority of any type. 37 CFR § 1.656(g) specifically requires that "any proposed conclusions of law shall be supported by a citation of cases, statutes, or other authority". Wattanasin's failure to cite

portions of the Record, and failure to advance appropriate authority, precludes consideration of its proposed findings, whether they be conclusions of law or findings of fact.

The proposed finding of item 2, that Wattanasin "has clearly demonstrated diligence" and item 3, that "no abandonment of the invention by Wattanasin is indicated or proved" are similarly not findings of fact, but rather conclusions of law. The court in Brokaw v. Vogel, 166 USPQ 428, 431 (CCPA 1970) specifically rejected the proposal that questions of diligence and abandonment, suppression or concealment are fact findings. Clearly, these conclusions of law are unsupported by citation, and the proposed findings offered by Wattanasin must be rejected.

The sole "proposed finding of fact" that may be offered by Wattanasin is that at item 4. This proposed finding of fact refers to satisfaction of "the utility requirement of the Count". Fujikawa and undersigned counsel are uncertain as to what is meant by "the utility requirement of the Count". The Count for Interference 102,648 is directed to a method of administration. The Count for Interference 102,975 is directed to a compound. There is no clear law referring to "a utility requirement", and the finding is rejected on this ground. To the extent that Wattanasin is referring to the requirement that it be proven that the subject

matter prepared be demonstrated to have the intended utility before an actual reduction to practice can be found, this is dealt with below.

II. SUBSTANTIVE OPPOSITION

As noted above, items 1, 2 and 3 of the Wattanasin Proposed Findings of Fact are conclusions of law, not findings of fact. As such, and because they are unsupported by case citation, they should be disregarded out of hand. Nonetheless, they are opposed substantively as well. With regard to item 1(a), Fujikawa respectfully submits that the finding is incorrect because, inter alia, Wattanasin did clearly cease activity with respect to his invention in the period between May 17, 1985 and March, 1987. This matter is discussed in detail beginning at page 54 of the Fujikawa Brief. Specifically, the only activity conducted by Wattanasin with regard to the invention at issue was the manufacture of other compounds outside the Count of the Interference. Thus, to the extent that there was a reduction to practice of the Count by May 17, 1985, until March, 1987, no work was done with respect to the subject matter within the Count. At best, work was done on compounds alleged by the attorney to be "chemically analogous" to

the subject matter of the Count of the Interference, but in any event, not part of the Wattanasin application involved herein. To rely on such activity, the work performed must be described in the application involved in the Interference. Hoffman v. Schoenwald, 15 USPQ 2nd 1512 (BOPAI 1990), Ginos v. Nedlec, 220 USPQ 831, (POBA 1983). Since the work conducted by Wattanasin in the 22 months involved was entirely unrelated to the subject matter of the Wattanasin application involved herein, even if to "analogous compounds", this cannot be held to be diligence, or otherwise an excuse for the absence of other activity. Smith v. Crivello, 215 USPQ 446, 453 (POBI 1982).

Moreover, the Wattanasin proposal at 1a contains an inherent contradiction. The proposal does not require a finding of actual reduction to practice by May 17, 1985, but rather only conception. Questions of abandonment, suppression or concealment do not arise until an actual reduction to practice is made out. Peeler v. Miller, 190 USPQ 117 (CCPA 1976), Connin v. Andrews, 223 USPQ 243, 249 (POBI 1984). As the Wattanasin proposal is in fact a non sequitur, it cannot be adopted.

As item 1b, Wattanasin urges that it be found that the invention was reduced to practice on July 28, 1987 and July 29, 1987, on the basis of the respective dates of completion of

synthesis of two compounds within the scope of the Count. Although Wattanasin points to no portion of the Record to support this finding, which is in fact a legal conclusion, it is per se incorrect, and must be rejected. Wattanasin apparently is relying on the teachings in the art with respect to related compounds that establish activity for compounds having "similar" chemical structures as supporting the conclusion that testing is unnecessary to establish an actual reduction to practice. The law is expressly to the contrary, the court holding in Blicke v. Treves, 112 USPQ 472 (CCPA 1957) that while this may be possible in non-pharmacological utilities, in a case involving pharmacological utilities, there is no substitute for proof of activity in the compound actually synthesized. It should be further noted that the Wattanasin brief acknowledges Blicke as controlling law. Moreover, Wattanasin himself recognized that he was uncertain whether compounds within the scope of the Count would have activity, see WX A-2, WB 24. See also, FR 446 and FR 484, where the art recognizes that even small changes in structure may have a substantial impact on activity, and that related structures are not reliable as predictors of activity. The proposition at item 1b of the Wattanasin proposal must be rejected.

The proposal at item 2 is irrelevant, even it were a proposed

finding of fact. Specifically, Wattanasin urges this Board conclude that Wattanasin demonstrated diligence from the time prior to the Fujikawa filing date of August 20, 1987 until "such testing and reductions to practice" were completed by Wattanasin. Since Wattanasin does not identify what the reductions to practice are, the proposal is irrelevant. If Wattanasin is relying on the constructive reduction to practice of filing of March 3, 1989, there is abundant absence of diligence. This is discussed at length in Fujikawa's Brief, beginning on page 59, section III 2 D of the Fujikawa Brief. The arguments presented therein are incorporated here by reference, and will not be duplicated to avoid further burdening the Record.

The proposal at item 3, that there was no abandonment of the invention by Wattanasin because of apparent delay between 1987 alleged reductions to practice and the Wattanasin application filing is again incompetent, because it does not refer to the specific reductions to practice considered. If the reductions to practice are after August 20, 1987, they are irrelevant with respect to item 3, as there is no assertion with respect to conception, and this would leave Fujikawa as first to conceive and first to reduce to practice. Abandonment by Wattanasin in this case would be irrelevant. In any event, Fujikawa has argued

throughout this Interference that Wattanasin, rather than abandoning the invention, deliberately suppressed or concealed it. This in fact appears to be admitted to in the Wattanasin Brief, WB 56. See also WR 305. This suppression or concealment persisted from the earliest work on the invention in 1985 until filing in 1989, and was done so deliberately, the invention being made into the form of a patent application, and subsequently published, only due to the Sandoz recognition that a third party had secured a patent on this same subject matter. Absence of abandonment is irrelevant, if the invention has been concealed or suppressed. The proposal at item 3 is irrelevant and should be rejected.

At item 4, Wattanasin urges this Board adopt findings that Wattanasin in vitro and in vivo testing meet the utility requirement of the Count. Fujikawa is uncertain as to what this "utility requirement" is, and so will disregard these propositions. To the extent that items 4a-4c are intended to urge this Board that the Wattanasin in vitro and in vivo assays are sufficient to demonstrate an actual reduction to practice, they are rejected. This is discussed in detail in the Fujikawa Brief, beginning on page 30. With respect to the in vitro assays, it was the testimony of Dr. Holmlund, an expert in the field, that the in vitro testing conducted by Scallen is not adequate to demonstrate that the

compounds tested will perform their intended function, cholesterol biosynthesis under conditions of use, that is, when administered to a patient in need of same. Note that this is the requirement for proof of actual reduction to practice, Bigham v. Godtfredson, 222 USPQ 632, 637 (POBA 1984). Holmlund concluded that the testing indicated that the compounds in question might be active in vivo, and might not be as well. FR 184-185. At FR 223-224, Holmlund testified that even if Scallen had first hand experience with in vivo activity of the compounds in question, the in vitro activity would not indicate activity in vivo, but rather, left a reasonable element of doubt as to that in vivo activity. This is confirmed by the references establishing the state-of-the-art, including those by Kathawala, the chief Sandoz researcher and Wattanasin's boss, see, e.g., FR 486-487. Clearly, the in vitro testing was inadequate to demonstrate the compounds in question will work in a patient in need of cholesterol biosynthesis inhibition.

The in vivo testing conducted by Dr. Engstrom is similarly ineffective to demonstrate utility for the compounds. In fact, according to the criteria established by Dr. Engstrom himself, there was no reliable evidence of activity in vivo, that is, evidence that Dr. Engstrom himself considered to statistically significant to demonstrate anything other than a zero control

level. Note that the ED_{50} values assigned by Dr. Engstrom are meaningless, and/or unreliable. FR 193-194 and 196-197. Moreover, the in vivo testing of Engstrom demonstrated that the in vitro testing of Scallen was not reliable, FR 196-197. Again, in cross-examination, FR 206, Holmlund reiterated that the testing did not indicate a statistically significant level of activity. All that could be inferred from the data was that the compounds may have significant activity at a higher level, not that they did have. FR 209. This is not the measure of an actual reduction to practice, or a demonstration that the compounds would have the activity in question. The Wattanasin proposal 4c must be rejected.

In view of the foregoing, it is respectfully submitted that the "Proposed Findings of Fact" offered by Wattanasin herein not be adopted.

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FUJIKAWA ET AL MOTION TO SUPPRESS EVIDENCE,
37 CFR § 1.656(h)

RECEIVED
AUG 16 1993
BOARD OF PATENT APPEALS
AND INTERFERENCES

HONORABLE COMMISSIONER OF PATENTS AND TRADEMARKS
WASHINGTON, D.C. 20231
BOX INTERFERENCE

SIR:

Pursuant to the provisions of the above-captioned rule, Fujikawa hereby moves to suppress the Declaration of Robert G. Engstrom pursuant to 37 CFR § 1.672, WR 203-206, and the Supplemental Declaration of Robert G. Engstrom pursuant to 37 CFR § 1.672, WR 207-208. The grounds for suppression are set forth in detail below, the objections having been raised and made of record at FR 192-193 and FR 199, respectively.

"RIBBON COPY FOR PARTY" Fujikawa et. al.

I. Engstrom Declaration at WR 203-206

Fujikawa objects to, and moves to suppress, the Engstrom Declaration at 204-206 on the grounds that it is inadmissible in violation of Federal Rule of Evidence 901(b)(9) and Federal Rule of Evidence 1006. The Declaration relies on and discusses Exhibit K-1, which is admittedly a computer-generated summary, prepared according to a processor system under Federal Rule of Evidence 901(b)(9), and is a summary or calculation, Rule 1006. It is to be noted that the Federal Rules of Evidence control, 37 CFR § 1.671(b).

It should be noted that the Engstrom Declaration acknowledges that Exhibit K-1, on which it extensively relies, constitute computer printouts of the protocol and results of specific nCi/dl studies, that is, <u>in vivo</u> assays. Moreover, on page 205, paragraph 7, the Engstrom Declaration acknowledges that the first page of Exhibit K-1 was obtained by feeding data obtained from one computer program into a second computer program. Thus, the data reflected on the first page of Exhibit K-1, WR 206, constitute the results of not one but two computer manipulations. The remaining data was clearly obtained by feeding data, not produced, through a computer program. WR 210, paragraph 2, the Declaration of Rodney Slaughter. Evidence of this type, that is, evidence obtained by computer

manipulation, is not admissible, unless and until sufficient evidence to assess the accuracy of the computer output is provided. Pritchard v. Liggett and Myers Tobacco Company, 295 F.2d 292, 301 (3d Cir. 1961). To the same effect, see Standard Oil of California v. Moore, 251 F.2d 188, 223 (9th Cir. 1957) cert. denied 356 US 975. Specifically, sufficient evidence must be provided to support a conclusion that the output from the computer program is accurate. Weinstein's Evidence, § 901(b)(9)[02], page 901-133 (1993 supplement). See also Transport Indemnity Company v. Seib, 178 Neb. 253, 132 NW 2d 871 (S.Ct. 1965). Thus, testimony must be offered not only as to the data on which the computer manipulation is based, but the reliability of the computer manipulation itself. As neither testimony was offered, the computer calculation is itself inadmissible. No reliable measured data satisfying a reasonable interrelation between the dosage and the activities (pharmacological activities) are given -- the pharmacological activities are not proven [NS=Not Significant (Exhibit K, p. 336, 338-339)]. In vivo values (ED_{50}) were calculated direclty by a computer. While it is possible that the computer used by Engstrom was programmed properly and operated in a manner giving rise to reliable results, simply no evidence with respect to that has been offered. Indeed, there is not even any evidence that computer

programming of this type was done on a routine basis, or that these records were generated in the ordinary course of business.

It should be further noted that this is not a case where the type of data involved would be so voluminous as to be impractical to be presented without the aid of computer or similar manipulation. The data is limited, and the raw data on which the statistical manipulation was performed, as well as the manner of manipulation, could easily have been presented. Simply, Wattanasin elected to present neither the program, nor the raw data, nor any information with respect to either which would provide the Board a reasonable assurance that the data reflected in Exhibit K-1 and discussed throughout the Engstrom Declaration was valid.

Paragraph 1 of the Engstrom Declaration is not objectionable on this ground.

Fujikawa also submits that the Engstrom Declaration is objectionable under Federal Rule of Evidence 1006, which provides the conditions under which summaries or calculations, and Exhibit K-1 and the Engstrom Declaration are certainly that, can be made admissible. Specifically, the Rule provides, without discretion, that the underlying data on which the summary or calculation is based must be made available for examination or copying prior to admission. U.S. v. Kim, 595 F.2d 755, 764 (DC.Ct. 1979). It

should be noted that this production of the original and underlying data is a requirement independent of any discovery that might have been exercised by Fujikawa et al herein. Weinstein's Evidence, § 1006 (04) (1993 Supplement). In other words, the burden was on Wattanasin to come forward with the original data, particularly in light of the Fujikawa objection on that basis. No data having been offered, or otherwise made available, and no other safeguard as to accuracy being provided, the Engstrom Declaration, and the basis thereof, Exhibit K-1 must be suppressed.

II. Supplemental Declaration

Fujikawa objects to the Supplemental Declaration of Robert G. Engstrom, WR 207-208, and Exhibit Q discussed therein, on all the grounds set forth above, and additional grounds as well. The grounds set forth above, specifically FRE 901(b)(9) and FRE 1006 are clearly applicable. Exhibit Q is acknowledged as a computer printout, and is clearly a summary of data based on calculations made by computer. Thus, Exhibit Q, and the Declaration which is dedicated thereto, are clearly inadmissible.

Moreover, the Supplemental Declaration of Robert G. Engstrom was not submitted during the testimony period provided for Wattanasin to introduce testimony in its case in chief. Rather,

this testimony was provided during the supplemental testimony period, which was provided for Wattanasin to introduce testimony with regard to abandonment, suppression or concealment. Clearly, the Engstrom Declaration does not go to issues of abandonment, suppression or concealment, but rather issues of actual reduction to practice, a priority issue, which should have been submitted in the original period. Wattanasin offers no explanation or qualification as to why the Supplemental Declaration could not have been submitted earlier, and accordingly, the Declaration was submitted in untimely fashion, and must be suppressed.

Moreover, the Supplemental Declaration not only confirms the lack of reliability of the original Declaration of Engstrom, but calls into question the entire computer program relied upon. Specifically, the Engstrom Declaration represents

> I note that I became aware of a computer entry error comprising the inadvertent switching of the ED_{50} data for compounds 64-933 and 64-935. The corrections in the printout are in my handwriting and would have been made on or about May 23, 1988 (Emphasis added).

How did Engstrom become aware of the computer entry error, and what

was the nature of the error? What other errors occurred, and how were they corrected? How did the "switching" referred to occur, and how did Engstrom determine that an error was present? Finally, if Engstrom was aware of the error, and made the corrections on or about May 23, 1988, how is it that his original Declaration dated November 13, 1992 did not include this correction? It is respectfully submitted that FRE 901(b)(9) and 1006 are in place specifically because of the type of questions raised above by the Supplemental Declaration. All the Supplemental Declaration does is establish that the computer programming or computer programmer responsible for the generation of Exhibits K-1 and Q was unreliable, and that absent original raw data, not presented anywhere in the Record, the Declarations are simply inadmissible. Note that more than just the numbers "933" and "935" were switched as summarized in the following table.

ED_{50} (mg/kg)			
	ORIGINAL DECLARATION		SUPPLEMENTAL DECLARATION
COMPOUND	(p 110)	K1 (p 340)	(p 418, 422)
64-933	0.49	> 1.0	2.40
64-935	> 1.0	0.49	0.49
64-936	> 1.0	> 1.0	> 1.0

The Supplemental Declaration of Robert G. Engstrom demonstrates that the original Declaration is unreliable, and is itself unreliable, in raising more questions than it answers, as both Declarations, and Exhibits K-1 and Q violate the provisions of not one, but two Federal Rules of Evidence, Fujikawa respectfully submits that these Declarations should be suppressed.

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

WATTANASIN	:	
	:	INTERFERENCE NO.: 102,648
V.	:	EXAMINER-IN-CHIEF:
FUJIKAWA ET AL	:	MICHAEL SOFOCLEOUS

FUJIKAWA ET AL MOTION TO SUPPRESS EVIDENCE,
37 CFR § 1.656(h)

HONORABLE COMMISSIONER OF PATENTS AND TRADEMARKS
WASHINGTON, D.C. 20231
BOX INTERFERENCE

SIR:

Pursuant to the provisions of the above-captioned rule, Fujikawa hereby moves to suppress the Declaration of Robert G. Engstrom pursuant to 37 CFR § 1.672, WR 203-206, and the Supplemental Declaration of Robert G. Engstrom pursuant to 37 CFR § 1.672, WR 207-208. The grounds for suppression are set forth in detail below, the objections having been raised and made of record at FR 192-193 and FR 199, respectively.

I. Engstrom Declaration at WR 203-206

Fujikawa objects to, and moves to suppress, the Engstrom Declaration at 204-206 on the grounds that it is inadmissible in violation of Federal Rule of Evidence 901(b)(9) and Federal Rule of Evidence 1006. The Declaration relies on and discusses Exhibit K-1, which is admittedly a computer-generated summary, prepared according to a processor system under Federal Rule of Evidence 901(b)(9), and is a summary or calculation, Rule 1006. It is to be noted that the Federal Rules of Evidence control, 37 CFR § 1.671(b).

It should be noted that the Engstrom Declaration acknowledges that Exhibit K-1, on which it extensively relies, constitute computer printouts of the protocol and results of specific nCi/dl studies, that is, in vivo assays. Moreover, on page 205, paragraph 7, the Engstrom Declaration acknowledges that the first page of Exhibit K-1 was obtained by feeding data obtained from one computer program into a second computer program. Thus, the data reflected on the first page of Exhibit K-1, WR 206, constitute the results of not one but two computer manipulations. The remaining data was clearly obtained by feeding data, not produced, through a computer program. WR 210, paragraph 2, the Declaration of Rodney Slaughter. Evidence of this type, that is, evidence obtained by computer

manipulation, is not admissible, unless and until sufficient evidence to assess the accuracy of the computer output is provided. Pritchard v. Liggett and Myers Tobacco Company, 295 F.2d 292, 301 (3d Cir. 1961). To the same effect, see Standard Oil of California v. Moore, 251 F.2d 188, 223 (9th Cir. 1957) cert. denied 356 US 975. Specifically, sufficient evidence must be provided to support a conclusion that the output from the computer program is accurate. Weinstein's Evidence, § 901(b)(9)[02], page 901-133 (1993 supplement). See also Transport Indemnity Company v. Seib, 178 Neb. 253, 132 NW 2d 871 (S.Ct. 1965). Thus, testimony must be offered not only as to the data on which the computer manipulation is based, but the reliability of the computer manipulation itself. As neither testimony was offered, the computer calculation is itself inadmissible. No reliable measured data satisfying a reasonable interrelation between the dosage and the activities (pharmacological activities) are given -- the pharmacological activities are not proven [NS=Not Significant (Exhibit K, p. 336, 338-339)]. In vivo values (ED_{50}) were calculated direclty by a computer. While it is possible that the computer used by Engstrom was programmed properly and operated in a manner giving rise to reliable results, simply no evidence with respect to that has been offered. Indeed, there is not even any evidence that computer

programming of this type was done on a routine basis, or that these records were generated in the ordinary course of business.

It should be further noted that this is not a case where the type of data involved would be so voluminous as to be impractical to be presented without the aid of computer or similar manipulation. The data is limited, and the raw data on which the statistical manipulation was performed, as well as the manner of manipulation, could easily have been presented. Simply, Wattanasin elected to present neither the program, nor the raw data, nor any information with respect to either which would provide the Board a reasonable assurance that the data reflected in Exhibit K-1 and discussed throughout the Engstrom Declaration was valid.

Paragraph 1 of the Engstrom Declaration is not objectionable on this ground.

Fujikawa also submits that the Engstrom Declaration is objectionable under Federal Rule of Evidence 1006, which provides the conditions under which summaries or calculations, and Exhibit K-1 and the Engstrom Declaration are certainly that, can be made admissible. Specifically, the Rule provides, without discretion, that the underlying data on which the summary or calculation is based must be made available for examination or copying prior to admission. U.S. v. Kim, 595 F.2d 755, 764 (DC.Ct. 1979). It

should be noted that this production of the original and underlying data is a requirement independent of any discovery that might have been exercised by Fujikawa et al herein. Weinstein's Evidence, § 1006 (04) (1993 Supplement). In other words, the burden was on Wattanasin to come forward with the original data, particularly in light of the Fujikawa objection on that basis. No data having been offered, or otherwise made available, and no other safeguard as to accuracy being provided, the Engstrom Declaration, and the basis thereof, Exhibit K-1 must be suppressed.

II. Supplemental Declaration

Fujikawa objects to the Supplemental Declaration of Robert G. Engstrom, WR 207-208, and Exhibit Q discussed therein, on all the grounds set forth above, and additional grounds as well. The grounds set forth above, specifically FRE 901(b)(9) and FRE 1006 are clearly applicable. Exhibit Q is acknowledged as a computer printout, and is clearly a summary of data based on calculations made by computer. Thus, Exhibit Q, and the Declaration which is dedicated thereto, are clearly inadmissible.

Moreover, the Supplemental Declaration of Robert G. Engstrom was not submitted during the testimony period provided for Wattanasin to introduce testimony in its case in chief. Rather,

this testimony was provided during the supplemental testimony period, which was provided for Wattanasin to introduce testimony with regard to abandonment, suppression or concealment. Clearly, the Engstrom Declaration does not go to issues of abandonment, suppression or concealment, but rather issues of actual reduction to practice, a priority issue, which should have been submitted in the original period. Wattanasin offers no explanation or qualification as to why the Supplemental Declaration could not have been submitted earlier, and accordingly, the Declaration was submitted in untimely fashion, and must be suppressed.

Moreover, the Supplemental Declaration not only confirms the lack of reliability of the original Declaration of Engstrom, but calls into question the entire computer program relied upon. Specifically, the Engstrom Declaration represents

> I note that I became aware of a computer entry error comprising the inadvertent switching of the ED_{50} data for compounds 64-933 and 64-935. The corrections in the printout are in my handwriting and would have been made on or about May 23, 1988 (Emphasis added).

How did Engstrom become aware of the computer entry error, and what

was the nature of the error? What other errors occurred, and how were they corrected? How did the "switching" referred to occur, and how did Engstrom determine that an error was present? Finally, if Engstrom was aware of the error, and made the corrections on or about May 23, 1988, how is it that his original Declaration dated November 13, 1992 did not include this correction? It is respectfully submitted that FRE 901(b)(9) and 1006 are in place specifically because of the type of questions raised above by the Supplemental Declaration. All the Supplemental Declaration does is establish that the computer programming or computer programmer responsible for the generation of Exhibits K-1 and Q was unreliable, and that absent original raw data, not presented anywhere in the Record, the Declarations are simply inadmissible. Note that more than just the numbers "933" and "935" were switched as summarized in the following table.

ED_{50} (mg/kg)			
	ORIGINAL DECLARATION		SUPPLEMENTAL DECLARATION
COMPOUND	(p 110)	K1 (p 340)	(p 418, 422)
64-933	0.49	> 1.0	2.40
64-935	> 1.0	0.49	0.49
64-936	> 1.0	> 1.0	> 1.0

The Supplemental Declaration of Robert G. Engstrom demonstrates that the original Declaration is unreliable, and is itself unreliable, in raising more questions than it answers, as both Declarations, and Exhibits K-1 and Q violate the provisions of not one, but two Federal Rules of Evidence, Fujikawa respectfully submits that these Declarations should be suppressed.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.

Steven B. Kelber
Registration No.: 30,073
Attorney for Fujikawa et al

#110

49-111-0

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

WATTANASIN	:	
	:	INTERFERENCE NO.: 102,648
V.	:	EXAMINER-IN-CHIEF:
FUJIKAWA ET AL	:	MICHAEL SOFOCLEOUS

**FUJIKAWA ET AL'S
SUBMISSION OF ERRATA SHEET FOR
BRIEF AT FINAL HEARING
AND
OPPOSITION TO WATTANASIN'S PROPOSED
FINDINGS OF FACT, 37 CFR §1.656(g)**

HONORABLE COMMISSIONER OF PATENTS AND TRADEMARKS
WASHINGTON, D.C. 20231
BOX INTERFERENCE

SIR:

Fujikawa et al submits errata sheets for the Brief at Final Hearing and Opposition to Wattanasin's Proposed Findings of Fact, 37 CFR §1.656(g) filed at the Board of Patent Appeals and Interferences on August 16, 1993 in the above-captioned Interference. The corrections are all of a typographical nature. Fujikawa regrets any inconvenience these errors may have caused the Board and Counsel for the Party Wattanasin.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.

Steven B. Kelber
Registration No.: 30,073
Attorney for Fujikawa et al

CERTIFICATE OF SERVICE

I hereby certify that true copies of:

1. **FUJIKAWA ET AL'S SUBMISSION OF ERRATA SHEET FOR BRIEF AT FINAL HEARING AND OPPOSITION TO WATTANASIN'S PROPOSED FINDINGS OF FACT, 37 CFR §1.656(g)**

2. **CERTIFICATE OF SERVICE**

were served upon Counsel for Wattanasin as follows:

Diane E. Furman
SANDOZ CORP.
59 Route 10
E. Hanover, New Jersey 07936

via FEDERAL EXPRESS, this 7TH day of SEPTEMBER, 1993.

STEVEN B. KELBER

Interference 102,648
Interference 102,975

#111

49-111-0

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

WATTANASIN	:	
	:	INTERFERENCE NO.: 102,648
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STEVEN B. KELBER

Interference 102,648
Interference 102,975

#111

ERRATA SHEET FOR
FUJIKAWA OPPOSITION TO WATTANASIN'S PROPOSED
FINDINGS OF FACT, 37 CFR §1.656(g)

PAGE NUMBER	LINE	CORRECTIONS TO FUJIKAWA OPPOSITION TO WATTANASIN'S PROPOSED FINDINGS OF FACT, 37 CFR §1.656(g)
4	13	Change "54" to --55--
7	9	Change "59" to --60--

#111

ERRATA SHEET FOR
FUJIKAWA OPPOSITION TO WATTANASIN'S PROPOSED
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4	13	Change "54" to --55--
7	9	Change "59" to --60--

#112

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

FYI

SEP 13 1993

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BOX INTERFERENCE

WATTANASIN v. FUJIKAWA ET AL.

INTERFERENCE NO. 102,648

REPLY BRIEF OF THE PARTY, WATTANASIN

FOR FINAL HEARING

Diane E. Furman
Sandoz Corporation
Patent and Trademark Department
Building 418
59 Route 10
E. Hanover, NJ 07936-1080
(201) 503-7332
Attorney for the party WATTANASIN

Of Counsel
Richard E. Vila
Melvyn M. Kassenoff
Sandoz Corporation
Patent and Trademark Department
Building 418
59 Route 10
E. Hanover, NJ 07936-1080
(201) 503-7852

September 4, 1993

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

WATTANASIN v. Fujikawa et al.

Interference No. 102,648

REPLY BRIEF OF THE PARTY, WATTANASIN FOR FINAL HEARING

TABLE OF CONTENTS

I. TABLE OF CASES

A. THE STANDARD OF PROOF OF PRIORITY APPLICABLE TO WATTANASIN IS "PREPONDERANCE OF THE EVIDENCE"

Lacking any apparent basis in the decisional law of this Board or any patent court, Fujikawa et al. advance an argument that the Wattanasin proof of priority in this interference must satisfy not a "preponderance of the evidence" standard, as stated in the Wattanasin opening briefs (at p. 12), but a higher standard of "clear and convincing evidence".

Like some of the other arguments raised by Fujikawa, this is at best viewed as a distraction, since it is clearly counter to the longstanding rule of Peeler v. Miller, 190 USPQ 117 (CCPA 1976), that "preponderance of the evidence" is the applicable standard of proof of priority required of a junior party whose involved subject matter was copending with the senior party's application. This standard applies even where, as in Peeler v. Miller itself, the senior party's application matures into a patent prior to the interference.

Nor are Fujikawa helped at all by the recent Federal Circuit decision of Price v. Symsek, 26 USPQ2d 1031 (Fed. Cir. 1993), clarifying that the "clear and convincing" standard applied in a situation where there was no copendency of interfering subject matter.

In effect, by requesting that Wattanasin be held to the higher standard of "clear and convincing evidence," Fujikawa are trying to succeed to the position of the defaulting party, Warner-Lambert, in these interferences.

The parties' respective application files reflect

that each of Fujikawa and Wattanasin had requested the Patent and Trademark Office to declare an interference with Warner-Lambert U.S. Patent No. 4,761,419 (Picard et al.), which was filed on December 7, 1987 and issued August 2, 1988.

But as soon as Interference No. 102,648 was declared as a three-way interference, Warner-Lambert requested entry of adverse judgment as to themselves. Accordingly, on April 10, 1992, such adverse judgment was entered against the Picard et al. patent, and in fact the Picard name has been stricken from the Patent and Trademark Office docket sheet for Int. No. 102,648. It is noted that Picard et al. were completely out of this interfeence before any matters, such as discovery and testimony which require a burden of proof were scheduled to take place.

Now, however, having been freed of the Warner-Lambert threat, Fujikawa want to improve their position further by stepping into Warner-Lambert's shoes vis-a-vis Wattanasin; and applying the higher burden of proof of "clear and convincing evidence" to Wattanasin.

There is also no small irony in Fujikawa's additionally relying on their '930 patent[1] -- which to the extent of claim 1 thereof is involved in Interference No. 102,975 (indeed, on Wattanasin's motion) -- to bootstrap an argument that Wattanasin be held to the higher standard of proof. Even aside from the fact that the '930 patent is only a divisional off the involved copending Fujikawa application, it is at least questionable that the involved claim 1 should ever have

1. U.S. Patent No. 5,011,930, filed February 23, 1990 and issued April 30, 1991.

been allowed by Fujikawa to issue in the first place; and in fact it has been Wattanasin's understanding that Fujikawa were taking this patent into reissue precisely for this reason.[2]

In sum, Fujikawa should not be permitted to step into the shoes of Warner-Lambert in these interferences as a matter of law or policy.

Finally, notwithstanding whether the applicable standard is "a preponderance of the evidence" or "clear and convincing evidence," Wattanasin has by its proofs clearly shown priority in relation to Fujikawa.

B. REVIEW OF FUJIKAWA ARGUMENT

For purposes of these interferences, Fujikawa stand on their earliest Japanese priority date of August 20, 1987 as a constructive reduction to practice of the subject matter of the counts of these interferences.

By way of review, count 3 of Interference No. 102,648 is a compound per se count which recites no utility at all. Count 1 of Interference No. 102,975 is a method of treatment count in which the subject compounds are administered to "a patient" in need of

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2. Said claim was introduced into the divisional application by amendment on July 17, 1990, and is directed to subject matter never even restricted out from the involved Fujikawa parent application. Claim 1 was thereafter allowed to issue out even though it fell squarely within the count proposed by Fujikawa for their interference with the Warner-Lambert patent requested nearly a year before. Note further that Fujikawa chose to direct claim 1 to a subgenus of quinoline compounds comprising both isopropyl and cyclopropyl-substituted species of the count.

such treatment in a pharmaceutical composition.

The essence of Fujikawa's argument seems to be that Wattanasin's in vitro testing of record is insufficient to prove a reduction to practice either of count 3, the compound per se count, or count 1, the method of treatment count; that in vivo testing is needed therefor, but that Wattanasin's in vivo testing is either inadequate for technical reasons or because it was performed on rats.[3] Thus, The Fujikawa view of the situation appears to be that none of Wattanasin's 1984, 1985 or 1987 in vitro testing, or the 1987 Wattanasin in vivo testing, demonstrate a reduction to practice. Fujikawa also present other arguments going to diligence, or the issue of abandonment, suppression or concealment.

C. SUMMARY OF THE WATTANASIN POSITION

Wattanasin respectully disagrees with each and every one of the Fujikawa arguments presented in their briefs.

It is Wattanasin's position that it reduced to practice the subject matter of the counts on each of the

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3. In fact, Fujikawa have moved to have the Engstrom declaration and raw in vivo data stricken from the record, on a technical rationale which is not entirely clear to Wattanasin. Wattanasin is opposing this motion in a paper being filed concurrently herewith. Although Wattanasin concedes that the Engstrom declaration contains a typographical error (later corrected), Fujikawa's confusion may be difficult to accommodate, particularly since Fujikawa chose not to take cross-examination of Dr. Engstrom, a Sandoz employee, even while their counsel spent a day at the Sandoz site in East Hanover, New Jersey, deposing three other Sandoz declarants.

in vitro testing dates of record herein; and that a further reduction to practice comprising both in vitro and in vivo testing occurred in October 1987, coupled with diligence from just prior to the August 20, 1987 Fujikawa benefit date. No inference of abandonment, suppression or concealment can be reached during the period from the last activities for the count, on December 9, 1987 up to the filing of the Wattanasin application on March 3, 1989, a period of 14 months, given the oustanding obligation to file, and the attorney activities which took place during that time period. Nor, for that matter was there abandonment during the mid-1985 to 1987 time period, when for reasons of a manpower shortage, Wattanasin needed to direct his laboratory work to analogous HMG-CoA reductase inhibitor compounds.

A significant part of Fujikawa's arguments are directed to Wattanasin's in vitro and in vivo testing results, and accordingly this data are further discussed in greater detail below.

All of the Wattanasin compounds under consideration are within the count of this interference, and Fujikawa have not argued otherwise. Nor has Fujikawa at all raised an issue concerning corroboration of the invention nor the admissibility of any document of record, with the exception of the Engstrom Declaration and Supplemental Declaration and accompanying Exhibits K-1 and Q.

D. THE WATTANASIN IN VITRO TESTING SATISFIES THE REQUIREMENTS OF AN ACTUAL REDUCTION TO PRACTICE OF COUNT 3 OF INTERFERENCE NO. 102,648 and COUNT 1 OF INTERFERENCE NO. 102,975

Based on the Kathawala article of record and the

affidavit testimony of Kathawala, Wattanasin, Scallen, Damon, it is apparent that from the beginning of his involvement with the quinoline compounds in late 1983, Wattanasin was working in a well-trodden scientific field, i.e. HMG-CoA reductase inhibitor compounds, a field which in fact is now nearly three decades old (Kathawala article, WR at 470-495). By the time Dr. Wattanasin had turned his attention to the quinolines, not only were HMG-CoA reductase inhibitor compounds such as compactin or mevinolin on market and available as standards against which to test the activity of the Wattanasin compounds; but the Sandoz compound XU 62-320 ("fluvastatin") became known as an even more potent standard against which candidate compounds could be tested[4]. Indeed, by 1982, when Sandoz filed on its fluvastatin compound (see WX-Z at 471), Sandoz had possession of a compound which was 146 times more active than compactin in vitro and 40-fold more active than compactin in vivo (WR at 482, 485).

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4. Wattanasin Exhibit Z (p. 471) shows that Kathawala filed his U.S. patent application covering the Sndoz fluvastatin compound (i.e. XU 63-320) on November 22, 1982. It is clear from the cover page of the Kathawala patent as well as the other filings made by Sandoz, that these patents disclose compounds for inhibiting cholesterol biosynthesis, pharmaceutical compositions containing such compounds, and methods of treatment of hypercholesteremia using said compounds.

Note that the European equivalent of the Kathawala fluvastatin application, i.e. EP 114,027 became available to the art in June 1984, and was even cited as prior art against the involved Fujikawa application. Thus in the Fujikawa '930 patent file the EPO search report cites the Kathawala patent publication on fluvastatin as "technological background" to the subject matter of the counts herein. Therefore by no later than June 1984, "technological background" concerning the specific Sandoz HMG-CoA reductase inhibitor compounds, compositions containing them and methods of treatment, was clearly available to one of ordinary skill in the art.

It is a matter of common knowledge that one objective of pharmaceutical research in an already developed field, such as conducted by Dr. Wattanasin herein, is not merely to meet the activity of a known standard such as compactin or fluvastatin, but to meet it and also exceed it. However, this is a different standard from that needed to demonstrate a reduction to practice of a species within a count of an interference, i.e. a practical utility.

As outlined in the Wattanasin opening briefs at page 18 et seq., Terence Scallen, M.D., Ph.D., of the Department of Biochemistry at the University of New Mexico, testified concerning the in vitro testing of compounds for HMG-CoA reductase inhibition which he carried out for Sandoz since 1980 (WR at 187). Dr. Scallen testified that he used an "established protocol" based on published methods dating from 1977 (WR at 188-189) to test the activity of compounds of the count. The in vitro testing involved the use of rat liver microsomes as the source of HMG-CoA reductase enzyme to treat radiolabeled HMG-CoA, i.e. the substrate of HMG-CoA reductase, in the presence of test compound. The amount of radiolabeled mevalonate, which is the product of the reaction of HMG-CoA reductase and its substrate, HMG-CoA, indicated the relative potency of the test inhibitor compound at a given concentration (WR at 189)[5]

The raw data generated by Dr. Scallen in Wattanasin Exhibits E-1 to E-5 shows the activity level of each tested compound at different concentrations.

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5. In Cross v. Iizuka (discussed below), a microsomal system was also used to test compounds in vitro alongisde known standards, see 224 USPQ at 744.

Fujikawa's rebuttal witness, Dr. Holmlund, indicated that a similar in vitro assay on compactin had been performed in his lab:

> Q. Was that [assay] fairly consistent with the in vitro assay presented in the [Wattanasin] exhibits?
> A. Yes.

FR at 231

Based on this assay, Dr. Holmlund himself verified that compactin, used as a standard in the Scallen assays, "functioned as a competitive inhibitor" of HMG-CoA reductase enzyme (FR at 231).

With this basic art-recognized assay, Dr. Scallen tested "numerous" Sandoz compounds for the same HMG-CoA reductase inhibition activity, which differed only by having a different organic radical substituent instead of quinoline (e.g., napthyl, indole, etc.) on the dihydroxy heptenoic acid side chain. A glance at Wattanasin Exhibit E-5, for example, reflects testing of 36 compounds for HMG-CoA reductase activity in the period from December 4-17, 1984; 32 compounds in the period from June 13-26, 1985; 9 compounds on October 8, 1987; and 7 compounds on October 13, 1987.

What is most important is that every one of these in vitro assays was done not only against standard controls, but also side-by-side with the industry standard, compactin (WR at 472). Most of the assays were also carried out with side-by-side testing of the known Sandoz HMG-CoA reductase inhibitor, fluvastatin (62-320) (WR at 482, 488-89).

This concerted in vitro testing program documented by Wattanasin is consistent with the kinds of established large-scale testing of compounds typically carried out by pharmaceutical research houses, for example by the junior party, Pfizer, as described in Bigham v. Godtfredsen, infra.

It is obvious from the IC_{50} data in the Damon declaration (WR 199, WX J-1) that all of the Wattanasin compounds were active in vitro, even if some were not as potent as compactin or fluvastatin against which they were tested.

The knowledge of the activities of the first group of tested compounds 63-366, 63-548 and 63-549 was enough to tell Wattanasin that the other compounds would be active. That is the reason why Wattanasin had the certainty that if the initial compounds had activity, he would want to make all of them. This is particularly true since the compound having greatest structural similarity to the highly active fluvastatin compound, i.e. compound 64-935, while the earliest conceived (WX A-2), remained to be synthesized in the "second phase" of activity begun in March 1987. Compound 64-935 on testing did prove to be the most active of the compounds tested in vitro (WR at 199).[6]

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6. Note that Fujikawa are not well-served by their citation to Bigham v. Godtfredsen, 222 USPQ 632, 637 (POBI 1984), to the extent that Board of Patent Interferences in that opinion accepted the junior party's in vitro testing of antiobiotic "prodrug" compounds in bacteria to satisfy the requirements of a reduction to practice of the subject matter of the compound per se counts therein at issue, "particularly since the activity of the test compound was compared with that of [the known antibiotic] ampicilin" (emphasis supplied), 222 USPQ at 637. In doing so, the Board hewed to the authority of Nelson v. Bowler, 206 USPQ 881 (CCPA 1980), previously cited by Wattanasin, that a

Dr. Scallen further testified that he had performed the in vitro testing of compactin and fluvastatin prior to December 31, 1984, and knew the in vivo activity levels of these compounds. On this basis, it was his judgment that the level of in vivo activity of a compound as a cholesterol inhibition "is typically highly correlatable to its in vitro activity in his assays (WR at 193) and "would be" active in vivo (WR at 194). Dr. Damon also testified that "there was a high probability" that each of the Wattanasin compounds would have in vivo activity (WR at 200-201).

In short, by the time the instant invention was made, there was an art-recognized correlation between the standard in vitro tests and the typical in vivo tests in the art, which was clearly indicative of practical utility in the manner of compactin and fluvastatin. It is also clear that the prior art, as evidenced by the Sandoz patent filings, contained ample direction as to dosage amount and methods of treatment for hypercholesterolemia in patients in need of such treatment.

On this basis, against the background of the prior art experience with preparing and testing HMG-CoA reductase compounds, Wattanasin submits that the in vitro tesing alone provided an actual reduction to practice of the subject matter of each of count 3 and

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(Footnote 6 continued from previous page)
standard in vitro test may be sufficient to demonstrate pharmacological activity of a compound, i.e. a "practical utility," id.

(Other cases cited by Fujikawa in their Briefs at 32-33, regardless of their dicta, are judged irrelevant; Kahl, Symmes, Newkirk and Alsenz all concern mechanical devices.)

and count 1 of the subject companion interferences, both prior to and continuing after the Fujikawa benefit date.

Fujikawa repeatedly assert that the in vitro testing conducted by Scallen does not meet the standards for an actual reduction to practice. According to Fujikawa, the standard is "not that they might work, but that the compounds would work" (Fuj. Brief at 37), or elsewhere, "will work" (Fuj. Brief at 33).[7]

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7. Note that the Federal Circuit court in Cross v. Iizuka, 224 USPQ 739 (Fed. Cir. 1985), has enunciated a standard of "reasonable correlation" between in vitro and in vivo activities for purposes of establishing practical utility:

> We *** find ourselves in agreement with the Board that, based upon the relevant evidence as a whole, there is a reasonable correlation between the disclosed in vitro utility and an in vivo activity, and therefore a rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence. Cf. Nelson, 626 F.2d at 856, 206 USPQ at 883-83.

And further:

> Employing a microsome assay, the skilled worker could determine the relative strength of the compounds of the count vis-a-vis the known parent imidazole and 1-methylimidazole compounds. Thus the dosage in the microsome assay milieu could be determined without inventive skill or undue experimentation.
>
> Today, under the circumstances of the instant case, where the Japanese priority application discloses an in vitro utility, i.e., the inhibition of thromboxane synthetase in human or bovine platelet microsomes, and where the disclosed in vitro utility is supplemented by the similar in vitro and in vivo pharmacological activity of structurally similar compounds, i.e., the parent imidazole and 1-methylimidazole compounds, we agree with the Board that this in vitro utility is sufficient to comply with the practical

As an example of the purported uncertainty in the Wattanasin in vitro assays, Fujikawa (Briefs at 37) go on to cite certain Holmlund testimony (actually elicited on cross-examination) (FR 236-237) to the effect that, given the 10 to 20 steps necessary to convert the starting material in the cholesterol biosynthetic pathway, namely acetate, to the end product, cholesterol, it is "almost impossible" to set up an in vitro assay for a cholesterol lowering compound where all the necessary requirements are present to be predictive of in vivo activity.

On the contrary, had Fujikawa or Dr. Holmlund himself really undertaken to understand the scientific basis of the Scallen assays, they would realize that these assays are highly accurate predictors of in vivo activity. This is because the starting material used in the Scallen assays is not the "omnibus" acetate material to which Dr. Holmlund was referring, which is not even

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(Footnote 7 continued from previous page)
utility requirement of §101.

*** in vivo testing is but an intermediate link in a screening chain which may eventually led to the use of the drug as a therapeutic agent in humans. We perceive no insurmountable difficulty, under appropriate circumstances, in finding that the first link in the screening chain, in vitro testing, may establish a practical utility for the compound in question.***

acted on by the HMG-CoA enzyme; but rather, is radio-labeled "HMG-CoA" substrate (i.e. β-hydroxy-β-methyl-glutaryl- CoenzymeA) (see WR at 189, WX E-1 to E-5).

It is this HMG-CoA substrate that the enzyme, HMG-CoA reductase (also referred to as "HMGR"), specifically acts on to reduce the HMG-CoA to mevalonic acid, the next compound in the cholesterol biosynthetic chain (WR at 552).

What is so critical is that the action of HMG-CoA reductase enzyme on HMG-CoA substrate constitutes the rate limiting step in the cholesterol biosynthetic pathway (WR at 496). Accordingly, an assay which tests precisely for inhibition of HMG-CoA reductase enzyme is an extremely specific, pinpoint indicator of whether and to what extent inhibition of this specific rate-limiting step will occur. Inhibition of HMG-CoA reductase enzyme is a proven approach to the treatment of hypercholesteremia (WR at 551).

In point of fact, Dr. Holmlund's testimony concerning the limitations of an in vitro assay using acetate as a starting material impeaches none other than Fujikawa's own in vitro assays on which they premise a constructive reduction to practice. Reference is made to "Tests A and B" of the involved Fujikawa application and priority documents, where-- just as Dr. Holmlund was describing -- radiolabeled sodium acetate was provided to an heterogenous enzyme mixture from rat liver tissue; and at the end a lipid product was extracted and its radioactivity measured. This is precisely the kind of assay that Dr. Homlund implied was not sufficiently meaningful of HMG-CoA reductase inhibition (FR at 234).

It is not judged irrelevant that Fujikawa's own

Japanese applications dating from August 20, 1987 and January 26, 1988 contain only in vitro data, and absolutely no in vivo data. [Despite the limitations of the Fujikawa assays described above, it is noted that they do test against the same standard as Wattanasin, i.e. compactin, as well as another industry standard, CS-514 (pravastatin).]

There is a certain inconsistency in Fujikawa's taking a position against Wattanasin's in vitro data on the basis that it does not demonstrate practical utility for purposes of an actual reduction to practice while, at the same time, Fujikawa relies on admittedly flawed in vitro testing to establish compliance with 35 USC §§101 and 112 for purposes of a constructive reduction to practice. Clearly, Fujikawa rely solely on in vitro results as an indication of practical utility of the subject matter of the count, and they projected in vivo dose ranges from such data. Thus Fujikawa must necessarily agree that in vitro testing in this art is recognized as indicative of in vivo practical utility.

In fact, it is hard to see how the Board could accept Fujikawa's allegations that Wattanasin failed to establish an actual reduction to practice by virtue of its in vitro assays, without sua sponte also depriving Fujikawa of their constructive reduction to practice benefit dates of August 20, 1987 and January 26, 1988 based solely on their in vitro testing.[8]

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8. In point of fact, it was not until Fujikawa's last filed priority application of August 3, 1988, some 10 months after Wattanasin did its in vivo testing, that any in vivo testing entered the Fujikawa filing. Of course, if Fujikawa were confined to the date of their application reflecting in vivo testing they would be well behind Wattanasin's in vivo testing in October of 1987.

Notwithstanding Fujikawa's assertions at page 42 of their Briefs that the Federal Circuit court in Cross v. Iizuka, 224 USPQ 739 (Fed. Cir. 1985) was concerned with a constructive reduction to practice situation (and is therefore unavailing to Wattanasin), the opinion does not appear to countenance such a distinction. In fact, not only did the court in Cross look for guidance to the rulings of its predecessor court in such cases as Nelson v. Bowler, 206 USPQ 881 (CCPA 1980), which dealt with the requirements of an actual reduction to practice, but the court went on to state as follows:

> We recognize that Nelson dealt with tests which were found adequate to establish an actual reduction to practice, as opposed to a constructive reduction to practice. We agree with the Board that principles applicable to a determination of an actual reduction to practice are generally germane to a constructive reduction to practice. (emphasis supplied)

224 USPQ at 744

As a further matter, Fujikawa persists throughout in confusing the difference between a compound that is inactive, and variations in potency which generally occur across any claim of a series of therapeutic compounds. As the Federal Circuit court stated in Cross:

> Variation in potency is a matter of degree of activity, but is still indicative of activity. There is no requirement that the compounds have the same degree of activity.

224 USPQ at 746.

Indeed, the Warner-Lambert article made of record by Fujikawa and relied on in their briefs at p. 38, speaks of just such variations in potency among the

quinoline compounds of the count. This article in fact affirms that the (4-fluorophenyl), 2-(1-methylethyl) substitution which characterizes the Wattanasin 64-935 compound, as well as the fluvastatin compound, "afforded optimum potency" (455). Another of the compounds was found to be "as potent in vitro as Compactin and Mevinolin and more potent than the corresponding free base, although slightly less potent in vivo (455). One compound was even found less potent in vitro but comparable to Compactin in vivo. There appears to be no indication that any of the tested compounds was inactive. If anything, this article stands as ex poste facto confirmation of the Wattanasin demonstration of the practical utility of the quinoline compounds at issue in this interference.

In their Briefs at 43-44, Fujikawa are arguing against the whole weight of developed knowledge in the HMG-CoA area concerning structure activity relationships (SAR) within a series. SAR are so powerfully predictive in this area that Kathawala found "surprising" even one departure from the established relationship in the indole series.

It is submitted that both legally and scientifically on the record in these interferences, Wattanasin demonstrated the practical utility of the subject matter of counts 1 and 3 at issue.

Even Dr. Homlund, acknowledged the following as a general proposition:

> Q. In any series of compounds in pharmaceutical research, if compounds active in vitro were found to be active in vivo subject to the exceptions that can always be encountered in research, would it be a fair assumption that for that given series, that it

is likely that a compound active *in vitro* would be then active *in vivo*?

A. You are referring to other members of a series of compounds, analogs.

Q. Where there is substantial background in the series of both *in vivo* and *in vitro* activity. We recognize that there are always exceptions.

A. I would have to say yes."

Q. Would you accept, subject to exceptions that might occur, that the failure to find that activity would be considered an exception, that there would be a reasonable expectancy against the background of the hypothetical I gave you?

A. I think I probably would accept that."

Accordingly, Wattanasin submits that the *in vitro* testing constituted a reduction to practice of the subject matter of each of counts 3 and 1 of the subject companion interferences.

E. THE WATTANASIN IN VIVO TESTING ALSO MEETS THE REQUIREMENTS OF A DEMONSTRATION OF PRACTICAL UTILITY OF COUNTS 1 AND 3

Wattanasin also submits that with the comparative *in vivo* testing in rats of the quinoline compounds of the Wattanasin invention against the known compactin or fluvastatin, the practical utility of the subject matter of each of counts 1 and 3 was confirmed.

First of all, Dr. Holmlund did acknowledge that the Engstrom *in vivo* assays were run on a very stringent basis, so that even compactin, with an ED_{50} of as high as 3.5, would have registered inactive:

Q. *** If you were to *** run an assay where the break point for ED_{50} is 1 and the ED_{50} of Compactin is 3.5, would it be your conclusion that you are running an assay for compounds that are considerably more active than Compactin?

A. Yes.
Q. So, it might be fair to say that you are setting a rather high standard?
A. Yes.

* * *

FR at 216-17.

And further:

Q. If a compound were revealed to have an ED_{50} of 3.5 in the in vivo assay, in other words, the same level as we have assumed for Compactin, would it be your judgment that that would be an active compound in this field?
A. ...Under the circumstances, I would say yes.
Q. That's a fair assumption, Doctor.
Would you say that there could be levels of activity above 3.5 where you could reach the same conclusion, 3.6, 3.7? I don't believe it is necessary to try and define what limits are, but higher than 3.5 could be considered an active useful compound in this field?
A. Yes, by the very definition of ED_{50}.
Q. But it would, nevertheless, in your mind at a dose bring the appropriate response in the body the same as Compactin might?
A. It would be classified as an active compound.
Q. As an HMG-CoA reductase inhibitor?
A. Yes, in vivo.

FR at 218-19

Concerning the raw in vivo data respecting compounds 64-933 and 64-936[9], for example, Dr. Holmlund

9. Fujikawa attempts to contrive an argument surrounding the absence of a sodium salt indication, i.e. "NA", from the Sandoz database printout included in Wattanasin Exhibit K-1 (at 336). However, notice that on pages 203, 205 and 209 of the Wattanasin record "64-936" is used interchangeably with the designation "64/936/NA", just as the Sandoz fluvastatin compound, a sodium salt (technically, "62-320/NA"), is typically referred to as, simply, 62-320 (WR at 484), without the added sodium designation. It is hard to see how

acknowledged as follows:

> Q. Then that does not rule out the possibility this compound could be judged active at a higher dose than tested here?
> A. That's correct.
> Q. Would it be your same testimony for the compound 64-936 on record page 336?
> A. Yes, it would be. Since there are no testing results available there is always the possibility for any compound, that at a higher dose, it may manifest activity.
> Q. Do you regard this compound as showing significant activity at the dose level of .3 milligrams per kilogram?
> A. Yes.

FR at 244

The three Wattanasin compounds 94-633, 94-635 and 94-636/NA were tested in vivo in a very stringent assay designed to find compounds essentially 3.5 times more active than compactin (the tested ED_{50} cut-off point was 1.0 whereas compactin has an ED_{50} of 3.5 in these tests.) Two of the tested compounds failed to have an ED_{50} of 1.0 and hence were inactive in the test (but could have shown activity in a higher scale test as acknolwedged by Dr. Holmlund). But one of the Wattanasin compounds, 64-935, showed a highly active ED_{50} of 0.49 in the in vivo test, which result was recorded in the official Sandoz database and reported by Wattanasin. Dr. Holmlund criticized this 0.49 reading, since the raw activitiy data at 0.3 was somewhat lower than the activity value at 0.1 (see Exhibit K-1), and indicated the test should have been repeated to be certain of the result. Whether or not Dr. Holmlund's observation has any technical value, the 0.49 result was

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(Footnote 9 continued from previous page)
Fujikawa could allege "problems" with usage that is common in the art, and is manifestly apparent throughout the Wattanasin record.

accepted by Sandoz which had long experience in such testing.

Moreover, Dr. Holmlund himself acknowledged that 64-935 was active under such stringent in vivo testing conditions because the result of the 1.0 milligram test dose was clearly above the 50% reduction level. This testimony appears at FR 243 as follows:

> Q. I would refer you to the result of 1 milligram per kilogram for this compound 64-935, the minus 65.8, I believe it is. Does that show that this compound is active at that dose?
> A. Yes.

Fujikawa has advanced various arguments for suppression of the Sandoz database printout included in Exhibit K-1. However, this ED_{50} data merely re-present the same data as are apparent from the notebook pages in Exhibit K-1. And Dr. Holmlund himself testified that he "had no quarrel" with the statistical analysis used to generate the Wattanasin ED_{50} data. Furthermore, based on the raw data included in Exhibit K-1, it is patentably obvious that the ED_{50} for either of 64-933 or 64-936/NA was inadvertently "switched" in the Engstrom declaration. This is an obvious typographical error which should not result in suppression of the in vivo data, as Fujikawa would have it. In fact, the typographical error in the original Engstrom declaration was not even noted until after the Engstrom supplemental declaration was put in. The supplemental declaration records activity for the count on May 23-24,1988; and therefore primarily goes to the issue of abandonment, suppression or concealment.

Finally, at page 35 of their Briefs, Fujikawa challenge Wattanasin's allegation that Dr. Holmlund

--despite his lengthy C.V. of record -- demonstrated only limited familiarity with the precise field of HMG-CoA inhibition which was not up to the level of an ordinary worker in the field.

Accordingly, Wattanasin notes that Dr. Homlund indicated that he "could not recall" the structure of even the industry standard, compactin (WR at 238), and Wattanasin proffers the following full quotation from the record:

> Q. Are you familiar with any heterocyclic inhibitors of HMG-CoA reductase.
> A. Not so that I could draw any structures for you.
> Q. Are you familiar with any of the findings in the art concerning these compounds, the activity levels of these compounds?
> A. I don't have any IC_{50} or ED_{50} values in mind for any of these compounds.
> Q. Do you know the structure of Mevinolin?
> A. Close. It is fairly similar in structure to mevalonate lactone itself. But I don't recall its exact structure.
> Q. Are you familiar with the Sandoz Fluvastatin compound?
> A. No.
> Q. You do not know its structure?
> A. I do not.
> Q. Do you know its structure activity relationships which are in the literature?
> A. I do not.
> Q. Do you know the structure activity relationships for the Pyrazole HMG-CoA reductase inhibitor?
> A. No.
> Q. For the Pyrimidine?
> A. No.
> Q. So you yourself have never actually run an <u>in vitro</u> or <u>in vivo</u> assay of an HMG-CoA reductase compound?
> A. That's correct.

WR at 234-40

Fujikawa have even gone so far as to suggest that the in vivo tests in rats performed by Wattanasin were inadequate to show utility in humans; but this argument is clearly contrary to the weight of the caselaw, see, e.g., Cross, supra, and of course is certainly contradicted by their own testing in rats.[10] Moreover, the Wattanasin application does teach, broadly, administration to "animals, e.g. mammals."

F. THERE WAS NO ABANDONMENT, SUPPRESSION, OR CONCEALMENT OF THE WATTANASIN INVENTION; NOR WAS THERE ANY LACK OF DILIGENCE IN CONNECTION THEREWITH

It is believed that the issue of diligence between the period just prior to the Fujikawa priority date of August 20, 1987 and the in vitro and in vivo testing which filed, has been fully addressed in the Wattanasin opening briefs in these interferences filed July 15, 1993; and it does not appear that Fujikawa contest diligence as to this period.

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10. Blicke v. Treves, 112 USPQ 472 (CCPA 1957) in fact addressed this type of situation:

> Here, Treves is relying for his constructive reduction to practice on applications which do not specifically mention human therapy, but merely state that the compounds disclosed are useful as mydriatics and antispasmodics, and, as evidence of such utility, describe tests on animals only. Having been granted patents on the basis of such disclosures, we fail to see that he is in a favorable position to argue that Blicke must show actual tests on human beings in order to establish an actual reduction to practice.

USPQ at 476

Parenthetically, Wattanasin's undersigned attorney, is dismayed by Fujikawa's statement in their Briefs that Wattanasin "seriously misrepresented" the Blicke decision by simply citing this case for the proposition that a reduction to practice must be considered on a case-by-case basis.

With respect to the issue of abandonment, suppression or concealment of the invention, it is likewise submitted that the Wattanasin briefs fairly and completely address this issue, both as it goes to the period from mid-1985 to March 1987; and as it goes to the period between December 9, 1987 (when Engstrom completed his activity for the count by entering the ED_{50} data in the Sandoz database), and the filing of the Wattanasin patent application on March 3, 1989 by attorney Joanne M. Giesser, a period of 14 months.

As concerns the Fujikawa argument that Wattanasin was not "diligent" in the period between mid-1985 and early 1987, when work resumed within the counts (Fuj. Briefs at 55-57): diligence need not be proved when an invention has been reduced to practice prior to entry of the other party; and the record shows a reduction to practice by Wattanasin three time by mid-1985.

G. FUJIKAWA ARE NOT ENTITLED TO PROPOSED COUNTS DIRECTED TO CYCLOPROPYL SPECIES OF THE COUNT

The EIC denied Fujikawa's motion to add counts to a separate cyclopropyl species already within the scope of counts 1 and 3 of these interferences. It is respectfully submitted that the decision of the EIC should stand.

As a first matter, Fujikawa's argument for separate counts is compromised by their own improvidential statement in their very request for interference of their involved application with the Warner-Lambert Picard et al. patent:

"there is absolutely no evidence of record that the varying species embraced by both claims [i.e. claim 1 of Fujikawa and claim 1 of the Picard patent, both encompassing the cyclopropyl species] are patentably distinct from the unsubstituted compound discussed above."

Additionally, it is noted that during prosecution of the involved Fujikawa application, Fujikawa resisted any restriction of their invention, then later took out subgeneric claim 1 of their '930 patent directed to both the isopropyl and cyclopropyl -substituted species. Now Fujikawa is in the position of arguing that their cyclopropyl species are patentably unobvious even over the isopropyl species.

The Kitahara Declarations of record do not seem to rationalize the Fujikawa argument for separate cyclopropyl counts. If anything, the data therein might arguably support a separate count to the combined isopropyl and cyclopropyl species; but of course such a count would encompass Wattanasin's proofs of prior reduction to practice.

Fujikawa have failed to establish two requisites for entering a separate cyclopropyl (4-fluorophenyl) species count in this interference:

(1) The claims proposed to be added by Wattanasin do not comply with 35 USC 112 in the Wattanasin application, and therefore do not meet the requirement of 37 CFR 1.637(c)(1)(iii).

(2) Fujikawa have failed to demonstrate the separate patentability of the cyclopropyl species over the genus of Counts 1 and 2.

It is concluded that the comparative data presented by Fujikawa, to the extent meaningful, merely indicate activity of the cylopropyl species as an HMG-CoA reductase inhibitor which is well within the range of normal expectancy across the genus of quinoline compounds corrresponding to Counts 1 and 2, particularly given the teachings and expectations of the prior art which point to ispropyl, cyclopropyl and 4-fluorophenyl as clearly preferred features (it also being noted that cyclopropyl is a mere ring homolog of isopropyl).

The Wattanasin paper filed in Interference 102,648 entitled: "Opposition of Wattanasin to Fujikawa et al. Motion to Add Counts and to Add Claims to Wattanasin Application" mailed July 1, 1992, is hereby incorporated by reference. A copy of said paper is enclosed in Appendix A hereto.

H. THE KASSENOFF TESTIMONY SHOULD NOT BE DISCREDITED

Fujikawa argues that Wattanasin has "relied heavily" on the testimony of its in-house patent attorney, Melvyn M. Kassenoff; and that since Mr. Kassenoff is indicated to have of counsel status on the Wattanasin briefs, his testimony, with certain exceptions, should be discredited.

To whatever degree Wattanasin has relied on the Kassenoff testimony, it is submitted that no such discrediting is appropriate under the present circumstances.

First, the testimony of Melvyn M. Kasssenoff for the party Wattanasin falls within the protected activity of 37 § 10.62(b)(2) and (3), because it constitutes testimony going to formalities and the factual

circumstances of his activities in relation to the Wattanasin invention;

Second, the testimony of Melvyn M. Kassenoff also falls within 37 CFR 10.62(b)(4), because otherwise the party Wattanasin would be deprived of Kassenoff's testimony, which would work a serious hardship;

Third, the Fujikawa motion is belated, as it could have been filed much earlier. The suggestion by Mr. Kelber that he only became aware of the situation upon filing of the Wattanasin Record is without merit. Mr. Kassenoff has been listed as deputy lead attorney from the beginning of this matter.

Fourth, discrediting the Kassenoff testimony would only serve to give Fujikawa undeserved advantage. Counsel for Fujikawa caused this testimony to be taken, and subjected Mr. Kassenoff to cross-examination under oath. Counsel for Fujikawa should face the testimony rather than have the Board discount it for no justifiable reason.

The Wattanasin "Opposition to Fujikawa Motion for Sanctions," dated June 14, 1993, in Interference Nos. 102,648 and 102,975, is hereby incorporated by reference and enclosed as Appendix B hereto.

I. CONCLUSION

For the reasons discussed above and in the Wattanasin opening briefs in Interference Nos. 102,648

and 102,975, it is respectfully submitted that Wattanasin has proved priority over Fujikawa by a preponderance of the evidence, or by clear and convincing evidence.

Respectfully submitted,

Diane Furman Diane Furman 9/7/93

Diane E. Furman
Attorney for the Party Wattanasin
Registration No. 31,104
201-503-7332

SANDOZ CORPORATION
59 Route 10
E. Hanover, NJ 07936

September 4, 1993

DEF:rmf

APPENDIX A

Case No. 600 /101/CONT
Patent

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

WATTANASIN

v.

PICARD et al.

v.

FUJIKAWA et al.

Interference No. 102,648

Examiner-in-Chief: M. Sofocleous

OPPOSITION OF WATTANASIN
TO FUJIKAWA ET AL. MOTION TO ADD COUNTS
AND TO ADD CLAIMS TO WATTANASIN APPLICATION

SUMMARY

The party Wattanasin hereby opposes the party Fujikawa et al.'s motion to redefine the interference by adding proposed Counts 3 and 4.

The opposition is on the ground that the party Fujikawa et al. (hereinafter "Fujikawa") are not in compliance with 37 CFR 1.637(c).

More particularly, Fujikawa have not met the requirements of either or both of, sub-sections (c)(1)(iii) and c(1)(v) of Rule 637.

First, with respect to 37 CFR (c)(1)(iii), there is no written description in the involved application of Wattanasin, of the subject matter of species claims 11 and 12 which Fujikawa have proposed to Wattanasin to correspond to proposed Counts 3 and 4. Since the Fujikawa proposed claims 11 and 12 do not comply with 35 USC 112, written description requirement, Fujikawa have failed to meet the requirement of 37 CFR 1.637(c)(1)(iii) that proposed claims be patentable to the other party. Accordingly, given that

Fujikawa are unable to propose claims to Wattanasin corresponding to their proposed narrow counts, which also meet the written description requirement of 35 USC 112, the Fujikawa motion to redefine the interference should be denied.

Second, the Fujikawa proposed Counts 3 and 4 do not define a separately patentable invention from the subject matter of Counts 1 and 2 of this interference, as required by 37 CFR 1.637(c)(1)(v).

The proposed counts 3 and 4 cover a cyclopropyl (4-fluorophenyl)-substituted quinoline species within the generic scope of Counts 1 and 2 of the present interference.

As the basis for separate patentability of the counts, Fujikawa allege that the cyclopropyl (4-fluorophenyl) species exhibits "unexpected improvement" in HMG-CoA reductase inhibition activity compared to that of its closest structural isomer, i.e. the corresponding isopropyl spcies.

It is the position of Wattanasin, however, that: (1) the state of the art even prior to the earliest Fujikawa priority date included a recognition that improved HMG-CoA reductase inhibition activity was exhibited by both isopropyl- and cyclopropyl-bearing nitrogen-containing (4-fluorophenyl bearing) heterocycles; (2) that the Fujikawa comparative data submitted into the record do

not indicate an improvement in activity of cyclopropyl (4-fluorophenyl) over isopropyl (4-fluorophenyl) that rises to the level of "unexpectedness," particularly given the clear direction in the art to prepare the cyclopropyl (4-fluorophenyl); and (3) that the Fujikawa comparative data of record are deficient in not presenting a comparison of the cyclopropyl species of the Fujikawa proposed counts 3 and 4 at issue with other cyclopropyl species within counts 1 and 2 of this interference which are excluded from the scope of the Fujikawa proposed counts.

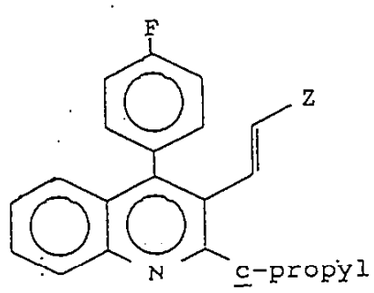
For the above reasons, which are more fully described below, Wattanasin requests that Fujikawa's motion be denied.

BACKGROUND

Fujikawa moved to redefine the present interference by adding proposed Counts 3 and 4.

Fujikawa's proposed Count 3 is directed in essence to a single species embraced by Count 1 (as well as Wattanasin's proposed Substitute Count 1). This species has the following structural formula:

(A)



(where Z is selected from the group consisting of 3,5-dihydroxy- substituted carboxylic acids, sodium and calcium salts, and C_{1-3}alkyl esters thereof, and the lactone formed by condensation of the carboxylic acid with the hydroxy at the 5-position)

Fujikawa's Proposed Count 4 is directed in essence to a method of using a compound of proposed Count 3.

It will be noted that in the above structural formula (A), the quinoline ring is substituted at the 2-position, i.e. between the nitrogen atom and the "Z" substituent, by cyclopropyl. Also, the quinoline ring is substituted at the 4-position by 4-fluorophenyl.

Compounds having structural formula (A) are hereinafter referred to collectively as the "cyclopropyl (4-fluorophenyl) species" (or alternately, the "cyclopropyl species").

It will be further noted that compounds disclosed by Fujikawa in their involved application which are similar in structure to the cyclopropyl species but which fall outside the scope of proposed Counts 3 and 4 comprise:

(i) compounds of structure (A), with the sole exception that cyclopropyl is replaced by isopropyl (see compound of claim 6 of Fujikawa application) [referred to herein as the "isopropyl" or "isopropyl (4-fluorophenyl)" species].

(ii) compounds of structure (A), with the sole exception that fluorine is replaced by chlorine (see compound of claim 18 of Fujikawa application).

The cyclopropyl species which is the subject of proposed Counts 3 and 4 is embraced by Counts 1 and 2 of this interference. Additionally, the cyclopropyl species falls within the scope of claims 1-5, and 32-34, and newly presented claims 41-44, of the Fujikawa involved application, as well as claim 1 of Fujikawa U.S. Patent No. 5,011,930, which Fujikawa have indicated is being taken into reissue. The cyclopropyl species also falls within the generic scope of claims 1-3 and 8-10 of Wattanasin's involved application.

To correspond to proposed Count 3, Fujikawa have proposed to Wattanasin added claim 11, which is directed to the cylopropyl (4-fluorophenyl) species.

As corresponding to proposed Count 4, Fujikawa also propose a claim 12 to Wattanasin which is directed to the use of a compound of claim 11.

In support of proposed Counts 3 and 4, Fujikawa represent that the cyclopropyl (4-fluorophenyl) species of the proposed counts has "unusually high" activity as an inhibitor of cholesterol biosynthesis relative to the genus covered by Count 1, and that "nothing of record" would predict the increased activity associated with the cyclopropyl substituent. A Declaration of one

of the named co-inventors, Masaki Kitihara, is presented for the purpose of demonstrating the "unexpectedly superior" activity of the cyclopropyl species relative to its structural isomer, i.e. the corresponding isopropyl species, as well as homologs of isopropyl.

ARGUMENT

Fujikawa's motion to add proposed claims 11 and 12 to the involved application of Wattanasin should be denied.

Wattanasin discloses quinoline compounds substituted at the 2-position by (1) isopropyl or (2) C_{3-7}cycloalkyl. However, while the involved application of Wattanasin certainly covers within its generic scope compounds which are substituted by cyclopropyl, there is no description by Wattanasin of a cyclopropyl species, as acknowledged by Fujikawa.

Neither the term "isopropyl" nor the term "C_{3-7}cycloalkyl" provides a written description of "cyclopropyl" for purposes of 35 USC 112.

Since Wattanasin does not provide a written description in its involved application of the species proposed by Fujikawa, Fujikawa has failed to comply with 35 USC 112.

Fujikawa, in proposing claims to Wattanasin, are required to show the patentability of the claims to Wattanasin, 37 CFR 1.637(c)(1)(5), MPEP 2338.

Since Fujikawa are unable to establish the patentability of their proposed claims to Wattanasin, the Fujikawa motion to redefine should be denied.

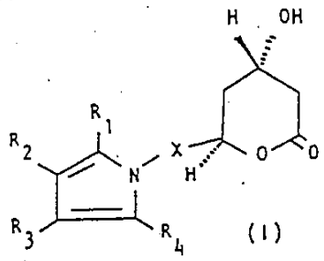
Even assuming arguendo that Fujikawa had fully complied with 37 CFR 1.637(c)(1)(iii) by proposing a claim to Wattanasin which fulfilled the requirements of 35 USC 112, the Fujikawa motion should still be denied because the proposed Counts 3 and 4 do not define a separately patentable invention.

It is self-evident that the question of separate patentability of the cyclopropyl (4-fluorophenyl) species, independent of the genus in which it is contained, involves the principle of selection. That is, the patentability of Fujikawa's proposed counts hinges on whether the cyclopropyl species possesses properties which are truly "surprising" or "unexpected," or which otherwise make it distinct from the generic invention. Fujikawa appear to rely on mere activity differences between the cyclopropyl species and certain other members of the genus. However, these differences are not beyond normal variations to be expected in a generic invention, and moreover, could even be expected based on the prior art.

First of all, the state of the art well prior to Fujikawa's earliest priority date, as reflected in actual prior art of record in Fujikawa's U.S. Patent No. 5,011,930, reflects a clear direction to prepare a species of an HMG-CoA inhibitor compound which contains either an isopropyl or a cyclopropyl substituent.

In particular, reference is made to Warner-Lambert European Patent Application 179,559 (published on April 30, 1986) which discloses a pyrrole series of HMG-CoA reductase inhibition compounds having the formula:

(B)



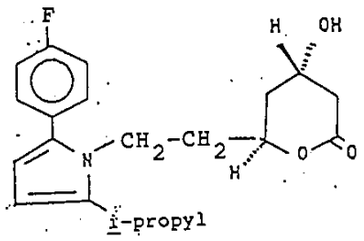
(I)

(or a ring-opened dihydroxyacid derived therefrom, or a pharmaceutically acceptable salt thereof).

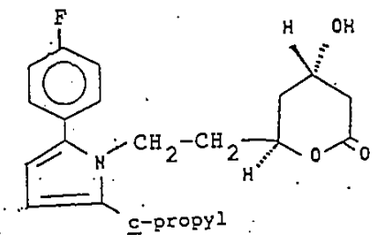
Most pertinent for present purposes is that in the above compounds of Warner-Lambert, R_4 is selected from the limited Markush group comprising: C_{1-4}alkyl, cyclopropyl, cyclobutyl or trifluoromethyl.

Furthermore, at pp. 13-14 of the publication Warner-Lambert express a "particular" preference for the following two compounds:

trans-6-[2-[2-(4-fluorophenyl)-5-(1-methylethyl)-1H-pyrrol-1-yl]-ethyl]tetrahydro-4-hydroxy-2H-pyran-2-one:



trans-6-[2-[2-cyclopropyl]-5-(4-fluorophenyl)-1H-pyrrol-1-yl]-ethyl]tetrahydro-4-hydroxy-2H-pyran-2-one:



Based on the Warner-Lambert disclosure alone, it is fair to say that by April 1986, i.e. well prior to the earliest Fujikawa filing date of August 20, 1987, there was a recognition in the art that: an isopropyl (4-fluorophenyl) species could provide enhanced HMG-CoA reductase activity; and further, that the isopropyl could be cyclized to form cyclopropyl; and finally that the resulting cyclopropyl (4-fluorophenyl) itself exhibited particular improvements in activity relative to a genus of compounds within the same series. Note that in both Warner-Lambert species, above, the isopropyl or cyclopropyl occupies a position on the pyrrole ring adjacent to the nitrogen, as in the case of the cyclopropyl species at issue.

Therefore, it is submitted that certain improved activity levels were already noted in the art in connection with a cyclopropyl-bearing compound well prior to Fujikawa's filing date, such that by August 1987 if not earlier, one of ordinary skill, guided by the Warner-Lambert publication and others, would have considered the activity levels of Fujikawa's cyclopropyl species, as being at best merely consistent with the preferences expressed in the prior art in connection with other nitrogen-containing heterocycles, and certainly well removed from the realm of surprise or unexpectedness.

Further noted in connection with the state of the art is U.S. patent No. 4,952,852 of Hoechst, the foreign counterpart of which would have published in December 1988. The Hoechst disclosure is directed to pyridinyl compounds such as, e.g., the compound of Examples 13ac and 13e, col. 62.

Note particularly in the Hoechst reference the activity level of various compounds which is indicated on Table 1, col. 13-14. Compare especially Example 13e on Table 1 (isopropyl) to Example 13ac (cyclopropyl), which indicates a higher activity level for cyclopropyl than for isopropyl.

It is noted that while the Hoechst publication was available only after Fujikawa's priority filings, it was in the art prior both to Fujikawa's assertion during prosecution of its involved application that the cyclopropyl species had "unobvious"

properties (Amendment of December 19, 1990), and also prior to the February 23, 1990 filing date of the divisional application which issued as the '330 patent.

Copies of relevant portions of the Warner-Lambert and Hoechst publications are enclosed.

The clear direction in the art surrounding Fujikawa's involved application virtually deprive Fujikawa of the argument that increased activity of its cyclopropyl (4-fluorophenyl) species over the other species within its scope would be "unexpected" or "surprising".

Put differently, given the preferences expressed in the art, Fujikawa is necessarily held to a very high threshold of improvement in activity of its cyclopropyl (4-fluorophenyl) species over, e.g., the isopropyl (4-fluorophenyl), in order to justify a conclusion of "unexpectedness" such as would give rise to separate patentability; and this threshold is simply not overcome by the comparative evidence of record.

Turning now to the Kitihara Declaration proffered in support of Fujikawa's motion to redefine, it is submitted that this data simply does not provide a basis for according separate patentability to the cyclopropyl species.

Kitihara provides Test A and Test B IC_{50} data for the sodium and calcium salts, ethyl ester and lactone forms of the cyclopropyl species of structure (A), above, which is covered by proposed Counts 3 and 4. Comparative data is provided with respect to quinoline compounds also having structure (A), with the sole exception that the cyclopropyl group is substituted by methyl, ethyl, isopropyl or C_6.

The data may be summarized as follows:

A. Test A:

Table (a), containing data for the sodium salts of cyclopropyl and the comparative compounds, demonstrates that:
i - cyclopropyl is more active than isopropyl by a factor of about 2.4, and
ii - isopropyl is more active than n-propyl by a factor of about 9.

Table (b) has only two data points for the calcium salts, which indicate that cyclopropyl is more active than isopropyl by a factor of about 5. However, it is difficult to determine how meaningful this activity difference is given the absence of additional comparative data.

Table (c), listing data on the ethyl esters, indicates that the cyclopropyl is more active than n-propyl by a factor of about 14, but no data is given for isopropyl.

Table (d), listing data on the lactones, indicates that the cyclopropyl is more active than the isopropyl by a factor of about 3.8. Again, given that no other compounds were tested, it is difficult to determine how meaningful this data is.

B. Test B

Table (a), listing data on the sodium salts, indicates that

i. cyclopropyl is about 5.7 times more active than isopropyl;

ii. isopropyl is about 7 times more active than n-propyl.

Table (b): the calcium salt of the cyclopropyl is about 3 times more active than the i-propyl; no other data is given.

Table (c), ethyl ester -- No data is given for the isopropyl. The cycopropyl is about 13 times more active than the n-propyl.

It is noted, first, that the above-summarized Kitihara data give no indication that toxicity does not also increase with actvitiy.

Second, given that the difference in activity level between isopropyl and its homologous species is typically substantially greater than the difference in activity betweeen cyclopropyl and isopropyl, Fujikawa is in the untenable position of claiming that

cyclopropyl is a separate and distinct invention from a genus of compounds which includes both the isopropyl and the other species tested above.

Third, the Kitihara Declaration is deficient in failing to make a complete comparison with compounds supported in its case which fall outside the scope of proposed Count 2.

Reference is made, for example, to claim 18 of Fujikawa's involved application, for example, which is directed to a compound having structural formula (A), above, with the sole exception that the quinoline ring is substituted at the "4" position not by 4-fluorophenyl, but by 4-chlorophenyl. This species falls outside the scope of proposed Counts 3 and 4 solely by virtue of the substitution of fluorine with another halogen, chlorine. No comparative data is offered by Fujikawa in respect of this chlorine species.

CONCLUSION

Fujikawa have failed to establish two requisites for entering a separate cyclopropyl (4-fluorophenyl) species count in this interference:

(1) The claims proposed to be added by Wattanasin do not comply with 35 USC 112 in the Wattanasin application, and therefore do not meet the requirement of 37 CFR 1.637(c)(1)(iii).

(2) Fujikawa have failed to demonstrate the separate patentability of the cyclopropyl species over the genus of Counts 1 and 2.

It is concluded that the comparative data presented by Fujikawa, to the extent meaningful, merely indicate activity of the cylopropyl species as an HMG-CoA reductase inhibitor which is well within the range of normal expectancy across the genus of quinoline compounds corrres- ponding to Counts 1 and 2, particularly given the teachings and expectations of the prior art which point to ispropyl, cyclopropyl and 4-fluorophenyl as clearly preferred features (it also being noted that cyclopropyl is a mere ring homolog of isopropyl).

Accordingly, it is repectfully requested that Fujikawa's motion to redefine the interference be denied.

Respectfully submitted,

Diane Furman

Diane E. Furman
Attorney for the Party Wattanasin
Registration No. 31,104
201-503-7332

SANDOZ CORPORATION
59 Route 10
E. Hanover, NJ 07936

DEF:rmf

July 1, 1992

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231, on July 1, 1992
(Date of Deposit)
Diane E. Furman
Name of applicant, assignee, or Registered Representative
Diane Furman
Signature
July 1, 1992
Date of Signature

CERTIFICATE OF SERVICE

It is hereby certified that a true copy of the paper entitled:

OPPOSITION OF WATTANASIN
TO FUJIKAWA ET AL.'S MOTION TO ADD COUNTS
AND TO ADD CLAIMS TO WATTANASIN APPLICATION

was served on counsel for the party Fujikawa et al., this 1st day of July 1992, by postage pre- paid first-class mail addressed to the following:

Oblon, Spivak, McClelland, Maier & Neustadt, P.C.
Attn: Steven B. Kelber, Esq.
1755 South Jefferson Davis Highway
Crystal Square 5, Ste. 400
Arlington, VA 22202

Diane Furman
Diane E. Furman

APPENDIX B

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

WATTANASIN

v.

FUJIKAWA et al.

Interference Nos. 102,648, 102,975

Examiner-in-Chief: M. Sofocleous

WATTANASIN OPPOSITION TO FUJIKAWA MOTION FOR SANCTIONS

STATUS

By motion of May 25, 1993 in the above-identified interferences, the party Fujikawa et al. have requested sanctions against the party Wattanasin for alleged violation of Sections 10.62(b) and 10.63(a) of 37 CFR.

The purported violation concerns Wattanasin's introduction of and reliance on testimony of Melvyn M. Kassenoff, Esq., a patent attorney on the staff of the Sandoz Corporation Patent and Trademark Department[1], going to the issue of abandonment, suppression or concealment, while he is at least apparently participating in the interferences as "deputy lead counsel".

The sanctions demanded by Fujikawa are as follows (in the alternative):

1. Disqualification of all members of the Sandoz Patent and Trademark Department from further participation in the interferences;

2. Striking the testimony of Kassenoff;

3. "Severely discounting" the testimony of Kassenoff.

---

1. Melvyn M. Kassenoff has been employed in the Sandoz Patent and Trademark Department for about 20 years.

Wattanasin now opposes the Fujikawa motion. It is respectfully submitted that the Fujikawa motion is completely devoid of support in fact or law; and that furthermore, that it is belated, having been raised over three months after the Kassenoff testimony was made of record, and over one year after Mr. Kassenoff's designation as a counsel in these interferences.

Accordingly, Wattanasin requests that the Fujikawa motion, and each and every sanction requested therein, be denied.

STATEMENT OF FACTS

1. When these interferences first went forward, management at Sandoz Pharmaceuticals Corporaton, the assignee of interest of the party Wattanasin, made a decision to rely for representation on the Sandoz in-house patent staff (consistent with the usual practice of Sandoz in patent interferences).

2. Effective March 23, 1992, the undersigned, Diane E. Furman, an attorney in the Sandoz Corporation Patent and Trademark Department, was designated the lead attorney of record for the interferences. Melvyn M. Kassenoff, Esq., also with Sandoz, was designated deputy lead counsel, with full power and authority to

act in the absence of the lead attorney.[1] (see Exhibit A)

3. The designation of Kassenoff was made in recognition of the fact that he has substantial experience, unique to the Sandoz Patent and Trademark Department, in the subject matter area of these interferences, i.e. HMG-CoA reductase inhibitor compounds. Melvyn Kassenoff is also regarded as the Sandoz Patent and Trademark Department's foremost expert on PTO rules and regulations, and had more experience in interference procedure under the new rules than any other member of the department.[2]

4. Kassenoff's role as an attorney in these interferences has been primarily as a consultant or "sounding board," providing occasional advice on procedural and scientific issues.

5. Kassenoff did not provide any testimony in these interferences as to priority.

6. It was only when Fujikawa raised the issue of abandonment, supression or concealment, that it became apparent that Mr.

---

1. Melvyn M. Kassenoff is also listed as an attorney of record on the involved Wattanasin application. Another Sandoz patent attorney of record on the application, Richard E. Vila, Esq., became active in the interference at the deposition stage.

2. It is noted that Mr. Kassenoff is the only member of the Sandoz staff who is a former patent examiner, and also is distinguished by having an advanced degree (M.S.) in chemistry.

Kassenoff had relevant testimony which needed to be taken in order for Wattanasin to present a complete defense. More specifically, Kassenoff's testimony goes to the period between the last documented laboratory work in connection with the Wattanasin invention and the filing of the involved Wattanasin application. Although Mr. Kassenoff himself did not draft the Wattanasin involved application, his testimony of record shows that he participated in information gathering for the application, and that he was familiar with Sandoz patent policies and procedures as they applied to filing the Wattanasin case[3].

7. Wattanasin filed the Kassenoff declaration in February of 1993 (Exhibit B). At that time, not one word was heard from Mr. Kelber as to any impropriety in Mr. Kassenoff's concurrent designation as deputy lead counsel or in his continuation in such capacity.

8. In fact, in March of 1993, virtually one year to the day from Mr. Kassenoff's designation as deputy lead counsel of record, Steven B. Kelber, counsel for Fujikawa, came to the Sandoz Patent

3. Until January 1, 1993, when Mr. Kassenoff became supervisor of Patents Group II, one of two patent groups comprising the Sandoz Patent and Trademark Department, he reported to Mr. Vila, (who is supervisor of Patents Group I), and had no formal supervisory responsibilities. However, since about 1982, Mr. Kassenoff had certain de facto responsibilities in relation to HMG-CoA reductase matters, including assisting of junior department members working in the area, i.e. Joanne M. Giesser, Esq. (now departed from Sandoz), who drafted the involved Wattanasin application, and the undersigned lead counsel.

and Trademark Department in East Hanover, New Jersey, and subjected Mr. Kassenoff to rigorous cross-examination by deposition (see Kassenoff cross-examination transcript at pages 233-318 of the Wattanasin Record), without ever raising the question of impropriety as to Mr. Kassenoff's continuing status as deputy lead counsel.[4]

9. Subsequently, the Wattanasin Record was filed and served. The Record cover pages (Exhibit C) bear a designation of Mr. Kassenoff and Richard E. Vila, Esq. as being "of counsel".[5] No change was made in the status of Mr. Kassenoff as deputy lead counsel.

10. Thereafter, a letter was received by the undersigned from Mr. Kelber (Exhibit D) identifying Mr. Kassenoff as a "critical fact witness" for Wattanasin and objecting to his participation as an attorney for Wattanasin.

---

4. During the cross-examination session at Sandoz, Mr. Kassenoff refrained from taking any testimony since he was a witness at the session, but the subject of his continued participation as deputy lead counsel was never questioned or discussed, let alone protested, by Mr. Kelber.

5. It should be noted that it has been the practice in the Sandoz Patent and Trademark Department, at least in cases before the Court of Appeals for the Federal Circuit, that the briefs and record would designate as of counsel, one or more of the immediate supervisors of the principal attorney of record, and/or to indicate that the named individuals had background or consultant status in connection with the case. This practice was followed in the current interferences.

11. On May 25, 1993, Fujikawa filed their motion for sanctions, which Wattanasin now opposes.

STATEMENT OF THE ISSUES

The critical issue is whether Melvyn M. Kassenoff's testimony for Wattanasin violates any known legal requirement, or even presents an appearance of impropriety, or needs to be discounted, in view of his status as deputy lead counsel (or "of counsel") in this matter.

APPLICABLE LAW AND ARGUMENTS

As a first matter, there is nothing in the Federal Rules of Evidence, which govern these interferences, which prevents an attorney from testifying on behalf of his client.

The most pertinent regulations bearing on the circumstances under which an attorney may serve as a witness for his client are located at 37 CFR §§10.62(b) and 10.63(a) (both effective 1985) (Exhibit E). These sections essentially track the language of the American Bar Association Code of Professional Responsibility, Disciplinary Rules (DR) 5-101(B) and 5-102(A), respectively.

1. 37 CFR §10.62, 10.63

(i) 37 CFR §10.62(b) indicates that prospective employment should be refused by a practitioner or another practitioner in his firm when the practitioner or his associate "ought to be" called as a witness for the client in the matter.

(ii) 37 CFR §10.63(a) likewise indicates that a practitioner who has already undertaken employment should withdraw if it becomes apparent that the practitioner or another in his firm "ought to" testify on behalf of the client.[6]

Of course, by their strict wording, both rules are directed to situations involving "firms," a term which is left undefined in the definitions section of Part 10 of 37 CFR. In conventional usage, however, the term "firm," would not even apply to an in-house corporate patent department.

However, assuming arguendo that Rules 10.62(b) and 10.63(a) would apply to in-house counsel, both rules are subject to four defined areas where an attorney's testimony for his client need not require him to withdraw from representation:

(1) If the testimony will relate solely to an uncontested matter.

6. 37 CFR §10.63(b) is directed to a case where the testimony is "other than" on behalf of the client, and is therefore inapplicable to the present situation..

> (2) If the testimony will relate solely to a matter of formality and there is no reason to believe that substantial evidence will be offered in opposition to the testimony.
>
> (3) If the testimony will relate solely to the nature and value of legal services rendered in the case by the practitioner or the practitioner's firm to the client.
>
> (4) As to any matter, if refusal would work a substantial hardship on the client because of the distinctive value of the practitioner or the practitioner's firm as counsel in the particular case.

Sub-paragraph (1)

Sub-paragraph (1) above may or may not apply to the present situation. However, it is respectfully submitted that the Kassenoff testimony certainly falls within any one or more of sub-paragraphs (2), (3) and (4).

Sub-paragraph (2)

Concerning sub-paragraph (2), Mr. Kassenoff's testimony in part clearly relates essential to formalities, e.g., the existence of his handwriting in certain documents of record [e.g., see pages 4-5 of the Kassenoff Declaration (WR at 230-231)].

Sub-paragraph (3)

Furthermore, Mr. Kassenoff's testimony should be entirely permitted under sub-paragraph (3), which goes to the nature and value of legal services. For example, he provided testimony concerning his involvement as a member of the Sandoz Patent and

Trademark Department in the activities leading to filing of the Wattanasin application, and policy and practices applied to the filing of the Wattanasin application, as well as examples of cases which he drafted in the HMG-CoA reductase area [e.g., see pages 1-5 of the Kassenoff Declaration (WR at 227-231)].

Indeed, if there were any doubt that the Kassenoff testimony falls squarely within the purview of at least sub-paragraph (3), the underlying PTO commentary makes this crystal clear:

> "One comment suggested that proposed §10.62 should specifically authorize a registered patent practitioner to testify concerning attorney diligence in patent cases. This suggestion is not to be adopted. However, it should be clear that in most cases, the exception of proposed §10.62 (b)(3) would apply.***[citation to Wilder v. Snyder, 201 USPQ 927 (Bd. Pat. Inter. 1977]
>
> [emphasis supplied] 1045 OG 36[7] (see Exhibit F)

Thus, while the PTO drafters did not incorporate into Rule 10.62(b) the above proposed language relating to admissible attorney testimony as to diligence -- probably in the desire to adhere strictly to language paralleling the sister ABA disciplinary rules, DR 5-101(B) and 5-102(A) -- the commentary

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7. Conspicuously absent from the Fujikawa motion is any reference to this PTO commentary, to which Fujikawa were expressly directed by Wattanasin in the undersigned's letter included as Exhibit A to the Fujikawa motion.

does clarify that the present circumstances should fall within the sub-paragraph (3) exception.

The commentary goes on to state that "the weight to be given testimony by a practitioner on behalf of his or her client would be determined on a case-by-case basis" -- which, of course, the Board is free to do with respect to any testimony.

In short, there is nothing in Mr. Kassenoff's testimony, required by Fujikawa's raising of the abandonment issue, which does not legitimately come within exception (3), above.

Sub-paragraph (4)

With respect to sub-paragraph (4), the "hardship exception," it is a given that disqualification of Mr. Kassenoff from this matter would work a substantial hardship on the party Wattanasin. As indicated above, Mr. Kassenoff not only has distinctive knowledge of the HMG-CoA reductase inhibitor area, but also considerable and valued expertise concerning PTO interference procedure. In particular, Mr. Kassenoff has been engaged in the drafting and prosecution of HMG-CoA cases, and building of a patent estate in this subject matter area, since about 1982. Mr. Kassenoff has been a primary liaison with Sandoz management concerning both Sandoz and third-party coverage in the HMG-CoA reductase area. Disqualification of Mr. Kassenoff as a counsel in these interferences would unfairly deprive Sandoz of Mr. Kassenoff's wide technical and patent knowledge gained from substantial experience in the HMG-CoA area. Furthermore, Mr. Kassenoff, as a member of the Sandoz Patent Committee, also has

intimate knowledge of the procedure and practices of the Committee in the rating of patent disclosures.

Accordingly, it is believed that the present facts amply justify application of subparagraph (4) permitting attorney testimony in hardship cases.

2. Caselaw

There appears to be no decisional law under the 1985-enacted 37 CFR 10.62 or 10.63, save for the Domino[8] case referred to by Fujikawa, where, in fact, the Commissioner was concerned with Rule 10.63(b) which is not at issue here, and in any event, denied a motion for disqualification.

This points up a fundamental problem with the legal authority relied on by Fujikawa in their brief: in the context of a highly fact-dependent inquiry such as one directed to attorney impropriety and sanctions, Fujikawa are casting about for support in various judicial dicta and broad-brush restatements of the law -- in complete disregard, however, of the underlying facts which distinguish their cited caselaw from the instant situation.[9]

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8. Little Caesar Enterprises Inc. v. Domino's Pizza Inc., 11 USPQ2d 1233 (Comm. 1989).

9. Fujikawa certainly cast wide for the broad dicta appearing in Lau Ah Tew v. Dulles, 257 F.2d 744 (9th. Cir. 1958), a naturalization case where the attorney's testimony in question concerned his ability to recognize the identity of his client, a petitioner for naturalization.

For example, the 1977 Wilder case (Exhibit G) mentioned in the PTO commentary on Rule 10.62(b) and also cited by Fujikawa, involved an interference situation where the Board, in fact, found "no reason not to accord weight" to testimony given by an attorney for the senior party.

Universal Athletic Sales Co. v. American Gym, Rec. & Ath. Equip. Corp., 192 USPQ 193 (3d Cir. 1976), cert. den. 193 USPQ 570 (1977) (Exhibit H), relied on extensively by Fujikawa, is concerned with a situation where an attorney in the law firm representing the infringement defendant testified as a purported expert as to the invalidity of plaintiff's patent at issue. The Third Circuit vacated the district judge's finding of patent invalidity on the ground that the arguable deficiency of the witness as an expert and his role as an attorney should have prevented his testimony from being given controlling weight to rebut the presumption of validity of an issued patent.

Therefore, the Universal case, notwithstanding its broad-brush restatements of the law amounting to dicta, is limited on its facts to a situation involving expert testimony by a law firm attorney -- which is recognized to be severely deficient to begin with -- being given controlling weight in overcoming the presumption of validity attaching to an issued U.S. patent. The Third Circuit ruling overturning the trial judge's unpatentability finding had to be colored by the obvious deficiencies of the witness's purported expert testimony.

By contrast, Mr. Kassenoff is an in-house counsel being relied on as a fact witness, as even Fujikawa acknowledge. Mr. Kassenoff is not being offered as an expert witness. Nor is Mr. Kassenoff testifying as to the validity of an issued patent. In sum, it is difficult to find any substantive influence that the Universal case on its facts could have as to these interferences.

In very illustration of this point, the court in the succeeding interference case of Wilder, while paying "lip service" to the broad pronouncements in Universal and similar language in 97 C.J.S. Witnesses §71, in fact, chose to admit into evidence the attorney testimony at issue in Wilder.

Even more instructive in an interference setting is a case overlooked by Fujikawa: Wick v. Zindler, 230 USDPQ 241 (Bd. Pat. Inter. 1984) (Exhibit I). In that case, the attorney, Holtz, who prepared the involved application of the senior party, also served as a designated co-counsel in the interference. Holtz's testimony was needed to corroborate the senior party's date of conception.

The junior party moved to exclude the Holtz testimony. In deciding the motion, the Board first referred to the Wilder case for authority that an attorney is competent to serve as a witness for or against his client. In dictum, the Board also recited that this testimony could be discounted. However, in fact, the Board went on to consider the testimony:

> Nevertheless, under the circumstances of this case where Holtz has identified certain documents that the inventor used to explain the invention during conferences with him, we believe that his testimony as to when the conferences occurred and that the invention was then explained and understood by him is entitled to sufficient weight to corroborate conception. We note that Holtz supported his tesitimony with documentary evidence in the form of calendar entries... and entries in his law firm's log of invention disclosures ... [emphasis supplied]

230 USPQ at 246

Finally, reference is made to the case of SMI Industries Canada Ltd. v. Caelter Industries, Inc., 223 USPQ 742 (NDNY 1984) (Exhibit J), which involved an action for patent and trademark infringement, and unfair competition. Denying plaintiff's motion to disqualify defendant's law firm under DR 5-102(A) of the ABA Code of Professional Responsibility, the parallel section to 37 CFR 10.63(a), the court stated that the resulting loss of services would create precisely the kind of hardship which is protected against by sub-paragraph (4) of DR 5-101(B) [analogous to 37 CFR 10.62(b)(4)]:

> Even assuming, arguendo, that members of the Limbach firm ought to be called as witnesses at trial, the court concludes that disqualification is not appropriate in this case. As noted previously, DR 5-101(B)(4) provides that an attorney may continue representation of his client in a proceeding in which the attorney is called upon to testify if disqualification would work a special and unwarranted hardship on the client by virtue of the distinctive value of the lawyer or his firm as counsel in the case.

> In the present case, George Limbach has represented the related predecessor coporation of defendant in patent and trademark matters since 1967, and the Limbach firm has represented defendant and its related companies since early in 1968. The attorney-client relationship has become intimate, and the firm has acquired specialized knowledge of defendant, defendant's related companies, and their operations. The Limbach firm's representation of defendant in the present action involves a complex set of legal and factual issues which the firm has been familiar with for many years. At this late juncture it would work a substantial hardship upon the defendant to require it to retain new counsel. Moreover, there is no basis for concluding that the continued representation by the Limbach firm will prejudice the plaintiff in this proceeding in any way or taint the underlying trial. Accordingly, plaintiff's motion to disqualify pursuant to Canon 5 is denied. [emphasis supplied]

223 USPQ at 748.

It is believed that the disqualification of Kassenoff or any other in-house Sandoz attorney would present no less hardship on the party Wattanasin than is described in the above SMI decision concerning the Limbach disqualification.

Counsel for Wattanasin can understand that there would be legitimate concern to separate the role of an attorney as a witness from the role of an advocate at trial before a jury. Avoiding prejudice before the jury is a guiding consideration in many disqualification cases. However, even in these cases, the courts have often simply prevented the attorney giving testimony from appearing in court before the jury as trial counsel for his client.

Of course, the present case does not involve a jury trial, but a proceeding conducted before a panel of Examiners-in-Chief. Surely the concern to avoid prejudice that informs the ABA's restraints against attorney testimony in jury trials, would not obtain in a patent interference proceeding.

Particularly in a case where an attorney is testifying on behalf of his client, there is a harsh injustice to the client to force him to choose between the attorney's legal knowledge and the attorney's often critical knowledge as fact witness. The hardship is even greater when an attorney is forced to abandon his legal role in mid-stream in order to have his testimony received into the record.

In particular, the policy which Fujikawa now seeks to apply against Wattanasin is manifestly unfair: If the EIC were to approve the Fujikawa motion, this would mean that any corporation which is a party of interest in an interference, would effectively be deprived of the unique legal and technical skill of its own in-house patent staff simply because one or more of those same attorneys may almost necessarily be called as a fact witness concerning activities within the scope of their employment in connection with an involved application.

In summary, the express terms of 37 CFR §10.62(b) and §10.63(a), and the weight of decisional authority as well as

policy considerations, are squarely against disqualification of the Sandoz Patent and Trademark Department, or Mr. Kassenoff individually, from the present interferences. Similarly, it is submitted that under the present circumstances, there is absolutely no reason or justification for discrediting the Kassenoff testimony.

Given the improbability under all relevant legal authorities of his obtaining disqualification of the Sandoz Patent and Trademark Department or of Mr. Kassenoff alone, what Mr. Kelber is transparently really after is "discounting" or "discrediting" of the Kassenoff testimony.

Why Mr. Kassenoff's testimony should be "discounted" as opposed to that of any other witness is not entirely clear. Like the other deposed Wattanasin witnesses, Mr. Kassenoff was subjected to rigorous cross-examination by Mr. Kelber. Even more so than the other, non-attorney witnesses, Mr. Kassenoff would have been conscious of his obligation, as member of the bar and an officer of the court, to uphold his oath. Likewise, Mr. Kassenoff would have been aware of the severe toll on his professional status that could attend violation of his oath. Mr. Kassenoff furthermore being an acknowledged fact witness, there is no good reason to discredit his testimony, and none is really offered by Fujikawa.

FUJIKAWA BELATEDNESS

For whatever reason, Fujikawa have until now -- over three months after the Kassenoff testimony was presented and over a year after Mr. Kassenoff's designation as a deputy counsel of record -- failed to raise any issue of disqualification or "discounting" of testimony, and even have taken cross-examination from Mr. Kassenoff without raising the issue.

In short, Fujikawa are raising an issue long after it should have been raised. To all appearances, Fujikawa saved their motion for a time when opposition to it would have been due one day before Wattanasin's main briefs.

It has to be concluded that the probable cause for the Fujikawa motion for sanctions is that counsel for Fujikawa happened to elicit from Mr. Kassenoff on cross-examination, information going to Sandoz Patent and Trademark Department procedure and the like, which could not be favorable to Fujikawa. Grasping for a rationale to eliminate or discredit this testimony, Fujikawa counsel have fabricated a strategy based on allegations of attorney impropriety. Such belated action and conduct should not be permitted.

CONCLUSION

Accordingly, the Fujikawa motion for sanctions should be denied on the basis of any one or more of the following reasons:

1. The testimony of Melvyn M. Kasssenoff for the party Wattanasin falls within the protected activity of 37 § 10.62(b)(2) and (3), because it constitutes testimony going to formalities and the factual circumstances of his activities in relation to the Wattanasin invention;

2. The testimony of Melvyn M. Kassenoff also falls within 37 CFR 10.62(b)(4), because otherwise the party Wattanasin would be deprived of Kassenoff's in-house technical and patent law expertise, which would work a serious hardhip;

3. The Fujikawa motion is belated, as it could have been filed much earlier. The suggestion by Mr. Kelber that he only became aware of the situation upon filing of the Wattanasin Record is without merit. Mr. Kassenoff has been listed as deputy lead attorney from the beginning of this matter.

4. None of the sanctions sought by Fujikawa is justified, and in fact would only serve to give Fujikawa undeserved advantage to the extent the Kassenoff testimony was discounted. Counsel for Fujikawa caused this testimony to be taken, and subjected Mr. Kassenoff to cross-examination under oath. Counsel for Fujikawa

should face the testimony rather than have the PTO discount it in advance for no justifiable reason.

Finally, Mr. Kassenoff has not been an active participant in these interferences (particularly following his changed responsibilities as of January 1993, referred to above); rather, he has served as a consultant on an intermittent basis concerning technical or PTO procedural matters. Wattanasin would be willing to remove Mr. Kassenoff as deputy lead counsel, but cannot without hardship meet Fujikawa's demands, which would deny the undersigned any right to consult with Melvyn Kassenoff concerning these interferences.

Respectfully submitted,

Diane Furman

Diane E. Furman
Attorney for Wattanasin
Registration No. 31,104
201-503-7332

SANDOZ CORPORATION
59 Route 10
East Hanover, NJ 07936

June 14, 1993

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231, on June 14, 1993
(Date of Deposit)
Diane E. Furman
Name of applicant, assignee, or Registered Representative
Diane Furman
Signature
June 14, 1993
Date of Signature

CERTIFICATE OF SERVICE

It is hereby certified that a true copy of the paper entitled:

WATTANASIN OPPOSITION
TO FUJIKAWA MOTION FOR SANCTIONS

was served on counsel for the party Fujikawa et al., this 14th day of June 1993, by first-class mail addressed to the following:

Oblon, Spivak, McClelland, Maier & Neustadt, P.C.
Attn: Steven B. Kelber, Esq.
1755 South Jefferson Davis Highway
Crystal Square 5, Ste. 400
Arlington, VA 22202

Diane Furman
Diane E. Furman

#112

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

WATTANASIN v. FUJIKAWA ET AL.

INTERFERENCE NO. 102,648

FYI

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REPLY BRIEF OF THE PARTY, WATTANASIN

FOR FINAL HEARING

Diane E. Furman
Sandoz Corporation
Patent and Trademark Department
Building 418
59 Route 10
E. Hanover, NJ 07936-1080
(201) 503-7332
Attorney for the party WATTANASIN

Of Counsel
Richard E. Vila
Melvyn M. Kassenoff
Sandoz Corporation
Patent and Trademark Department
Building 418
59 Route 10
E. Hanover, NJ 07936-1080
(201) 503-7852

September 4, 1993

9/7/93

"RIBBON COPY FOR PARTY" Wattanasin

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

WATTANASIN v. Fujikawa et al.

Interference No. 102,648

REPLY BRIEF OF THE PARTY, WATTANASIN FOR FINAL HEARING

TABLE OF CONTENTS

I. TABLE OF CASES

A. THE STANDARD OF PROOF OF PRIORITY APPLICABLE TO WATTANASIN IS "PREPONDERANCE OF THE EVIDENCE"

Lacking any apparent basis in the decisional law of this Board or any patent court, Fujikawa et al. advance an argument that the Wattanasin proof of priority in this interference must satisfy not a "preponderance of the evidence" standard, as stated in the Wattanasin opening briefs (at p. 12), but a higher standard of "clear and convincing evidence".

Like some of the other arguments raised by Fujikawa, this is at best viewed as a distraction, since it is clearly counter to the longstanding rule of Peeler v. Miller, 190 USPQ 117 (CCPA 1976), that "preponderance of the evidence" is the applicable standard of proof of priority required of a junior party whose involved subject matter was copending with the senior party's application. This standard applies even where, as in Peeler v. Miller itself, the senior party's application matures into a patent prior to the interference.

Nor are Fujikawa helped at all by the recent Federal Circuit decision of Price v. Symsek, 26 USPQ2d 1031 (Fed. Cir. 1993), clarifying that the "clear and convincing" standard applied in a situation where there was no copendency of interfering subject matter.

In effect, by requesting that Wattanasin be held to the higher standard of "clear and convincing evidence," Fujikawa are trying to succeed to the position of the defaulting party, Warner-Lambert, in these interferences.

The parties' respective application files reflect

that each of Fujikawa and Wattanasin had requested the Patent and Trademark Office to declare an interference with Warner-Lambert U.S. Patent No. 4,761,419 (Picard et al.), which was filed on December 7, 1987 and issued August 2, 1988.

But as soon as Interference No. 102,648 was declared as a three-way interference, Warner-Lambert requested entry of adverse judgment as to themselves. Accordingly, on April 10, 1992, such adverse judgment was entered against the Picard et al. patent, and in fact the Picard name has been stricken from the Patent and Trademark Office docket sheet for Int. No. 102,648. It is noted that Picard et al. were completely out of this interfeence before any matters, such as discovery and testimony which require a burden of proof were scheduled to take place.

Now, however, having been freed of the Warner-Lambert threat, Fujikawa want to improve their position further by stepping into Warner-Lambert's shoes vis-a-vis Wattanasin; and applying the higher burden of proof of "clear and convincing evidence" to Wattanasin.

There is also no small irony in Fujikawa's additionally relying on their '930 patent[1] -- which to the extent of claim 1 thereof is involved in Interference No. 102,975 (indeed, on Wattanasin's motion) -- to bootstrap an argument that Wattanasin be held to the higher standard of proof. Even aside from the fact that the '930 patent is only a divisional off the involved copending Fujikawa application, it is at least questionable that the involved claim 1 should ever have

1. U.S. Patent No. 5,011,930, filed February 23, 1990 and issued April 30, 1991..

been allowed by Fujikawa to issue in the first place; and in fact it has been Wattanasin's understanding that Fujikawa were taking this patent into reissue precisely for this reason.[2]

In sum, Fujikawa should not be permitted to step into the shoes of Warner-Lambert in these interferences as a matter of law or policy.

Finally, notwithstanding whether the applicable standard is "a preponderance of the evidence" or "clear and convincing evidence," Wattanasin has by its proofs clearly shown priority in relation to Fujikawa.

B. REVIEW OF FUJIKAWA ARGUMENT

For purposes of these interferences, Fujikawa stand on their earliest Japanese priority date of August 20, 1987 as a constructive reduction to practice of the subject matter of the counts of these interferences.

By way of review, count 3 of Interference No. 102,648 is a compound per se count which recites no utility at all. Count 1 of Interference No. 102,975 is a method of treatment count in which the subject compounds are administered to "a patient" in need of

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2. Said claim was introduced into the divisional application by amendment on July 17, 1990, and is directed to subject matter never even restricted out from the involved Fujikawa parent application. Claim 1 was thereafter allowed to issue out even though it fell squarely within the count proposed by Fujikawa for their interference with the Warner-Lambert patent requested nearly a year before. Note further that Fujikawa chose to direct claim 1 to a subgenus of quinoline compounds comprising both isopropyl and cyclopropyl-substituted species of the count.

such treatment in a pharmaceutical composition.

The essence of Fujikawa's argument seems to be that Wattanasin's in vitro testing of record is insufficient to prove a reduction to practice either of count 3, the compound per se count, or count 1, the method of treatment count; that in vivo testing is needed therefor, but that Wattanasin's in vivo testing is either inadequate for technical reasons or because it was performed on rats.[3] Thus, The Fujikawa view of the situation appears to be that none of Wattanasin's 1984, 1985 or 1987 in vitro testing, or the 1987 Wattanasin in vivo testing, demonstrate a reduction to practice. Fujikawa also present other arguments going to diligence, or the issue of abandonment, suppression or concealment.

C. SUMMARY OF THE WATTANASIN POSITION

Wattanasin respectully disagrees with each and every one of the Fujikawa arguments presented in their briefs.

It is Wattanasin's position that it reduced to practice the subject matter of the counts on each of the

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3. In fact, Fujikawa have moved to have the Engstrom declaration and raw in vivo data stricken from the record, on a technical rationale which is not entirely clear to Wattanasin. Wattanasin is opposing this motion in a paper being filed concurrently herewith. Although Wattanasin concedes that the Engstrom declaration contains a typographical error (later corrected), Fujikawa's confusion may be difficult to accommodate, particularly since Fujikawa chose not to take cross-examination of Dr. Engstrom, a Sandoz employee, even while their counsel spent a day at the Sandoz site in East Hanover, New Jersey, deposing three other Sandoz declarants.

in vitro testing dates of record herein; and that a further reduction to practice comprising both in vitro and in vivo testing occurred in October 1987, coupled with diligence from just prior to the August 20, 1987 Fujikawa benefit date. No inference of abandonment, suppression or concealment can be reached during the period from the last activities for the count, on December 9, 1987 up to the filing of the Wattanasin application on March 3, 1989, a period of 14 months, given the oustanding obligation to file, and the attorney activities which took place during that time period. Nor, for that matter was there abandonment during the mid-1985 to 1987 time period, when for reasons of a manpower shortage, Wattanasin needed to direct his laboratory work to analogous HMG-CoA reductase inhibitor compounds.

A significant part of Fujikawa's arguments are directed to Wattanasin's in vitro and in vivo testing results, and accordingly this data are further discussed in greater detail below.

All of the Wattanasin compounds under consideration are within the count of this interference, and Fujikawa have not argued otherwise. Nor has Fujikawa at all raised an issue concerning corroboration of the invention nor the admissibility of any document of record, with the exception of the Engstrom Declaration and Supplemental Declaration and accompanying Exhibits K-1 and Q.

D. THE WATTANASIN IN VITRO TESTING SATISFIES THE REQUIREMENTS OF AN ACTUAL REDUCTION TO PRACTICE OF COUNT 3 OF INTERFERENCE NO. 102,648 and COUNT 1 OF INTERFERENCE NO. 102,975

Based on the Kathawala article of record and the

affidavit testimony of Kathawala, Wattanasin, Scallen, Damon, it is apparent that from the beginning of his involvement with the quinoline compounds in late 1983, Wattanasin was working in a well-trodden scientific field, i.e. HMG-CoA reductase inhibitor compounds, a field which in fact is now nearly three decades old (Kathawala article, WR at 470-495). By the time Dr. Wattanasin had turned his attention to the quinolines, not only were HMG-CoA reductase inhibitor compounds such as compactin or mevinolin on market and available as standards against which to test the activity of the Wattanasin compounds; but the Sandoz compound XU 62-320 ("fluvastatin") became known as an even more potent standard against which candidate compounds could be tested[4]. Indeed, by 1982, when Sandoz filed on its fluvastatin compound (see WX-Z at 471), Sandoz had possession of a compound which was 146 times more active than compactin in vitro and 40-fold more active than compactin in vivo (WR at 482, 485).

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4. Wattanasin Exhibit Z (p. 471) shows that Kathawala filed his U.S. patent application covering the Sndoz fluvastatin compound (i.e. XU 63-320) on November 22, 1982. It is clear from the cover page of the Kathawala patent as well as the other filings made by Sandoz, that these patents disclose compounds for inhibiting cholesterol biosynthesis, pharmaceutical compositions containing such compounds, and methods of treatment of hypercholesteremia using said compounds.

Note that the European equivalent of the Kathawala fluvastatin application, i.e. EP 114,027 became available to the art in June 1984, and was even cited as prior art against the involved Fujikawa application. Thus in the Fujikawa '930 patent file the EPO search report cites the Kathawala patent publication on fluvastatin as "technological background" to the subject matter of the counts herein. Therefore by no later than June 1984, "technological background" concerning the specific Sandoz HMG-CoA reductase inhibitor compounds, compositions containing them and methods of treatment, was clearly available to one of ordinary skill in the art.

It is a matter of common knowledge that one objective of pharmaceutical research in an already developed field, such as conducted by Dr. Wattanasin herein, is not merely to meet the activity of a known standard such as compactin or fluvastatin, but to meet it and also exceed it. However, this is a different standard from that needed to demonstrate a reduction to practice of a species within a count of an interference, i.e. a practical utility.

As outlined in the Wattanasin opening briefs at page 18 et seq., Terence Scallen, M.D., Ph.D., of the Department of Biochemistry at the University of New Mexico, testified concerning the in vitro testing of compounds for HMG-CoA reductase inhibition which he carried out for Sandoz since 1980 (WR at 187). Dr. Scallen testified that he used an "established protocol" based on published methods dating from 1977 (WR at 188-189) to test the activity of compounds of the count. The in vitro testing involved the use of rat liver microsomes as the source of HMG-CoA reductase enzyme to treat radiolabeled HMG-CoA, i.e. the substrate of HMG-CoA reductase, in the presence of test compound. The amount of radiolabeled mevalonate, which is the product of the reaction of HMG-CoA reductase and its substrate, HMG-CoA, indicated the relative potency of the test inhibitor compound at a given concentration (WR at 189)[5]

The raw data generated by Dr. Scallen in Wattanasin Exhibits E-1 to E-5 shows the activity level of each tested compound at different concentrations.

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5. In Cross v. Iizuka (discussed below), a microsomal system was also used to test compounds in vitro alongisde known standards, see 224 USPQ at 744.

Fujikawa's rebuttal witness, Dr. Holmlund, indicated that a similar in vitro assay on compactin had been performed in his lab:

> Q. Was that [assay] fairly consistent with the in vitro assay presented in the [Wattanasin] exhibits?
> A. Yes.

FR at 231

Based on this assay, Dr. Holmlund himself verified that compactin, used as a standard in the Scallen assays, "functioned as a competitive inhibitor" of HMG-CoA reductase enzyme (FR at 231).

With this basic art-recognized assay, Dr. Scallen tested "numerous" Sandoz compounds for the same HMG-CoA reductase inhibition activity, which differed only by having a different organic radical substituent instead of quinoline (e.g., napthyl, indole, etc.) on the dihydroxy heptenoic acid side chain. A glance at Wattanasin Exhibit E-5, for example, reflects testing of 36 compounds for HMG-CoA reductase activity in the period from December 4-17, 1984; 32 compounds in the period from June 13-26, 1985; 9 compounds on October 8, 1987; and 7 compounds on October 13, 1987.

What is most important is that every one of these in vitro assays was done not only against standard controls, but also side-by-side with the industry standard, compactin (WR at 472). Most of the assays were also carried out with side-by-side testing of the known Sandoz HMG-CoA reductase inhibitor, fluvastatin (62-320) (WR at 482, 488-89).

This concerted in vitro testing program documented by Wattanasin is consistent with the kinds of established large-scale testing of compounds typically carried out by pharmaceutical research houses, for example by the junior party, Pfizer, as described in Bigham v. Godtfredsen, infra.

It is obvious from the IC_{50} data in the Damon declaration (WR 199, WX J-1) that all of the Wattanasin compounds were active in vitro, even if some were not as potent as compactin or fluvastatin against which they were tested.

The knowledge of the activities of the first group of tested compounds 63-366, 63-548 and 63-549 was enough to tell Wattanasin that the other compounds would be active. That is the reason why Wattanasin had the certainty that if the initial compounds had activity, he would want to make all of them. This is particularly true since the compound having greatest structural similarity to the highly active fluvastatin compound, i.e. compound 64-935, while the earliest conceived (WX A-2), remained to be synthesized in the "second phase" of activity begun in March 1987. Compound 64-935 on testing did prove to be the most active of the compounds tested in vitro (WR at 199).[6]

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6. Note that Fujikawa are not well-served by their citation to Bigham v. Godtfredsen, 222 USPQ 632, 637 (POBI 1984), to the extent that Board of Patent Interferences in that opinion accepted the junior party's in vitro testing of antiobiotic "prodrug" compounds in bacteria to satisfy the requirements of a reduction to practice of the subject matter of the compound per se counts therein at issue, "particularly since the activity of the test compound was compared with that of [the known antibiotic] ampicilin" (emphasis supplied), 222 USPQ at 637. In doing so, the Board hewed to the authority of Nelson v. Bowler, 206 USPQ 881 (CCPA 1980), previously cited by Wattanasin, that a

Dr. Scallen further testified that he had performed the in vitro testing of compactin and fluvastatin prior to December 31, 1984, and knew the in vivo activity levels of these compounds. On this basis, it was his judgment that the level of in vivo activity of a compound as a cholesterol inhibition "is typically highly correlatable to its in vitro activity in his assays (WR at 193) and "would be" active in vivo (WR at 194). Dr. Damon also testified that "there was a high probability" that each of the Wattanasin compounds would have in vivo activity (WR at 200-201).

In short, by the time the instant invention was made, there was an art-recognized correlation between the standard in vitro tests and the typical in vivo tests in the art, which was clearly indicative of practical utility in the manner of compactin and fluvastatin. It is also clear that the prior art, as evidenced by the Sandoz patent filings, contained ample direction as to dosage amount and methods of treatment for hypercholesterolemia in patients in need of such treatment.

On this basis, against the background of the prior art experience with preparing and testing HMG-CoA reductase compounds, Wattanasin submits that the in vitro tesing alone provided an actual reduction to practice of the subject matter of each of count 3 and

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(Footnote 6 continued from previous page)
standard in vitro test may be sufficient to demonstrate pharmacological activity of a compound, i.e. a "practical utility," id.

(Other cases cited by Fujikawa in their Briefs at 32-33, regardless of their dicta, are judged irrelevant; Kahl, Symmes, Newkirk and Alsenz all concern mechanical devices.)

and count 1 of the subject companion interferences, both prior to and continuing after the Fujikawa benefit date.

Fujikawa repeatedly assert that the in vitro testing conducted by Scallen does not meet the standards for an actual reduction to practice. According to Fujikawa, the standard is "not that they might work, but that the compounds would work" (Fuj. Brief at 37), or elsewhere, "will work" (Fuj. Brief at 33).[7]

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7. Note that the Federal Circuit court in Cross v. Iizuka, 224 USPQ 739 (Fed. Cir. 1985), has enunciated a standard of "reasonable correlation" between in vitro and in vivo activities for purposes of establishing practical utility:

> We *** find ourselves in agreement with the Board that, based upon the relevant evidence as a whole, there is a reasonable correlation between the disclosed in vitro utility and an in vivo activity, and therefore a rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence. Cf. Nelson, 626 F.2d at 856, 206 USPQ at 883-83.

And further:

> Employing a microsome assay, the skilled worker could determine the relative strength of the compounds of the count vis-a-vis the known parent imidazole and 1-methylimidazole compounds. Thus the dosage in the microsome assay milieu could be determined without inventive skill or undue experimentation.
>
> Today, under the circumstances of the instant case, where the Japanese priority application discloses an in vitro utility, i.e., the inhibition of thromboxane synthetase in human or bovine platelet microsomes, and where the disclosed in vitro utility is supplemented by the similar in vitro and in vivo pharmacological activity of structurally similar compounds, i.e., the parent imidazole and 1-methylimidazole compounds, we agree with the Board that this in vitro utility is sufficient to comply with the practical

As an example of the purported uncertainty in the Wattanasin in vitro assays, Fujikawa (Briefs at 37) go on to cite certain Holmlund testimony (actually elicited on cross-examination) (FR 236-237) to the effect that, given the 10 to 20 steps necessary to convert the starting material in the cholesterol biosynthetic pathway, namely acetate, to the end product, cholesterol, it is "almost impossible" to set up an in vitro assay for a cholesterol lowering compound where all the necessary requirements are present to be predictive of in vivo activity.

On the contrary, had Fujikawa or Dr. Holmlund himself really undertaken to understand the scientific basis of the Scallen assays, they would realize that these assays are highly accurate predictors of in vivo activity. This is because the starting material used in the Scallen assays is not the "omnibus" acetate material to which Dr. Holmlund was referring, which is not even

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(Footnote 7 continued from previous page)
utility requirement of §101.

*** in vivo testing is but an intermediate link in a screening chain which may eventually led to the use of the drug as a therapeutic agent in humans. We perceive no insurmountable difficulty, under appropriate circumstances, in finding that the first link in the screening chain, in vitro testing, may establish a practical utility for the compound in question.***

acted on by the HMG-CoA enzyme; but rather, is radio-labeled "HMG-CoA" substrate (i.e. β-hydroxy-β-methyl-glutaryl- CoenzymeA) (see WR at 189, WX E-1 to E-5).

It is this HMG-CoA substrate that the enzyme, HMG-CoA reductase (also referred to as "HMGR"), specifically acts on to reduce the HMG-CoA to mevalonic acid, the next compound in the cholesterol biosynthetic chain (WR at 552).

What is so critical is that the action of HMG-CoA reductase enzyme on HMG-CoA substrate constitutes the rate limiting step in the cholesterol biosynthetic pathway (WR at 496). Accordingly, an assay which tests precisely for inhibition of HMG-CoA reductase enzyme is an extremely specific, pinpoint indicator of whether and to what extent inhibition of this specific rate-limiting step will occur. Inhibition of HMG-CoA reductase enzyme is a proven approach to the treatment of hypercholesteremia (WR at 551).

In point of fact, Dr. Holmlund's testimony concerning the limitations of an in vitro assay using acetate as a starting material impeaches none other than Fujikawa's own in vitro assays on which they premise a constructive reduction to practice. Reference is made to "Tests A and B" of the involved Fujikawa application and priority documents, where-- just as Dr. Holmlund was describing -- radiolabeled sodium acetate was provided to an heterogenous enzyme mixture from rat liver tissue; and at the end a lipid product was extracted and its radioactivity measured. This is precisely the kind of assay that Dr. Homlund implied was not sufficiently meaningful of HMG-CoA reductase inhibition (FR at 234).

It is not judged irrelevant that Fujikawa's own

Japanese applications dating from August 20, 1987 and January 26, 1988 contain only in vitro data, and absolutely no in vivo data. [Despite the limitations of the Fujikawa assays described above, it is noted that they do test against the same standard as Wattanasin, i.e. compactin, as well as another industry standard, CS-514 (pravastatin).]

There is a certain inconsistency in Fujikawa's taking a position against Wattanasin's in vitro data on the basis that it does not demonstrate practical utility for purposes of an actual reduction to practice while, at the same time, Fujikawa relies on admittedly flawed in vitro testing to establish compliance with 35 USC §§101 and 112 for purposes of a constructive reduction to practice. Clearly, Fujikawa rely solely on in vitro results as an indication of practical utility of the subject matter of the count, and they projected in vivo dose ranges from such data. Thus Fujikawa must necessarily agree that in vitro testing in this art is recognized as indicative of in vivo practical utility.

In fact, it is hard to see how the Board could accept Fujikawa's allegations that Wattanasin failed to establish an actual reduction to practice by virtue of its in vitro assays, without sua sponte also depriving Fujikawa of their constructive reduction to practice benefit dates of August 20, 1987 and January 26, 1988 based solely on their in vitro testing.[8]

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8. In point of fact, it was not until Fujikawa's last filed priority application of August 3, 1988, some 10 months after Wattanasin did its in vivo testing, that any in vivo testing entered the Fujikawa filing. Of course, if Fujikawa were confined to the date of their application reflecting in vivo testing they would be well behind Wattanasin's in vivo testing in October of 1987.

Notwithstanding Fujikawa's assertions at page 42 of their Briefs that the Federal Circuit court in Cross v. Iizuka, 224 USPQ 739 (Fed. Cir. 1985) was concerned with a constructive reduction to practice situation (and is therefore unavailing to Wattanasin), the opinion does not appear to countenance such a distinction. In fact, not only did the court in Cross look for guidance to the rulings of its predecessor court in such cases as Nelson v. Bowler, 206 USPQ 881 (CCPA 1980), which dealt with the requirements of an actual reduction to practice, but the court went on to state as follows:

> We recognize that Nelson dealt with tests which were found adequate to establish an actual reduction to practice, as opposed to a constructive reduction to practice. We agree with the Board that principles applicable to a determination of an actual reduction to practice are generally germane to a constructive reduction to practice. (emphasis supplied)

224 USPQ at 744

As a further matter, Fujikawa persists throughout in confusing the difference between a compound that is inactive, and variations in potency which generally occur across any claim of a series of therapeutic compounds. As the Federal Circuit court stated in Cross:

> Variation in potency is a matter of degree of activity, but is still indicative of activity. There is no requirement that the compounds have the same degree of activity.

224 USPQ at 746.

Indeed, the Warner-Lambert article made of record by Fujikawa and relied on in their briefs at p. 38, speaks of just such variations in potency among the

quinoline compounds of the count. This article in fact affirms that the (4-fluorophenyl), 2-(1-methylethyl) substitution which characterizes the Wattanasin 64-935 compound, as well as the fluvastatin compound, "afforded optimum potency" (455). Another of the compounds was found to be "as potent in vitro as Compactin and Mevinolin and more potent than the corresponding free base, although slightly less potent in vivo (455). One compound was even found less potent in vitro but comparable to Compactin in vivo. There appears to be no indication that any of the tested compounds was inactive. If anything, this article stands as ex poste facto confirmation of the Wattanasin demonstration of the practical utility of the quinoline compounds at issue in this interference.

In their Briefs at 43-44, Fujikawa are arguing against the whole weight of developed knowledge in the HMG-CoA area concerning structure activity relationships (SAR) within a series. SAR are so powerfully predictive in this area that Kathawala found "surprising" even one departure from the established relationship in the indole series.

It is submitted that both legally and scientifically on the record in these interferences, Wattanasin demonstrated the practical utility of the subject matter of counts 1 and 3 at issue.

Even Dr. Homlund, acknowledged the following as a general proposition:

> Q. In any series of compounds in pharmaceutical research, if compounds active in vitro were found to be active in vivo subject to the exceptions that can always be encountered in research, would it be a fair assumption that for that given series, that it

is likely that a compound active *in vitro* would be then active *in vivo*?

A. You are referring to other members of a series of compounds, analogs.

Q. Where there is substantial background in the series of both *in vivo* and *in vitro* activity. We recognize that there are always exceptions.

A. I would have to say yes."

Q. Would you accept, subject to exceptions that might occur, that the failure to find that activity would be considered an exception, that there would be a reasonable expectancy against the background of the hypothetical I gave you?

A. I think I probably would accept that."

Accordingly, Wattanasin submits that the *in vitro* testing constituted a reduction to practice of the subject matter of each of counts 3 and 1 of the subject companion interferences.

E. THE WATTANASIN IN VIVO TESTING ALSO MEETS THE REQUIREMENTS OF A DEMONSTRATION OF PRACTICAL UTILITY OF COUNTS 1 AND 3

Wattanasin also submits that with the comparative *in vivo* testing in rats of the quinoline compounds of the Wattanasin invention against the known compactin or fluvastatin, the practical utility of the subject matter of each of counts 1 and 3 was confirmed.

First of all, Dr. Holmlund did acknowledge that the Engstrom *in vivo* assays were run on a very stringent basis, so that even compactin, with an ED_{50} of as high as 3.5, would have registered inactive:

Q. *** If you were to *** run an assay where the break point for ED_{50} is 1 and the ED_{50} of Compactin is 3.5, would it be your conclusion that you are running an assay for compounds that are considerably more active than Compactin?

A. Yes.
Q. So, it might be fair to say that you are setting a rather high standard?
A. Yes.

* * *

FR at 216-17.

And further:

> Q. If a compound were revealed to have an ED_{50} of 3.5 in the in vivo assay, in other words, the same level as we have assumed for Compactin, would it be your judgment that that would be an active compound in this field?
> A. ...Under the circumstances, I would say yes.
> Q. That's a fair assumption, Doctor. Would you say that there could be levels of activity above 3.5 where you could reach the same conclusion, 3.6, 3.7? I don't believe it is necessary to try and define what limits are, but higher than 3.5 could be considered an active useful compound in this field?
> A. Yes, by the very definition of ED_{50}.
> Q. But it would, nevertheless, in your mind at a dose bring the appropriate response in the body the same as Compactin might?
> A. It would be classified as an active compound.
> Q. As an HMG-CoA reductase inhibitor?
> A. Yes, in vivo.

FR at 218-19

Concerning the raw in vivo data respecting compounds 64-933 and 64-936[9], for example, Dr. Holmlund

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9. Fujikawa attempts to contrive an argument surrounding the absence of a sodium salt indication, i.e. "NA", from the Sandoz database printout included in Wattanasin Exhibit K-1 (at 336). However, notice that on pages 203, 205 and 209 of the Wattanasin record "64-936" is used interchangeably with the designation "64/936/NA", just as the Sandoz fluvastatin compound, a sodium salt (technically, "62-320/NA"), is typically referred to as, simply, 62-320 (WR at 484), without the added sodium designation. It is hard to see how

acknowledged as follows:

> Q. Then that does not rule out the possibility this compound could be judged active at a higher dose than tested here?
> A. That's correct.
> Q. Would it be your same testimony for the compound 64-936 on record page 336?
> A. Yes, it would be. Since there are no testing results available there is always the possibility for any compound, that at a higher dose, it may manifest activity.
> Q. Do you regard this compound as showing significant activity at the dose level of .3 milligrams per kilogram?
> A. Yes.

FR at 244

The three Wattanasin compounds 94-633, 94-635 and 94-636/NA were tested in vivo in a very stringent assay designed to find compounds essentially 3.5 times more active than compactin (the tested ED_{50} cut-off point was 1.0 whereas compactin has an ED_{50} of 3.5 in these tests.) Two of the tested compounds failed to have an ED_{50} of 1.0 and hence were inactive in the test (but could have shown activity in a higher scale test as acknolwedged by Dr. Holmlund). But one of the Wattanasin compounds, 64-935, showed a highly active ED_{50} of 0.49 in the in vivo test, which result was recorded in the official Sandoz database and reported by Wattanasin. Dr. Holmlund criticized this 0.49 reading, since the raw activitiy data at 0.3 was somewhat lower than the activity value at 0.1 (see Exhibit K-1), and indicated the test should have been repeated to be certain of the result. Whether or not Dr. Holmlund's observation has any technical value, the 0.49 result was

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(Footnote 9 continued from previous page)
Fujikawa could allege "problems" with usage that is common in the art, and is manifestly apparent throughout the Wattanasin record.

accepted by Sandoz which had long experience in such testing.

Moreover, Dr. Holmlund himself acknowledged that 64-935 was active under such stringent in vivo testing conditions because the result of the 1.0 milligram test dose was clearly above the 50% reduction level. This testimony appears at FR 243 as follows:

> Q. I would refer you to the result of 1 milligram per kilogram for this compound 64-935, the minus 65.8, I believe it is. Does that show that this compound is active at that dose?
> A. Yes.

Fujikawa has advanced various arguments for suppression of the Sandoz database printout included in Exhibit K-1. However, this ED_{50} data merely re-present the same data as are apparent from the notebook pages in Exhibit K-1. And Dr. Holmlund himself testified that he "had no quarrel" with the statistical analysis used to generate the Wattanasin ED_{50} data. Furthermore, based on the raw data included in Exhibit K-1, it is patentably obvious that the ED_{50} for either of 64-933 or 64-936/NA was inadvertently "switched" in the Engstrom declaration. This is an obvious typographical error which should not result in suppression of the in vivo data, as Fujikawa would have it. In fact, the typographical error in the original Engstrom declaration was not even noted until after the Engstrom supplemental declaration was put in. The supplemental declaration records activity for the count on May 23-24,1988; and therefore primarily goes to the issue of abandonment, suppression or concealment.

Finally, at page 35 of their Briefs, Fujikawa challenge Wattanasin's allegation that Dr. Holmlund

--despite his lengthy C.V. of record -- demonstrated only limited familiarity with the precise field of HMG-CoA inhibition which was not up to the level of an ordinary worker in the field.

Accordingly, Wattanasin notes that Dr. Homlund indicated that he "could not recall" the structure of even the industry standard, compactin (WR at 238), and Wattanasin proffers the following full quotation from the record:

> Q. Are you familiar with any heterocyclic inhibitors of HMG-CoA reductase.
> A. Not so that I could draw any structures for you.
> Q. Are you familiar with any of the findings in the art concerning these compounds, the activity levels of these compounds?
> A. I don't have any IC_{50} or ED_{50} values in mind for any of these compounds.
> Q. Do you know the structure of Mevinolin?
> A. Close. It is fairly similar in structure to mevalonate lactone itself. But I don't recall its exact structure.
> Q. Are you familiar with the Sandoz Fluvastatin compound?
> A. No.
> Q. You do not know its structure?
> A. I do not.
> Q. Do you know its structure activity relationships which are in the literature?
> A. I do not.
> Q. Do you know the structure activity relationships for the Pyrazole HMG-CoA reductase inhibitor?
> A. No.
> Q. For the Pyrimidine?
> A. No.
> Q. So you yourself have never actually run an *in vitro* or *in vivo* assay of an HMG-CoA reductase compound?
> A. That's correct.

WR at 234-40

Fujikawa have even gone so far as to suggest that the in vivo tests in rats performed by Wattanasin were inadequate to show utility in humans; but this argument is clearly contrary to the weight of the caselaw, see, e.g., Cross, supra, and of course is certainly contradicted by their own testing in rats.[10] Moreover, the Wattanasin application does teach, broadly, administration to "animals, e.g. mammals."

F. THERE WAS NO ABANDONMENT, SUPPRESSION, OR CONCEALMENT OF THE WATTANASIN INVENTION; NOR WAS THERE ANY LACK OF DILIGENCE IN CONNECTION THEREWITH

It is believed that the issue of diligence between the period just prior to the Fujikawa priority date of August 20, 1987 and the in vitro and in vivo testing which filed, has been fully addressed in the Wattanasin opening briefs in these interferences filed July 15, 1993; and it does not appear that Fujikawa contest diligence as to this period.

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10. Blicke v. Treves, 112 USPQ 472 (CCPA 1957) in fact addressed this type of situation:

> Here, Treves is relying for his constructive reduction to practice on applications which do not specifically mention human therapy, but merely state that the compounds disclosed are useful as mydriatics and antispasmodics, and, as evidence of such utility, describe tests on animals only. Having been granted patents on the basis of such disclosures, we fail to see that he is in a favorable position to argue that Blicke must show actual tests on human beings in order to establish an actual reduction to practice.

USPQ at 476

Parenthetically, Wattanasin's undersigned attorney, is dismayed by Fujikawa's statement in their Briefs that Wattanasin "seriously misrepresented" the Blicke decision by simply citing this case for the proposition that a reduction to practice must be considered on a case-by-case basis.

With respect to the issue of abandonment, suppression or concealment of the invention, it is likewise submitted that the Wattanasin briefs fairly and completely address this issue, both as it goes to the period from mid-1985 to March 1987; and as it goes to the period between December 9, 1987 (when Engstrom completed his activity for the count by entering the ED_{50} data in the Sandoz database), and the filing of the Wattanasin patent application on March 3, 1989 by attorney Joanne M. Giesser, a period of 14 months.

As concerns the Fujikawa argument that Wattanasin was not "diligent" in the period between mid-1985 and early 1987, when work resumed within the counts (Fuj. Briefs at 55-57): diligence need not be proved when an invention has been reduced to practice prior to entry of the other party; and the record shows a reduction to practice by Wattanasin three time by mid-1985.

G. FUJIKAWA ARE NOT ENTITLED TO PROPOSED COUNTS DIRECTED TO CYCLOPROPYL SPECIES OF THE COUNT

The EIC denied Fujikawa's motion to add counts to a separate cyclopropyl species already within the scope of counts 1 and 3 of these interferences. It is respectfully submitted that the decision of the EIC should stand.

As a first matter, Fujikawa's argument for separate counts is compromised by their own improvidential statement in their very request for interference of their involved application with the Warner-Lambert Picard et al. patent:

"there is absolutely no evidence of record that the varying species embraced by both claims [i.e. claim 1 of Fujikawa and claim 1 of the Picard patent, both encompassing the cyclopropyl species] are patentably distinct from the unsubstituted compound discussed above."

Additionally, it is noted that during prosecution of the involved Fujikawa application, Fujikawa resisted any restriction of their invention, then later took out subgeneric claim 1 of their '930 patent directed to both the isopropyl and cyclopropyl -substituted species. Now Fujikawa is in the position of arguing that their cyclopropyl species are patentably unobvious even over the isopropyl species.

The Kitahara Declarations of record do not seem to rationalize the Fujikawa argument for separate cyclopropyl counts. If anything, the data therein might arguably support a separate count to the combined isopropyl and cyclopropyl species; but of course such a count would encompass Wattanasin's proofs of prior reduction to practice.

Fujikawa have failed to establish two requisites for entering a separate cyclopropyl (4-fluorophenyl) species count in this interference:

(1) The claims proposed to be added by Wattanasin do not comply with 35 USC 112 in the Wattanasin application, and therefore do not meet the requirement of 37 CFR 1.637(c)(1)(iii).

(2) Fujikawa have failed to demonstrate the separate patentability of the cyclopropyl species over the genus of Counts 1 and 2.

It is concluded that the comparative data presented by Fujikawa, to the extent meaningful, merely indicate activity of the cylopropyl species as an HMG-CoA reductase inhibitor which is well within the range of normal expectancy across the genus of quinoline compounds corrresponding to Counts 1 and 2, particularly given the teachings and expectations of the prior art which point to ispropyl, cyclopropyl and 4-fluorophenyl as clearly preferred features (it also being noted that cyclopropyl is a mere ring homolog of isopropyl).

The Wattanasin paper filed in Interference 102,648 entitled: "Opposition of Wattanasin to Fujikawa et al. Motion to Add Counts and to Add Claims to Wattanasin Application" mailed July 1, 1992, is hereby incorporated by reference. A copy of said paper is enclosed in Appendix A hereto.

H. THE KASSENOFF TESTIMONY SHOULD NOT BE DISCREDITED

Fujikawa argues that Wattanasin has "relied heavily" on the testimony of its in-house patent attorney, Melvyn M. Kassenoff; and that since Mr. Kassenoff is indicated to have of counsel status on the Wattanasin briefs, his testimony, with certain exceptions, should be discredited.

To whatever degree Wattanasin has relied on the Kassenoff testimony, it is submitted that no such discrediting is appropriate under the present circumstances.

First, the testimony of Melvyn M. Kasssenoff for the party Wattanasin falls within the protected activity of 37 § 10.62(b)(2) and (3), because it constitutes testimony going to formalities and the factual

circumstances of his activities in relation to the Wattanasin invention;

Second, the testimony of Melvyn M. Kassenoff also falls within 37 CFR 10.62(b)(4), because otherwise the party Wattanasin would be deprived of Kassenoff's testimony, which would work a serious hardship;

Third, the Fujikawa motion is belated, as it could have been filed much earlier. The suggestion by Mr. Kelber that he only became aware of the situation upon filing of the Wattanasin Record is without merit. Mr. Kassenoff has been listed as deputy lead attorney from the beginning of this matter.

Fourth, discrediting the Kassenoff testimony would only serve to give Fujikawa undeserved advantage. Counsel for Fujikawa caused this testimony to be taken, and subjected Mr. Kassenoff to cross-examination under oath. Counsel for Fujikawa should face the testimony rather than have the Board discount it for no justifiable reason.

The Wattanasin "Opposition to Fujikawa Motion for Sanctions," dated June 14, 1993, in Interference Nos. 102,648 and 102,975, is hereby incorporated by reference and enclosed as Appendix B hereto.

I. CONCLUSION

For the reasons discussed above and in the Wattanasin opening briefs in Interference Nos. 102,648

and 102,975, it is respectfully submitted that Wattanasin has proved priority over Fujikawa by a preponderance of the evidence, or by clear and convincing evidence.

Respectfully submitted,

Diane E. Furman
Attorney for the Party Wattanasin
Registration No. 31,104
201-503-7332

SANDOZ CORPORATION
59 Route 10
E. Hanover, NJ 07936

September 4, 1993

DEF:rmf

APPENDIX A

Case No. 600 /101/CONT
Patent

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

WATTANASIN
v.
PICARD et al.
v.
FUJIKAWA et al.

Interference No. 102,648
Examiner-in-Chief: M. Sofocleous

OPPOSITION OF WATTANASIN
TO FUJIKAWA ET AL. MOTION TO ADD COUNTS
AND TO ADD CLAIMS TO WATTANASIN APPLICATION

SUMMARY

The party Wattanasin hereby opposes the party Fujikawa et al.'s motion to redefine the interference by adding proposed Counts 3 and 4.

The opposition is on the ground that the party Fujikawa et al. (hereinafter "Fujikawa") are not in compliance with 37 CFR 1.637(c).

More particularly, Fujikawa have not met the requirements of either or both of, sub-sections (c)(1)(iii) and c(1)(v) of Rule 637.

First, with respect to 37 CFR (c)(1)(iii), there is no written description in the involved application of Wattanasin, of the subject matter of species claims 11 and 12 which Fujikawa have proposed to Wattanasin to correspond to proposed Counts 3 and 4. Since the Fujikawa proposed claims 11 and 12 do not comply with 35 USC 112, written description requirement, Fujikawa have failed to meet the requirement of 37 CFR 1.637(c)(1)(iii) that proposed claims be patentable to the other party. Accordingly, given that

Fujikawa are unable to propose claims to Wattanasin corresponding to their proposed narrow counts, which also meet the written description requirement of 35 USC 112, the Fujikawa motion to redefine the interference should be denied.

Second, the Fujikawa proposed Counts 3 and 4 do not define a separately patentable invention from the subject matter of Counts 1 and 2 of this interference, as required by 37 CFR 1.637(c)(1)(v).

The proposed counts 3 and 4 cover a cyclopropyl (4-fluorophenyl)-substituted quinoline species within the generic scope of Counts 1 and 2 of the present interference.

As the basis for separate patentability of the counts, Fujikawa allege that the cyclopropyl (4-fluorophenyl) species exhibits "unexpected improvement" in HMG-CoA reductase inhibition activity compared to that of its closest structural isomer, i.e. the corresponding isopropyl spcies.

It is the position of Wattanasin, however, that: (1) the state of the art even prior to the earliest Fujikawa priority date included a recognition that improved HMG-CoA reductase inhibition activity was exhibited by both isopropyl- and cyclopropyl-bearing nitrogen-containing (4-fluorophenyl bearing) heterocycles; (2) that the Fujikawa comparative data submitted into the record do

not indicate an improvement in activity of cyclopropyl (4-fluorophenyl) over isopropyl (4-fluorophenyl) that rises to the level of "unexpectedness," particularly given the clear direction in the art to prepare the cyclopropyl (4-fluorophenyl); and (3) that the Fujikawa comparative data of record are deficient in not presenting a comparison of the cyclopropyl species of the Fujikawa proposed counts 3 and 4 at issue with other cyclopropyl species within counts 1 and 2 of this interference which are excluded from the scope of the Fujikawa proposed counts.

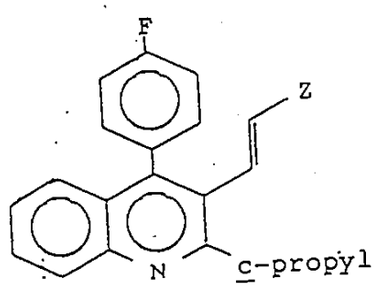
For the above reasons, which are more fully described below, Wattanasin requests that Fujikawa's motion be denied.

BACKGROUND

Fujikawa moved to redefine the present interference by adding proposed Counts 3 and 4.

Fujikawa's proposed Count 3 is directed in essence to a single species embraced by Count 1 (as well as Wattanasin's proposed Substitute Count 1). This species has the following structural formula:

(A)



(where Z is selected from the group consisting of 3,5-dihydroxy- substituted carboxylic acids, sodium and calcium salts, and C_{1-3}alkyl esters thereof, and the lactone formed by condensation of the carboxylic acid with the hydroxy at the 5-position)

Fujikawa's Proposed Count 4 is directed in essence to a method of using a compound of proposed Count 3.

It will be noted that in the above structural formula (A), the quinoline ring is substituted at the 2-position, i.e. between the nitrogen atom and the "Z" substituent, by cyclopropyl. Also, the quinoline ring is substituted at the 4-position by 4-fluorophenyl.

Compounds having structural formula (A) are hereinafter referred to collectively as the "cyclopropyl (4-fluorophenyl) species" (or alternately, the "cyclopropyl species").

It will be further noted that compounds disclosed by Fujikawa in their involved application which are similar in structure to the cyclopropyl species but which fall outside the scope of proposed Counts 3 and 4 comprise:

(i) compounds of structure (A), with the sole exception that cyclopropyl is replaced by isopropyl (see compound of claim 6 of Fujikawa application) [referred to herein as the "isopropyl" or "isopropyl (4-fluorophenyl)" species].

(ii) compounds of structure (A), with the sole exception that fluorine is replaced by chlorine (see compound of claim 18 of Fujikawa application).

The cyclopropyl species which is the subject of proposed Counts 3 and 4 is embraced by Counts 1 and 2 of this interference. Additionally, the cyclopropyl species falls within the scope of claims 1-5, and 32-34, and newly presented claims 41-44, of the Fujikawa involved application, as well as claim 1 of Fujikawa U.S. Patent No. 5,011,930, which Fujikawa have indicated is being taken into reissue. The cyclopropyl species also falls within the generic scope of claims 1-3 and 8-10 of Wattanasin's involved application.

To correspond to proposed Count 3, Fujikawa have proposed to Wattanasin added claim 11, which is directed to the cylopropyl (4-fluorophenyl) species.

As corresponding to proposed Count 4, Fujikawa also propose a claim 12 to Wattanasin which is directed to the use of a compound of claim 11.

In support of proposed Counts 3 and 4, Fujikawa represent that the cyclopropyl (4-fluorophenyl) species of the proposed counts has "unusually high" activity as an inhibitor of cholesterol biosynthesis relative to the genus covered by Count 1, and that "nothing of record" would predict the increased activity associated with the cyclopropyl substituent. A Declaration of one

of the named co-inventors, Masaki Kitihara, is presented for the purpose of demonstrating the "unexpectedly superior" activity of the cyclopropyl species relative to its structural isomer, i.e. the corresponding isopropyl species, as well as homologs of isopropyl.

ARGUMENT

Fujikawa's motion to add proposed claims 11 and 12 to the involved application of Wattanasin should be denied.

Wattanasin discloses quinoline compounds substituted at the 2-position by (1) isopropyl or (2) C_{3-7}cycloalkyl. However, while the involved application of Wattanasin certainly covers within its generic scope compounds which are substituted by cyclopropyl, there is no description by Wattanasin of a cyclopropyl species, as acknowledged by Fujikawa.

Neither the term "isopropyl" nor the term "C_{3-7}cycloalkyl" provides a written description of "cyclopropyl" for purposes of 35 USC 112.

Since Wattanasin does not provide a written description in its involved application of the species proposed by Fujikawa, Fujikawa has failed to comply with 35 USC 112.

Fujikawa, in proposing claims to Wattanasin, are required to show the patentability of the claims to Wattanasin, 37 CFR 1.637(c)(1)(5), MPEP 2338.

Since Fujikawa are unable to establish the patentability of their proposed claims to Wattanasin, the Fujikawa motion to redefine should be denied.

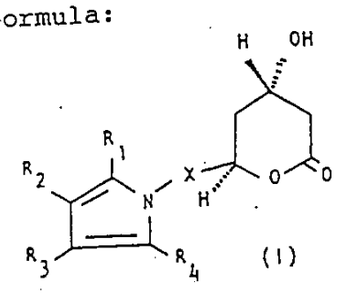
Even assuming arguendo that Fujikawa had fully complied with 37 CFR 1.637(c)(1)(iii) by proposing a claim to Wattanasin which fulfilled the requirements of 35 USC 112, the Fujikawa motion should still be denied because the proposed Counts 3 and 4 do not define a separately patentable invention.

It is self-evident that the question of separate patentability of the cyclopropyl (4-fluorophenyl) species, independent of the genus in which it is contained, involves the principle of selection. That is, the patentability of Fujikawa's proposed counts hinges on whether the cyclopropyl species possesses properties which are truly "surprising" or "unexpected," or which otherwise make it distinct from the generic invention. Fujikawa appear to rely on mere activity differences between the cyclopropyl species and certain other members of the genus. However, these differences are not beyond normal variations to be expected in a generic invention, and moreover, could even be expected based on the prior art.

First of all, the state of the art well prior to Fujikawa's earliest priority date, as reflected in actual prior art of record in Fujikawa's U.S. Patent No. 5,011,930, reflects a clear direction to prepare a species of an HMG-CoA inhibitor compound which contains either an isopropyl or a cyclopropyl substituent.

In particular, reference is made to Warner-Lambert European Patent Application 179,559 (published on April 30, 1986) which discloses a pyrrole series of HMG-CoA reductase inhibition compounds having the formula:

(B)



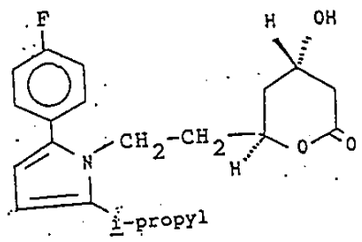
(I)

(or a ring-opened dihydroxyacid derived therefrom, or a pharmaceutically acceptable salt thereof).

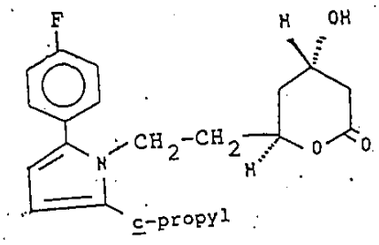
Most pertinent for present purposes is that in the above compounds of Warner-Lambert, R_4 is selected from the limited Markush group comprising: C_{1-4}alkyl, cyclopropyl, cyclobutyl or trifluoromethyl.

Furthermore, at pp. 13-14 of the publication Warner-Lambert express a "particular" preference for the following two compounds:

trans-6-[2-[2-(4-fluorophenyl)-5-(1-methylethyl)-1H-pyrrol-1-yl]-ethyl]tetrahydro-4-hydroxy-2H-pyran-2-one:



trans-6-[2-[2-cyclopropyl]-5-(4-fluorophenyl)-1H-pyrrol-1-yl]-ethyl]tetrahydro-4-hydroxy-2H-pyran-2-one:



Based on the Warner-Lambert disclosure alone, it is fair to say that by April 1986, i.e. well prior to the earliest Fujikawa filing date of August 20, 1987, there was a recognition in the art that: an isopropyl (4-fluorophenyl) species could provide enhanced HMG-CoA reductase activity; and further, that the isopropyl could be cyclized to form cyclopropyl; and finally that the resulting cyclopropyl (4-fluorophenyl) itself exhibited particular improvements in activity relative to a genus of compounds within the same series. Note that in both Warner-Lambert species, above, the isopropyl or cyclopropyl occupies a position on the pyrrole ring adjacent to the nitrogen, as in the case of the cyclopropyl species at issue.

Therefore, it is submitted that certain improved activity levels were already noted in the art in connection with a cyclopropyl-bearing compound well prior to Fujikawa's filing date, such that by August 1987 if not earlier, one of ordinary skill, guided by the Warner-Lambert publication and others, would have considered the activity levels of Fujikawa's cyclopropyl species, as being at best merely consistent with the preferences expressed in the prior art in connection with other nitrogen-containing heterocycles, and certainly well removed from the realm of surprise or unexpectedness.

Further noted in connection with the state of the art is U.S. patent No. 4,952,852 of Hoechst, the foreign counterpart of which would have published in December 1988. The Hoechst disclosure is directed to pyridinyl compounds such as, e.g., the compound of Examples 13ac and 13e, col. 62.

Note particularly in the Hoechst reference the activity level of various compounds which is indicated on Table 1, col. 13-14. Compare especially Example 13e on Table 1 (isopropyl) to Example 13ac (cyclopropyl), which indicates a higher activity level for cyclopropyl than for isopropyl.

It is noted that while the Hoechst publication was available only after Fujikawa's priority filings, it was in the art prior both to Fujikawa's assertion during prosecution of its involved application that the cyclopropyl species had "unobvious"

properties (Amendment of December 19, 1990), and also prior to the February 23, 1990 filing date of the divisional application which issued as the '330 patent.

Copies of relevant portions of the Warner-Lambert and Hoechst publications are enclosed.

The clear direction in the art surrounding Fujikawa's involved application virtually deprive Fujikawa of the argument that increased activity of its cyclopropyl (4-fluorophenyl) species over the other species within its scope would be "unexpected" or "surprising".

Put differently, given the preferences expressed in the art, Fujikawa is necessarily held to a very high threshold of improvement in activity of its cyclopropyl (4-fluorophenyl) species over, e.g., the isopropyl (4-fluorophenyl), in order to justify a conclusion of "unexpectedness" such as would give rise to separate patentability; and this threshold is simply not overcome by the comparative evidence of record.

Turning now to the Kitihara Declaration proffered in support of Fujikawa's motion to redefine, it is submitted that this data simply does not provide a basis for according separate patentability to the cyclopropyl species.

Kitihara provides Test A and Test B IC_{50} data for the sodium and calcium salts, ethyl ester and lactone forms of the cyclopropyl species of structure (A), above, which is covered by proposed Counts 3 and 4. Comparative data is provided with respect to quinoline compounds also having structure (A), with the sole exception that the cyclopropyl group is substituted by methyl, ethyl, isopropyl or C_6.

The data may be summarized as follows:

A. Test A:

Table (a), containing data for the sodium salts of cyclopropyl and the comparative compounds, demonstrates that:
i - cyclopropyl is more active than isopropyl by a factor of about 2.4, and
ii - isopropyl is more active than n-propyl by a factor of about 9.

Table (b) has only two data points for the calcium salts, which indicate that cyclopropyl is more active than isopropyl by a factor of about 5. However, it is difficult to determine how meaningful this activity difference is given the absence of additional comparative data.

Table (c), listing data on the ethyl esters, indicates that the cyclopropyl is more active than n-propyl by a factor of about 14, but no data is given for isopropyl.

Table (d), listing data on the lactones, indicates that the cyclopropyl is more active than the isopropyl by a factor of about 3.8. Again, given that no other compounds were tested, it is difficult to determine how meaningful this data is.

B. Test B

Table (a), listing data on the sodium salts, indicates that

i. cyclopropyl is about 5.7 times more active than isopropyl;

ii. isopropyl is about 7 times more active than n-propyl.

Table (b): the calcium salt of the cyclopropyl is about 3 times more active than the i-propyl; no other data is given.

Table (c), ethyl ester -- No data is given for the isopropyl. The cycopropyl is about 13 times more active than the n-propyl.

It is noted, first, that the above-summarized Kitihara data give no indication that toxicity does not also increase with actvitiy.

Second, given that the difference in activity level between isopropyl and its homologous species is typically substantially greater than the difference in activity betweeen cyclopropyl and isopropyl, Fujikawa is in the untenable position of claiming that

cyclopropyl is a separate and distinct invention from a genus of compounds which includes both the isopropyl and the other species tested above.

Third, the Kitihara Declaration is deficient in failing to make a complete comparison with compounds supported in its case which fall outside the scope of proposed Count 2.

Reference is made, for example, to claim 18 of Fujikawa's involved application, for example, which is directed to a compound having structural formula (A), above, with the sole exception that the quinoline ring is substituted at the "4" position not by 4-fluorophenyl, but by 4-chlorophenyl. This species falls outside the scope of proposed Counts 3 and 4 solely by virtue of the substitution of fluorine with another halogen, chlorine. No comparative data is offered by Fujikawa in respect of this chlorine species.

CONCLUSION

Fujikawa have failed to establish two requisites for entering a separate cyclopropyl (4-fluorophenyl) species count in this interference:

(1) The claims proposed to be added by Wattanasin do not comply with 35 USC 112 in the Wattanasin application, and therefore do not meet the requirement of 37 CFR 1.637(c)(1)(iii).

(2) Fujikawa have failed to demonstrate the separate patentability of the cyclopropyl species over the genus of Counts 1 and 2.

It is concluded that the comparative data presented by Fujikawa, to the extent meaningful, merely indicate activity of the cylopropyl species as an HMG-CoA reductase inhibitor which is well within the range of normal expectancy across the genus of quinoline compounds corrres- ponding to Counts 1 and 2, particularly given the teachings and expectations of the prior art which point to ispropyl, cyclopropyl and 4-fluorophenyl as clearly preferred features (it also being noted that cyclopropyl is a mere ring homolog of isopropyl).

Accordingly, it is repectfully requested that Fujikawa's motion to redefine the interference be denied.

Respectfully submitted,

Diane Furman

Diane E. Furman
Attorney for the Party Wattanasin
Registration No. 31,104
201-503-7332

SANDOZ CORPORATION
59 Route 10
E. Hanover, NJ 07936

DEF:rmf

July 1, 1992

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231, on July 1, 1992
(Date of Deposit)
Diane E. Furman
Name of applicant, assignee, or Registered Representative
Diane Furman
Signature
July 1, 1992
Date of Signature

CERTIFICATE OF SERVICE

It is hereby certified that a true copy of the paper entitled:

OPPOSITION OF WATTANASIN
TO FUJIKAWA ET AL.'S MOTION TO ADD COUNTS
AND TO ADD CLAIMS TO WATTANASIN APPLICATION

was served on counsel for the party Fujikawa et al., this 1st day of July 1992, by postage pre- paid first-class mail addressed to the following:

Oblon, Spivak, McClelland, Maier & Neustadt, P.C.
Attn: Steven B. Kelber, Esq.
1755 South Jefferson Davis Highway
Crystal Square 5, Ste. 400
Arlington, VA 22202

Diane Furman
Diane E. Furman

APPENDIX B

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

WATTANASIN

v.

FUJIKAWA et al.

Interference Nos. 102,648, 102,975

Examiner-in-Chief: M. Sofocleous

WATTANASIN OPPOSITION TO FUJIKAWA MOTION FOR SANCTIONS

STATUS

By motion of May 25, 1993 in the above-identified interferences, the party Fujikawa et al. have requested sanctions against the party Wattanasin for alleged violation of Sections 10.62(b) and 10.63(a) of 37 CFR.

The purported violation concerns Wattanasin's introduction of and reliance on testimony of Melvyn M. Kassenoff, Esq., a patent attorney on the staff of the Sandoz Corporation Patent and Trademark Department[1], going to the issue of abandonment, suppression or concealment, while he is at least apparently participating in the interferences as "deputy lead counsel".

The sanctions demanded by Fujikawa are as follows (in the alternative):

1. Disqualification of all members of the Sandoz Patent and Trademark Department from further participation in the interferences;

2. Striking the testimony of Kassenoff;

3. "Severely discounting" the testimony of Kassenoff.

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1. Melvyn M. Kassenoff has been employed in the Sandoz Patent and Trademark Department for about 20 years.

Wattanasin now opposes the Fujikawa motion. It is respectfully submitted that the Fujikawa motion is completely devoid of support in fact or law; and that furthermore, that it is belated, having been raised over three months after the Kassenoff testimony was made of record, and over one year after Mr. Kassenoff's designation as a counsel in these interferences.

Accordingly, Wattanasin requests that the Fujikawa motion, and each and every sanction requested therein, be denied.

STATEMENT OF FACTS

1. When these interferences first went forward, management at Sandoz Pharmaceuticals Corporaton, the assignee of interest of the party Wattanasin, made a decision to rely for representation on the Sandoz in-house patent staff (consistent with the usual practice of Sandoz in patent interferences).

2. Effective March 23, 1992, the undersigned, Diane E. Furman, an attorney in the Sandoz Corporation Patent and Trademark Department, was designated the lead attorney of record for the interferences. Melvyn M. Kassenoff, Esq., also with Sandoz, was designated deputy lead counsel, with full power and authority to

act in the absence of the lead attorney.[1] (see Exhibit A)

3. The designation of Kassenoff was made in recognition of the fact that he has substantial experience, unique to the Sandoz Patent and Trademark Department, in the subject matter area of these interferences, i.e. HMG-CoA reductase inhibitor compounds. Melvyn Kassenoff is also regarded as the Sandoz Patent and Trademark Department's foremost expert on PTO rules and regulations, and had more experience in interference procedure under the new rules than any other member of the department.[2]

4. Kassenoff's role as an attorney in these interferences has been primarily as a consultant or "sounding board," providing occasional advice on procedural and scientific issues.

5. Kassenoff did not provide any testimony in these interferences as to priority.

6. It was only when Fujikawa raised the issue of abandonment, supression or concealment, that it became apparent that Mr.

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1. Melvyn M. Kassenoff is also listed as an attorney of record on the involved Wattanasin application. Another Sandoz patent attorney of record on the application, Richard E. Vila, Esq., became active in the interference at the deposition stage.

2. It is noted that Mr. Kassenoff is the only member of the Sandoz staff who is a former patent examiner, and also is distinguished by having an advanced degree (M.S.) in chemistry.

Kassenoff had relevant testimony which needed to be taken in order for Wattanasin to present a complete defense. More specifically, Kassenoff's testimony goes to the period between the last documented laboratory work in connection with the Wattanasin invention and the filing of the involved Wattanasin application. Although Mr. Kassenoff himself did not draft the Wattanasin involved application, his testimony of record shows that he participated in information gathering for the application, and that he was familiar with Sandoz patent policies and procedures as they applied to filing the Wattanasin case[3].

7. Wattanasin filed the Kassenoff declaration in February of 1993 (Exhibit B). At that time, not one word was heard from Mr. Kelber as to any impropriety in Mr. Kassenoff's concurrent designation as deputy lead counsel or in his continuation in such capacity.

8. In fact, in March of 1993, virtually one year to the day from Mr. Kassenoff's designation as deputy lead counsel of record, Steven B. Kelber, counsel for Fujikawa, came to the Sandoz Patent

3. Until January 1, 1993, when Mr. Kassenoff became supervisor of Patents Group II, one of two patent groups comprising the Sandoz Patent and Trademark Department, he reported to Mr. Vila, (who is supervisor of Patents Group I), and had no formal supervisory responsibilities. However, since about 1982, Mr. Kassenoff had certain de facto responsibilities in relation to HMG-CoA reductase matters, including assisting of junior department members working in the area, i.e. Joanne M. Giesser, Esq. (now departed from Sandoz), who drafted the involved Wattanasin application, and the undersigned lead counsel.

and Trademark Department in East Hanover, New Jersey, and subjected Mr. Kassenoff to rigorous cross-examination by deposition (see Kassenoff cross-examination transcript at pages 233-318 of the Wattanasin Record), without ever raising the question of impropriety as to Mr. Kassenoff's continuing status as deputy lead counsel.[4]

9. Subsequently, the Wattanasin Record was filed and served. The Record cover pages (Exhibit C) bear a designation of Mr. Kassenoff and Richard E. Vila, Esq. as being "of counsel".[5] No change was made in the status of Mr. Kassenoff as deputy lead counsel.

10. Thereafter, a letter was received by the undersigned from Mr. Kelber (Exhibit D) identifying Mr. Kassenoff as a "critical fact witness" for Wattanasin and objecting to his participation as an attorney for Wattanasin.

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4. During the cross-examination session at Sandoz, Mr. Kassenoff refrained from taking any testimony since he was a witness at the session, but the subject of his continued participation as deputy lead counsel was never questioned or discussed, let alone protested, by Mr. Kelber.

5. It should be noted that it has been the practice in the Sandoz Patent and Trademark Department, at least in cases before the Court of Appeals for the Federal Circuit, that the briefs and record would designate as of counsel, one or more of the immediate supervisors of the principal attorney of record, and/or to indicate that the named individuals had background or consultant status in connection with the case. This practice was followed in the current interferences.

11. On May 25, 1993, Fujikawa filed their motion for sanctions, which Wattanasin now opposes.

STATEMENT OF THE ISSUES

The critical issue is whether Melvyn M. Kassenoff's testimony for Wattanasin violates any known legal requirement, or even presents an appearance of impropriety, or needs to be discounted, in view of his status as deputy lead counsel (or "of counsel") in this matter.

APPLICABLE LAW AND ARGUMENTS

As a first matter, there is nothing in the Federal Rules of Evidence, which govern these interferences, which prevents an attorney from testifying on behalf of his client.

The most pertinent regulations bearing on the circumstances under which an attorney may serve as a witness for his client are located at 37 CFR §§10.62(b) and 10.63(a) (both effective 1985) (Exhibit E). These sections essentially track the language of the American Bar Association Code of Professional Responsibility, Disciplinary Rules (DR) 5-101(B) and 5-102(A), respectively.

1. 37 CFR §10.62, 10.63

(i) 37 CFR §10.62(b) indicates that prospective employment should be refused by a practitioner or another practitioner in his firm when the practitioner or his associate "ought to be" called as a witness for the client in the matter.

(ii) 37 CFR §10.63(a) likewise indicates that a practitioner who has already undertaken employment should withdraw if it becomes apparent that the practitioner or another in his firm "ought to" testify on behalf of the client.[6]

Of course, by their strict wording, both rules are directed to situations involving "firms," a term which is left undefined in the definitions section of Part 10 of 37 CFR. In conventional usage, however, the term "firm," would not even apply to an in-house corporate patent department.

However, assuming arguendo that Rules 10.62(b) and 10.63(a) would apply to in-house counsel, both rules are subject to four defined areas where an attorney's testimony for his client need not require him to withdraw from representation:

(1) If the testimony will relate solely to an uncontested matter.

6. 37 CFR §10.63(b) is directed to a case where the testimony is "other than" on behalf of the client, and is therefore inapplicable to the present situation.

(2) If the testimony will relate solely to a matter of formality and there is no reason to believe that substantial evidence will be offered in opposition to the testimony.

(3) If the testimony will relate solely to the nature and value of legal services rendered in the case by the practitioner or the practitioner's firm to the client.

(4) As to any matter, if refusal would work a substantial hardship on the client because of the distinctive value of the practitioner or the practitioner's firm as counsel in the particular case.

Sub-paragraph (1)

Sub-paragraph (1) above may or may not apply to the present situation. However, it is respectfully submitted that the Kassenoff testimony certainly falls within any one or more of sub-paragraphs (2), (3) and (4).

Sub-paragraph (2)

Concerning sub-paragraph (2), Mr. Kassenoff's testimony in part clearly relates essential to formalities, e.g., the existence of his handwriting in certain documents of record [e.g., see pages 4-5 of the Kassenoff Declaration (WR at 230-231)].

Sub-paragraph (3)

Furthermore, Mr. Kassenoff's testimony should be entirely permitted under sub-paragraph (3), which goes to the nature and value of legal services. For example, he provided testimony concerning his involvement as a member of the Sandoz Patent and

Trademark Department in the activities leading to filing of the Wattanasin application, and policy and practices applied to the filing of the Wattanasin application, as well as examples of cases which he drafted in the HMG-CoA reductase area [e.g., see pages 1-5 of the Kassenoff Declaration (WR at 227-231)].

Indeed, if there were any doubt that the Kassenoff testimony falls squarely within the purview of at least sub-paragraph (3), the underlying PTO commentary makes this crystal clear:

> "One comment suggested that proposed §10.62 should specifically authorize a registered patent practitioner to testify concerning attorney diligence in patent cases. This suggestion is not to be adopted. However, it should be clear that in most cases, the exception of proposed §10.62 (b)(3) would apply.***[citation to Wilder v. Snyder, 201 USPQ 927 (Bd. Pat. Inter. 1977]
>
> [emphasis supplied] 1045 OG 36[7] (see Exhibit F)

Thus, while the PTO drafters did not incorporate into Rule 10.62(b) the above proposed language relating to admissible attorney testimony as to diligence -- probably in the desire to adhere strictly to language paralleling the sister ABA disciplinary rules, DR 5-101(B) and 5-102(A) -- the commentary

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7. Conspicuously absent from the Fujikawa motion is any reference to this PTO commentary, to which Fujikawa were expressly directed by Wattanasin in the undersigned's letter included as Exhibit A to the Fujikawa motion.

does clarify that the present circumstances should fall within the sub-paragraph (3) exception.

The commentary goes on to state that "the weight to be given testimony by a practitioner on behalf of his or her client would be determined on a case-by-case basis" -- which, of course, the Board is free to do with respect to any testimony.

In short, there is nothing in Mr. Kassenoff's testimony, required by Fujikawa's raising of the abandonment issue, which does not legitimately come within exception (3), above.

Sub-paragraph (4)

With respect to sub-paragraph (4), the "hardship exception," it is a given that disqualification of Mr. Kassenoff from this matter would work a substantial hardship on the party Wattanasin. As indicated above, Mr. Kassenoff not only has distinctive knowledge of the HMG-CoA reductase inhibitor area, but also considerable and valued expertise concerning PTO interference procedure. In particular, Mr. Kassenoff has been engaged in the drafting and prosecution of HMG-CoA cases, and building of a patent estate in this subject matter area, since about 1982. Mr. Kassenoff has been a primary liaison with Sandoz management concerning both Sandoz and third-party coverage in the HMG-CoA reductase area. Disqualification of Mr. Kassenoff as a counsel in these interferences would unfairly deprive Sandoz of Mr. Kassenoff's wide technical and patent knowledge gained from substantial experience in the HMG-CoA area. Furthermore, Mr. Kassenoff, as a member of the Sandoz Patent Committee, also has

intimate knowledge of the procedure and practices of the Committee in the rating of patent disclosures.

Accordingly, it is believed that the present facts amply justify application of subparagraph (4) permitting attorney testimony in hardship cases.

2. Caselaw

There appears to be no decisional law under the 1985-enacted 37 CFR 10.62 or 10.63, save for the Domino[8] case referred to by Fujikawa, where, in fact, the Commissioner was concerned with Rule 10.63(b) which is not at issue here, and in any event, denied a motion for disqualification.

This points up a fundamental problem with the legal authority relied on by Fujikawa in their brief: in the context of a highly fact-dependent inquiry such as one directed to attorney impropriety and sanctions, Fujikawa are casting about for support in various judicial dicta and broad-brush restatements of the law -- in complete disregard, however, of the underlying facts which distinguish their cited caselaw from the instant situation.[9]

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8. Little Caesar Enterprises Inc. v. Domino's Pizza Inc., 11 USPQ2d 1233 (Comm. 1989).

9. Fujikawa certainly cast wide for the broad dicta appearing in Lau Ah Tew v. Dulles, 257 F.2d 744 (9th. Cir. 1958), a naturalization case where the attorney's testimony in question concerned his ability to recognize the identity of his client, a petitioner for naturalization.

For example, the 1977 Wilder case (Exhibit G) mentioned in the PTO commentary on Rule 10.62(b) and also cited by Fujikawa, involved an interference situation where the Board, in fact, found "no reason not to accord weight" to testimony given by an attorney for the senior party.

Universal Athletic Sales Co. v. American Gym, Rec. & Ath. Equip. Corp., 192 USPQ 193 (3d Cir. 1976), cert. den. 193 USPQ 570 (1977) (Exhibit H), relied on extensively by Fujikawa, is concerned with a situation where an attorney in the law firm representing the infringement defendant testified as a purported expert as to the invalidity of plaintiff's patent at issue. The Third Circuit vacated the district judge's finding of patent invalidity on the ground that the arguable deficiency of the witness as an expert and his role as an attorney should have prevented his testimony from being given controlling weight to rebut the presumption of validity of an issued patent.

Therefore, the Universal case, notwithstanding its broad-brush restatements of the law amounting to dicta, is limited on its facts to a situation involving expert testimony by a law firm attorney -- which is recognized to be severely deficient to begin with -- being given controlling weight in overcoming the presumption of validity attaching to an issued U.S. patent. The Third Circuit ruling overturning the trial judge's unpatentability finding had to be colored by the obvious deficiencies of the witness's purported expert testimony.

By contrast, Mr. Kassenoff is an in-house counsel being relied on as a fact witness, as even Fujikawa acknowledge. Mr. Kassenoff is not being offered as an expert witness. Nor is Mr. Kassenoff testifying as to the validity of an issued patent. In sum, it is difficult to find any substantive influence that the Universal case on its facts could have as to these interferences.

In very illustration of this point, the court in the succeeding interference case of Wilder, while paying "lip service" to the broad pronouncements in Universal and similar language in 97 C.J.S. Witnesses §71, in fact, chose to admit into evidence the attorney testimony at issue in Wilder.

Even more instructive in an interference setting is a case overlooked by Fujikawa: Wick v. Zindler, 230 USDPQ 241 (Bd. Pat. Inter. 1984) (Exhibit I). In that case, the attorney, Holtz, who prepared the involved application of the senior party, also served as a designated co-counsel in the interference. Holtz's testimony was needed to corroborate the senior party's date of conception.

The junior party moved to exclude the Holtz testimony. In deciding the motion, the Board first referred to the Wilder case for authority that an attorney is competent to serve as a witness for or against his client. In dictum, the Board also recited that this testimony could be discounted. However, in fact, the Board went on to consider the testimony:

> Nevertheless, under the circumstances of this case where Holtz has identified certain documents that the inventor used to explain the invention during conferences with him, we believe that his testimony as to when the conferences occurred and that the invention was then explained and understood by him is entitled to sufficient weight to corroborate conception. We note that Holtz supported his tesitimony with documentary evidence in the form of calendar entries... and entries in his law firm's log of invention disclosures ... [emphasis supplied]

230 USPQ at 246

Finally, reference is made to the case of SMI Industries Canada Ltd. v. Caelter Industries, Inc., 223 USPQ 742 (NDNY 1984) (Exhibit J), which involved an action for patent and trademark infringement, and unfair competition. Denying plaintiff's motion to disqualify defendant's law firm under DR 5-102(A) of the ABA Code of Professional Responsibility, the parallel section to 37 CFR 10.63(a), the court stated that the resulting loss of services would create precisely the kind of hardship which is protected against by sub-paragraph (4) of DR 5-101(B) [analogous to 37 CFR 10.62(b)(4)]:

> Even assuming, arguendo, that members of the Limbach firm ought to be called as witnesses at trial, the court concludes that disqualification is not appropriate in this case. As noted previously, DR 5-101(B)(4) provides that an attorney may continue representation of his client in a proceeding in which the attorney is called upon to testify if disqualification would work a special and unwarranted hardship on the client by virtue of the distinctive value of the lawyer or his firm as counsel in the case.

> In the present case, George Limbach has represented the related predecessor coporation of defendant in patent and trademark matters since 1967, and the Limbach firm has represented defendant and its related companies since early in 1968. The attorney-client relationship has become intimate, and the firm has acquired specialized knowledge of defendant, defendant's related companies, and their operations. The Limbach firm's representation of defendant in the present action involves a complex set of legal and factual issues which the firm has been familiar with for many years. At this late juncture it would work a substantial hardship upon the defendant to require it to retain new counsel. Moreover, there is no basis for concluding that the continued representation by the Limbach firm will prejudice the plaintiff in this proceeding in any way or taint the underlying trial. Accordingly, plaintiff's motion to disqualify pursuant to Canon 5 is denied. [emphasis supplied]

223 USPQ at 748.

It is believed that the disqualification of Kassenoff or any other in-house Sandoz attorney would present no less hardship on the party Wattanasin than is described in the above SMI decision concerning the Limbach disqualification.

Counsel for Wattanasin can understand that there would be legitimate concern to separate the role of an attorney as a witness from the role of an advocate at trial before a jury. Avoiding prejudice before the jury is a guiding consideration in many disqualification cases. However, even in these cases, the courts have often simply prevented the attorney giving testimony from appearing in court before the jury as trial counsel for his client.

Of course, the present case does not involve a jury trial, but a proceeding conducted before a panel of Examiners-in-Chief. Surely the concern to avoid prejudice that informs the ABA's restraints against attorney testimony in jury trials, would not obtain in a patent interference proceeding.

Particularly in a case where an attorney is testifying on behalf of his client, there is a harsh injustice to the client to force him to choose between the attorney's legal knowledge and the attorney's often critical knowledge as fact witness. The hardship is even greater when an attorney is forced to abandon his legal role in mid-stream in order to have his testimony received into the record.

In particular, the policy which Fujikawa now seeks to apply against Wattanasin is manifestly unfair: If the EIC were to approve the Fujikawa motion, this would mean that any corporation which is a party of interest in an interference, would effectively be deprived of the unique legal and technical skill of its own in-house patent staff simply because one or more of those same attorneys may almost necessarily be called as a fact witness concerning activities within the scope of their employment in connection with an involved application.

In summary, the express terms of 37 CFR §10.62(b) and §10.63(a), and the weight of decisional authority as well as

policy considerations, are squarely against disqualification of the Sandoz Patent and Trademark Department, or Mr. Kassenoff individually, from the present interferences. Similarly, it is submitted that under the present circumstances, there is absolutely no reason or justification for discrediting the Kassenoff testimony.

Given the improbability under all relevant legal authorities of his obtaining disqualification of the Sandoz Patent and Trademark Department or of Mr. Kassenoff alone, what Mr. Kelber is transparently really after is "discounting" or "discrediting" of the Kassenoff testimony.

Why Mr. Kassenoff's testimony should be "discounted" as opposed to that of any other witness is not entirely clear. Like the other deposed Wattanasin witnesses, Mr. Kassenoff was subjected to rigorous cross-examination by Mr. Kelber. Even more so than the other, non-attorney witnesses, Mr. Kassenoff would have been conscious of his obligation, as member of the bar and an officer of the court, to uphold his oath. Likewise, Mr. Kassenoff would have been aware of the severe toll on his professional status that could attend violation of his oath. Mr. Kassenoff furthermore being an acknowledged fact witness, there is no good reason to discredit his testimony, and none is really offered by Fujikawa.

FUJIKAWA BELATEDNESS

For whatever reason, Fujikawa have until now -- over three months after the Kassenoff testimony was presented and over a year after Mr. Kassenoff's designation as a deputy counsel of record -- failed to raise any issue of disqualification or "discounting" of testimony, and even have taken cross-examination from Mr. Kassenoff without raising the issue.

In short, Fujikawa are raising an issue long after it should have been raised. To all appearances, Fujikawa saved their motion for a time when opposition to it would have been due one day before Wattanasin's main briefs.

It has to be concluded that the probable cause for the Fujikawa motion for sanctions is that counsel for Fujikawa happened to elicit from Mr. Kassenoff on cross-examination, information going to Sandoz Patent and Trademark Department procedure and the like, which could not be favorable to Fujikawa. Grasping for a rationale to eliminate or discredit this testimony, Fujikawa counsel have fabricated a strategy based on allegations of attorney impropriety. Such belated action and conduct should not be permitted.

CONCLUSION

Accordingly, the Fujikawa motion for sanctions should be denied on the basis of any one or more of the following reasons:

1. The testimony of Melvyn M. Kasssenoff for the party Wattanasin falls within the protected activity of 37 § 10.62(b)(2) and (3), because it constitutes testimony going to formalities and the factual circumstances of his activities in relation to the Wattanasin invention;

2. The testimony of Melvyn M. Kassenoff also falls within 37 CFR 10.62(b)(4), because otherwise the party Wattanasin would be deprived of Kassenoff's in-house technical and patent law expertise, which would work a serious hardhip;

3. The Fujikawa motion is belated, as it could have been filed much earlier. The suggestion by Mr. Kelber that he only became aware of the situation upon filing of the Wattanasin Record is without merit. Mr. Kassenoff has been listed as deputy lead attorney from the beginning of this matter.

4. None of the sanctions sought by Fujikawa is justified, and in fact would only serve to give Fujikawa undeserved advantage to the extent the Kassenoff testimony was discounted. Counsel for Fujikawa caused this testimony to be taken, and subjected Mr. Kassenoff to cross-examination under oath. Counsel for Fujikawa

should face the testimony rather than have the PTO discount it in advance for no justifiable reason.

Finally, Mr. Kassenoff has not been an active participant in these interferences (particularly following his changed responsibilities as of January 1993, referred to above); rather, he has served as a consultant on an intermittent basis concerning technical or PTO procedural matters. Wattanasin would be willing to remove Mr. Kassenoff as deputy lead counsel, but cannot without hardship meet Fujikawa's demands, which would deny the undersigned any right to consult with Melvyn Kassenoff concerning these interferences.

Respectfully submitted,

Diane Furman

Diane E. Furman
Attorney for Wattanasin
Registration No. 31,104
201-503-7332

SANDOZ CORPORATION
59 Route 10
East Hanover, NJ 07936

June 14, 1993

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231, on June 14, 1993
(Date of Deposit)
Diane E. Furman
Name of applicant, assignee, or Registered Representative
Diane Furman
Signature
June 14, 1993
Date of Signature

CERTIFICATE OF SERVICE

It is hereby certified that a true copy of the paper entitled:

WATTANASIN OPPOSITION
TO FUJIKAWA MOTION FOR SANCTIONS

was served on counsel for the party Fujikawa et al., this 14th day of June 1993, by first-class mail addressed to the following:

Oblon, Spivak, McClelland, Maier & Neustadt, P.C.
Attn: Steven B. Kelber, Esq.
1755 South Jefferson Davis Highway
Crystal Square 5, Ste. 400
Arlington, VA 22202

Diane Furman

Diane E. Furman

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

#112

WATTANASIN

V. Interference No. 102,648

FUJIKAWA et al. Examiner-in-Chief: M. Sofocleous

WATTANASIN FILING OF REPLY BRIEF

Honorable Commissioner of Patents
and Trademarks
Washington, D.C. 20231

SEP 13 1993

RECEIVED IN
BOX INTERFERENCE

Sir:

Appended are an original and three copies of the Watttanasin Reply Brief for the above-identified interference.

Respectfully submitted,

Diane Furman

Diane E. Furman
Attorney for the Party Wattanasin
Registration No. 31,104
201-503-7332

Enclosures: Reply Brief (original and 3 copies)

SANDOZ CORPORATION
59 Route 10
E. Hanover, NJ 07936

DEF:rmf
September 7, 1993

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231, on Sept. 7, 1993
(Date of Deposit)

Diane E. Furman
Name of applicant, assignee, or Registered Representative

Diane Furman
Signature

9/7/93
Date of Signature

CERTIFICATE OF SERVICE

It is hereby certified that a true copy of the paper entitled:

WATTANASIN FILING OF REPLY BRIEF

and a copy of the Reply Brief appended thereto were served on counsel for the party Fujikawa et al., this 7th day of September 1993, by postage pre-paid first-class mail addressed to the following:

Oblon, Spivak, McClelland, Maier & Neustadt, P.C.
Attn: Steven B. Kelber, Esq.
1755 South Jefferson Davis Highway
Crystal Square 5, Ste. 400
Arlington, VA 22202

Diane Furman

Diane E. Furman

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

#113

WATTANASIN

V. Interference No. 102,648

FUJIKAWA et al. Examiner-in-Chief: M. Sofocleous

WATTANASIN OPPOSITION
TO FUJIKAWA MOTION TO SUPPRESS EVIDENCE

FYI

Honorable Commissioner of Patents
and Trademarks
Washington, D.C. 20231

SEP 13 1993

RECEIVED IN
BOX INTERFERENCE

Sir:

Fujikawa have moved to supress the Declaration and Supplemental Declaration of Robert E. Engstrom, the Sandoz researcher who conducted in vivo testing of the Wattanasin compounds in rats, together with Exhibits K-1 and Q which accompany his respective declarations. For the convenience of the Board, copies of these declarations and exhibits (as well as the companion Rodney Slaughter declaration) are appended hereto.

Fujikawa are apparently objecting to the ED_{50} data in the Engstrom declaration (WR 206) because they "constitute the results of not one but two computer manipulations."

Whatever, Fujikawa intend by this, the following things are evident from these declaration and exhibit pages:

1. Pages 334 and 337 (see upper right hand corner of exhibit page) are summary pages generated for each of the screenings carried out starting October 22 and October 29, 1987, respectively, and simply record the type of test solutions utilized;

"RIBBON COPY FOR PARTY" Wattanasin

2. Pages 335-336 and 338-339 show the actual counts in nanocuries per 100 ml. of rat serum obtained for each in vivo testing.

As described more fully by Engstrom at WR 204, the rats were administered the test substance dissolved or as a suspension in a formulation comprising carboxymethylcellulose. The rats were therafter injected with a given amount of radiolabeled sodium acetate. Serum samples were then obtained, the sterols were precipitated, and their radioactivity detected by liquid scintillation spectrometry.

The count in nanoCuries per 100 ml. rat serum is listed down the fifth column of the WX K-1 computer printout. This is the actual raw data obtained from the experiments. From the nanoCurie values received for the six rats in each testing, various computations were made including a "% change" in nanoCurie count. A % change greater than 50% would indicate activity in the assay. (This is a quite stringent assay, where the industry standard, compactin, itself had an ED50 of 3.5, as described by Wattanasin in the Reply Brief at 21-22.)

This data were then inputed into a computer program which generated an ED_{50} number for each compound tested, and the ED_{50} was downloaded in the Sandoz database maintained in the ordinary course of business. (Notice that the database accepted only ED_{50} values which were smaller than 1.) However, in Exhibit Q (at page 418), a Biological Activity Data Report on the Wattanasin compounds shows that compound 64-933 was also calculated to have a specific ED_{50} value of 2.40.

Calculation of ED_{50} in this manner was hardly new to the art as of December 1987. In fact, the whole Engstom in vivo testing procedure appears almost verbatim at page 33 of the Kathawala 1984 European patent publication on fluvastatin, EP 114,027 which was cited as "technological background" against the involved Fujikawa '930 patent (copy of relevant pages also appended).

Even the Fujikawa rebuttal witness, Dr. Homlund, acknowledged that he had "no quarrel with the techniques for determining statistical activity" used by Wattanasin (FR at 204).

Given the art-recognized status of this in vivo assay, it is hard to understand why Fujikawa insist on being provided with computer programs or logorithms so that they can trace the exact progress of each byte of information.

The Board has discretion in applying the rules of evidence, and there is submitted to be no convincing argument that a "rule of reason" should not apply here where the raw data is attested to by the individuals who actually performed the experiments, and the resulting ED_{50} calculation was generated thereon by Sandoz in the ordinary course of business.

Fujikawa affect discomfort that the ED_{50} data for one of 64-933 and 64-936/NA was inadvertently "switched" at page 206 of the original Engstrom declaration. Regardless of whether this typographical error is related in any way to an acknowledged Engstrom "goof" showing up in Exhibit Q, all of the other Wattanasin Exhibits are uniform in assigning an ED_{50} value to

compound 64-935, alone, of 0.49 (see, e.g., Exhibit S-1 (relevant page also appended))[1].

Like any other business or technical information maintained in the ordinary course of business by Sandoz, the ED_{50} data in a sense speaks for itself, and should not be invalidated by a purported lack of foundation, particularly since the underlying computer programs or logorithms are not themselves likely to be comprehensible.

Accordingly, the Fujikawa motion to suppress should be denied.

SANDOZ CORP.
50 route 10
E. Hanover, NJ 07936
Attachments as noted
September 7, 1993

Respectfully submitted,

Diane E. Furman
Attorney for the Party Wattanasin
Registration No. 31,104
201-503-7332

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231, on Sept. 7, 1993
(Date of Deposit)
Diane E. Furman
Name of applicant, assignee, or Registered Representative
Signature
Sept 7, 1993
Date of Signature

1. Fujikawa also attempt an argument surrounding the absence of a sodium salt indication, i.e. "NA", from the Sandoz database printout for 64-936(NA) included in Wattanasin Exhibit K-1 (at 336). However, notice that on pages 203, 205 and 209 of the Wattanasin record "64-936" is used interchangeably with the designation "64-936/NA", just as the Sandoz fluvastatin compound, a sodium salt (technically, "62-320/NA"), is typically referred to as, simply, 62-320 (WR at 484), without the added sodium designation. It is hard to see how Fujikawa could allege difficulty with practices that are customary in the art, and manifested throughout the Wattanasin record in relation to compounds of known strucutre such as fluvastatin.

CERTIFICATE OF SERVICE

It is hereby certified that a true copy of the paper entitled:

WATTANASIN OPPOSITION
TO FUJIKAWA MOTION TO SUPPRESS EVIDENCE

and the attachments thereto were served on counsel for the party Fujikawa et al., this 7th day of September 1993, by postage pre-paid first-class mail addressed to the following:

Oblon, Spivak, McClelland, Maier & Neustadt, P.C.
Attn: Steven B. Kelber, Esq.
1755 South Jefferson Davis Highway
Crystal Square 5, Ste. 400
Arlington, VA 22202

Diane Furman

Diane E. Furman

107

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

WATTANASIN
v.
Fujikawa et al.

Interference No. 102,648, 102,975
Examiner-in-Chief: M. Sofocleous

DECLARATION OF ROBERT G. ENGSTROM PURSUANT TO 37 CFR §1.672

I, Robert G. Engstrom, do hereby declare as follows:

(1) That I have been employed by Sandoz Pharmaceuticals Corporation since 1964 as a Research Scientist. Among my responsibilities has been supervising the testing of new HMG Co-A reductase inhibiting compounds synthesized by Sandoz chemists.

(2) That all activities referred to in this Declaration took place in the United States.

IN VIVO TESTING OF
WATTANASIN COMPOUNDS 64-933, 64-935 and 64-936/Na

1. On or before October 29, 1987, in my laboratory under my supervision, Rodney Slaughter began performing the below-indicated protocol on compounds 64-933, 64-935 and 64-936/Na:

In vivo studies utilized male Wistar Royal Hart rats weighing 150 ± 20 g. which have been kept for 7-10 days on an altered light cycle (6:30 A.M. - 6:30 P.M. dark) housed two per cage and fed powdered Purina Rat Chow and water ad libitum. Three hours before the diurnal maximum of cholesterol systhesis at mid-day the rats were administered the test substances dissolved or as a suspension in 0.5% carboxymethylcellulose in a volume of 1 ml./100 g. body weight. Controls received vehicle alone. One hour after receiving the test substance, the rats were injected intraperitoneally with about 25 μCi/100 g. body weight of sodium [1-^{14}C]acetate 1-3 mCi/mmol. Two hours after mid-dark, blood samples were obtained under sodium hexobarbitol anesthesia, and the serum was separated by centrifugation. The resulting serum samples were saponified and neutralized, and the 3β-hydroxy sterols were precipitated with digitonin basically as described by Sperry et al., J. Biol. Chem. 187,97(1950). The [^{14}C]digitonides were counted by liquid scintillation spectrometry. The assay is based on the conversion of ^{14}C-acetate to ^{14}C-cholesterol in vivo.

2. The counts in DPM of digitonin precipitable sterol (β-hydroxy sterol, mostly cholesterol in the rat) were entered by Rodney Slaughter into my computer program, which converted them to nCi of sterol found per 100 ml. of serum at 4 hours after the injection of the ^{14}C-acetate.

3. I have reviewed Exhibit K-1 hereto, which comprises true copies of pages 133, 134, and 135, 136, 137 and 138 of R. Slaughter's Laboratory Notebook #917. I witnessed Rodney Slaughter's signature on each of these pages, and each page bears my true signature as a witness.

4. Notebook pages 133-135 contain true copies of a computer printout for the protocol and results in nCi/dl of Study #H318, which was commenced on October 22, 1987. I initialed the first page of this computer printout on or before October 22, 1987. This computer printout on page 135 indicates that an in vivo assay of compound 64-936 was started on October 22, 1987.

5. Notebook pages 136-138 contain true copies of a computer printout for the protocol and results in nCi/dl of Study #H319, which was commenced on October 29, 1987. I initialed the first page of this computer printout on page 136 on or prior to October 29, 1987. This computer printout on page 137-138 indicates that an in vivo assay of compound 64-933 and 64-935 was started on October 29, 1987.

6. Both studies were completed on or prior to December 9, 1987, the date indicated at the bottom of pages 135 and 138.

7. It was my responsibility to enter the nCi/dl data into a separate computer program which calculates the ED_{50} values of a compound tested in vivo from the reduction in the nCi of sterols formed from test groups compared to controls for each assay, and forms a database of the ED_{50} values. On or before December 9, 1987, I entered the data for compounds 64-933, 64-935 and 64-936/Na.

8. The 1st page of Exhibit K-1 comprises a true copy of part of the ED_{50} database. This page indicates that the ED_{50} for compounds 64-933, 64-935 and 64-936/Na was in the system as of December 9, 1987. Therefore, the information was available to other Sandoz employees having access to the computer database as of December 9, 1987.

The ED50 for these compounds are:

COMPOUND	ED_{50} (mg/kg)
64-933	0.49
64-935	>1.0
64-936	>1.0

. . .

The undersigned declares further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

I hereby subscribe my name to the foregoing DECLARATION this 13 day of November 1992.

Robert G. Engstrom

Robert G. Engstrom

///

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

WATTANASIN
v.
FUJIKAWA et al.

Interference Nos. 102,648, 102,975
Examiner-in-Chief: M. Sofocleous

DECLARATION OF RODNEY SLAUGHTER PURSUANT TO 37 CFR §1.672

I, Rodney Slaughter, do hereby declare as follows:

(1) That I have been employed by Sandoz Pharmaceuticals Corporation since 1982, and during the time periods referred to herein, I worked in the Department of Lipid Metabolism.

(2) That it has been my responsibility to carry out an in vivo testing program of various HMG-CoA reductase inhibitor compounds, including Wattanasin compounds 64-933, 64-935 and 64-936.

(3) That all of the below-indicated activities took place in the United States.

IN VIVO TESTING OF
WATTANASIN COMPOUNDS 64-933, 64-935 and 64-936

1. On or before October 29, 1987, I carried out the below-indicated protocol on compounds 64-933, 64-935 and 64-936:

In vivo studies utilized male Wistar Royal Hart rats weighing 150 ± 20 g. which have been kept for 7-10 days on an altered light cycle (6:30 A.M. - 6:30 P.M. dark) housed two per cage and fed powdered Purina Rat Chow and water ad libitum. Three hours before the diurnal maximum of cholesterol systhesis at mid-day the rats were administered the test substances dissolved or as a suspension in 0.5% carboxymethylcellulose in a volume of 1 ml./100 g. body weight. Controls received vehicle alone. One hour after receiving the test substance, the rats were injected intraperitoneally with about 25 μCi/100 g. body weight of sodium [1-^{14}C]acetate 1-3 mCi/mmol. Two hours after mid-dark, blood samples were obtained under sodium hexobarbitol anesthesia, and the serum was separated by centrifugation. The resulting serum samples were saponified and neutralized, and the 3β-hydroxy sterols were precipitated with digitonin basically as described by Sperry et al., J. Biol. Chem. 187,97(1950). The [^{14}C]digitonides were counted by liquid scintillation spectrometry. The assay is based on the conversion of ^{14}C-acetate to ^{14}C-cholesterol in vivo.

2. I entered the counts in DPM of digitonin precipitable sterol (β-hydroxy sterol, mostly cholesterol in the rat) into a computer program, which converted them to nCi of sterol found per 100 ml. of serum at 4 hours after the injection of the ^{14}C-acetate.

3. I have reviewed Exhibit K-1 hereto, which comprises true copies of pages 133, 134, 135, 136, 137 and 138 of my Laboratory Notebook #917.

4. Notebook pages 133-135 contain true copies of a computer printout for the protocol and results in nCi/dl of Study #H318, which I started on October 22, 1987. These pages contain the date of 10/22/87 at the top in my handwriting.

5. Notebook pages 136-138 contain true copies of a computer printout for the protocol and results in nCi/dl of Study #H319, which I started on October 29, 1987. These pages contain the date of 10/29/87 at the top in my handwriting.

6. Both studies were completed on or prior to December 9, 1987, the date indicated at the bottom of the computer printouts on pages 135 and 138.

7. It was my practice to paste the computer printouts into my notebook and to sign the notebook page when I did this.

The undersigned declares further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

I hereby subscribe my name to the foregoing DECLARATION this 13 day of November 1992.

Rodney Slaughter

Date 10/22/87 Proj. H318

Title Cholesterol Synthesis Inhibition Screen

From 134

135

334

CHOLESTEROL BIOSYNTHESIS INH

LIPID METABOLISM DEPARTMENT
HMGR SCREENING UNIT
Sandoz Research Institute
To: Dr. D. Weinstein, Departmenthead
Mr. R. Slaughter, Responsible Technician
From: Mr. R. Engstrom, Responsible Investigator
CC: D.N., M.L.R., ARC

STUDY #: H318
STUDY ON 10/22/87
BK.REF. 917-33
APPROVAL
DATE 10/21/87
GEN. ARC86-006

Title: In vivo single dose assay to test for inhibition of biosynthesis by compounds: 83-748, 84-844, 84-936

Purpose: Determine the invivo effects of test compounds in rats on cholesterol biosynthesis.

Experimental design: IN VIVO CHOLESTEROL BIOSYNTHESIS INHIBITION
DT0085 Invivo single dose assay of inhibition of
Reference method: 340/001. Stock solutions and dilutions prepared in 0.5% CMC, administered p.o. at 1ml/100gm weight.
Rats bled via carotid incision using hexobarbital anesthesia.
Animal use will be in compliance with ARC regulations.
Duration = 1 hr. No/group = 6. No of groups = 14. UCR rats.

Rats	COMPOUND	REGNO	DOSE mg/kg	STOCK mg/20ml	WORKING SOLUTION ml stock q.s. to 15ml
1-6	Control	------	------	------	----------
7-12	83-748	36628	1	2	UNDILUTED
13-18	"	"	0.3	-	4.5
19-24	"	"	0.1	-	1.5
25-30	84-844	30290	0.3	2	4.5
31-36	"	"	0.1	-	1.5
37-42	"	"	0.03	-	0.45
43-48	84-936	30458	1	2	UNDILUTED
49-54	"	"	0.3	-	4.5
55-60	"	"	0.1	-	1.5
61-66	82-810	30559	0.3	2	4.5
67-72	"	"	0.1	-	1.5
73-78	"	"	0.03	-	0.45
79-84	Control	------	------	------	----------

WATTANASIN EXHIBIT
K-1
Wattanasin v. Fujikawa et al.
Interference No. 102,648
Interference No. 102,975

Performed by- [signature]

Witness- [signature]

Cont'd to- 157

134

Title- Cholesterol Synthesis Inhibition Screen

Date 10/27/87 Proj 123

Cont'd From- 133

335

IN VIVO CHOLESTEROL SYNTHESIS INHIBITION SCREEN H318

RAT COMPOUND REGNO DOSE µCi/dM STATISTICS
µg/kg

BLANK
14C-STANDARD 20178 x EFFIC= .59

1	CONTROL			493			
2	CONTROL			677	MEAN =		537.7
3	CONTROL			580	STD =		128.6
4	CONTROL			455	SE =		37.1
5	CONTROL			490			
6	CONTROL			365			
79	CONTROL			462			
80	CONTROL			316			
81	CONTROL			559			
82	CONTROL			650			
83	CONTROL			610			
84	CONTROL			745			
8	63-748	26688	1.00	170	MEAN =		155.9
9	63-748	26688	1.00	278	STD =		73.1
10	63-748	26688	1.00	113	SE =		32.7
11	63-748	26688	1.00	113	t =		7.7
12	63-748	26688	1.00	106	p		<.01
7	63-748	26688	1.00	528*	%CHG =		-71
13	63-748	26688	.300	388	MEAN =		319.3
14	63-748	26688	.300	356	STD =		68.3
15	63-748	26688	.300	391	SE =		39.5
17	63-748	26688	.300	199	t =		4.0
18	63-748	26688	.300	253	p		<.01
16	63-748	26688	.300	794*	%CHG =		-40.6
19	63-748	26688	.100	348	MEAN =		456.7
20	63-748	26688	.100	725	STD =		213.5
21	63-748	26688	.100	310	SE =		87.2
22	63-748	26688	.100	650	t =		0.8
23	63-748	26688	.100	536	p		N.S.
24	63-748	26688	.100	178	%CHG =		-14.7
25	64-844	30280	.300	288	MEAN =		185.8
26	64-844	30280	.300	170	STD =		57.3
27	64-844	30280	.300	155	SE =		23.4
28	64-844	30280	.300	125	t =		6.5
29	64-844	30280	.300	174	p		<.01
30	64-844	30280	.300	101	%CHG =		-69.2
31	64-844	30280	.100	306	MEAN =		218.8
32	64-844	30280	.100	273	STD =		68.9
33	64-844	30280	.100	195	SE =		28.9
35	64-844	30280	.100	157	t =		8.7
36	64-844	30280	.100	165	p		<.01
34	64-844	30280	.100	695*	%CHG =		-58.1

Performed by- Todd R. Shaughnessy

Witness- R Eyster

Cont'd to- 135

Date 10/22/87 Proj# 3,1,8

Title Cholesterol Synthesis Inhibition Screen

135

Cont'd From- 134

336

INVIVO CHOLESTEROL SYNTHESIS INHIBITION SCREEN HS18

RAT	COMPOUND	REGNO	DOSE mg/kg	nCi/dl	STATISTICS	
37	64-844	30280	.030	354	MEAN =	419.7
38	64-844	30280	.030	518	STD =	136.6
39	64-844	30280	.030	639	SE =	56.6
40	64-844	30280	.030	246	t =	1.7
41	64-844	30280	.030	356	p	N.S.
42	64-844	30280	.030	402	%CHG =	-21.9
43	64-936	30486	1.00	580	MEAN =	489.4
44	64-936	30486	1.00	642	STD =	132.8
45	64-936	30486	1.00	280	SE =	54.2
46	64-936	30486	1.00	388	t =	0.7
47	64-936	30486	1.00	532	p	N.S.
48	64-936	30486	1.00	513	%CHG =	-9.0
49	64-936	30486	.300	187	MEAN =	325.7
50	64-936	30486	.300	231	STD =	165.0
51	64-936	30486	.300	586	SE =	87.4
52	64-936	30486	.300	278	t =	2.7
53	64-936	30486	.300	323	p	<.02
54	64-936	30486	.300	473	%CHG =	-39.2
55	64-936	30486	.100	485	MEAN =	416.5
56	64-936	30486	.100	181	STD =	168.8
57	64-936	30486	.100	639	SE =	62.9
58	64-936	30486	.100	696	t =	1.8
59	64-936	30486	.100	867	p	N.S.
60	64-936	30486	.100	439	%CHG =	-22.5
61	62-320	30559	.300	72	MEAN =	67.5
62	62-320	30559	.300	89	STD =	12.1
63	62-320	30559	.300	73	SE =	5.4
64	62-320	30559	.300	53	t =	12.5
65	62-320	30559	.300	84	p	<.01
66	62-320	30559	.300	55	%CHG =	-87.5
67	62-320	30559	.100	135	MEAN =	195.3
68	62-320	30559	.100	238	STD =	51.1
70	62-320	30559	.100	198	SE =	32.8
71	62-320	30559	.100	109	t =	8.5
69	62-320	30559	.100	149	p	<.01
72	62-320	30559	.100	158	%CHG =	-69.5
73	62-320	30559	.030	323	MEAN =	351.2
74	62-320	30559	.030	360	STD =	173.3
75	62-320	30559	.030	77	SE =	70.8
76	62-320	30559	.030	579	t =	3.3
77	62-320	30559	.030	463	p	<.05
78	62-320	30559	.030	277	%CHG =	-34.7

* = rejected by "Q" test Computed 12-09-87

* =LACK OF SAMPLE

Performed by- Ruth Ann Slaughter

Witness- [signature]

Cont'd to-

136 Title- Cholesterol Synthesis Inhibition Screen

Date 10/29/87 Proj: 3.9

Cont'd From-

337 -

CHOLESTEROL BIOSYNTHESIS INHIBITION SCREEN

LIPID METABOLISM DEPARTMENT
RMGR SCREENING UNIT
Sandoz Research Institute
To: Dr. D. Weinstein, Departmenthead
Mr. R. Slaughter, Responsible Technician
From: Mr. R. Engstrom, Responsible Investigator
CC: D.N., M.L.R., ARC

STUDY # H319
STUDY ON 10/29/87
BK.REF. 917-135
APPROVAL
DATE 10/29/87
GEN. #RC=06-006

Title: In vivo single dose assay to test for inhibition of biosynthesis by compounds: 64-296, 64-938, 63-935

Purpose: Determine the invivo effects of test compounds in rats on cholesterol biosynthesis.

Experimental design: IN VIVO CHOLESTEROL BIOSYNTHESIS INHIBITION GT0065 Invivo single dose assay of inhibition of Reference method: 740/001. Stock solutions and dilutions prepared in 0.5% CMC, administered p.o. at 1ml/100gm weight. Rats bled via carotid incision using hexobarbital anesthesia. Animal use will be in compliance with ARC regulations. Duration = 1 hr. No/group = 6. No of groups = 14. WCR rats.

RAT#	COMPOUND	REGNO	DOSE mg/kg	STOCK mg/20ml	WORKING SOLUTION a) stock q.s. to 15ml
1-6	Control	------	------	------	------
7-12	64-296	29277	1	2	UNDILUTED
13-18	"	"	0.3	-	4.5
19-24	"	"	0.1	-	1.5
25-30	64-938	30447	1	2	UNDILUTED
31-36	"	"	0.3	-	4.5
37-42	"	"	0.1	-	1.5
43-48	64-935	30441	1	2	UNDILUTED
49-54	"	"	0.3	-	4.5
55-60	"	"	0.1	-	1.5
61-66	63-300	30655	0.3	2	4.5
67-72	"	"	0.1	-	1.5
73-78	"	"	0.03	-	0.45
79-84	Control	------	------	------	------

Performed by-

Witness-

Cont'd to- 337

Date ../../.. Proj. ....

Cont'd.From- ....

Title- ....

137

338

INVIVO CHOLESTEROL SYNTHESIS INHIBITION SCREEN H31S

RAT	COMPOUND	REGNO	DOSE mg/kg	nCi/ml	STATISTICS	
	BLANK			7		
	IAC-STANDARD			20176	% EFFIC=	SS
1	CONTROL			983		
2	CONTROL			515	MEAN =	671.8
3	CONTROL			646	STD =	211.0
4	CONTROL			578	SE =	60.9
5	CONTROL			534		
6	CONTROL			354		
78	CONTROL			756		
80	CONTROL			847		
81	CONTROL			814		
82	CONTROL			549		
83	CONTROL			872		
84	CONTROL			714		
7	64-298	28277	1.00	203	MEAN =	151.7
8	64-298	28277	1.00	381	STD =	113.8
9	64-298	28277	1.00	82	SE =	46.4
10	64-298	28277	1.00	78	t =	6.8
11	64-298	28277	1.00	71	p	<.01
12	64-298	28277	1.00	115	%CHG =	-77
13	64-298	28277	.300	311	MEAN =	235.1
14	64-298	28277	.300	284	STD =	81.4
15	64-298	28277	.300	257	SE =	33.2
16	64-298	28277	.300	307	t =	5.3
17	64-298	28277	.300	114	p	<.01
18	64-298	28277	.300	157	%CHG =	-65.0
19	64-298	28277	.100	581	MEAN =	386.7
20	64-298	28277	.100	387	STD =	81.5
21	64-298	28277	.100	245	SE =	33.3
22	64-298	28277	.100	392	t =	4.1
23	64-298	28277	.100	499	p	<.01
24	64-298	28277	.100	425	%CHG =	-42.1
25	64-933	30447	1.00	838	MEAN =	438.1
26	64-933	30447	1.00	275	STD =	253.4
27	64-933	30447	1.00	136	SE =	103.5
28	64-933	30447	1.00	584	t =	2.0
29	64-933	30447	1.00	288	p	N.S.
30	64-933	30447	1.00	447	%CHG =	-36.2
31	64-933	30447	.300	830	MEAN =	557.4
32	64-933	30447	.300	646	STD =	100.5
33	64-933	30447	.300	525	SE =	41.0
34	64-933	30447	.300	598	t =	1.8
35	64-933	30447	.300	365	p	N.S.
36	64-933	30447	.300	615	%CHG =	-17.0

Performed by- ....

138

Title-

Date 12/[illegible]/87 Proj.

Cont'd From-[illegible]37

IN VIVO CHOLESTEROL SYNTHESIS INHIBITION SCREEN H319-[illegible]

RAT	COMPOUND REGNO	DOSE mg/kg	nCi/dl	STATISTICS		
37	64-933	30447	.100	555	MEAN =	547.0
38	64-933	30447	.100	735	STD =	147.2
39	64-933	30447	.100	370	SE =	60.1
40	64-933	30447	.100	378	t =	1.5
41	64-933	30447	.100	581	p	N.S.
42	64-933	30447	.100	652	%CHG =	-16.6
43	64-935	30441	1.00	182	MEAN =	230.0
44	64-935	30441	1.00	307	STD =	78.2
45	64-935	30441	1.00	198	SE =	31.9
46	64-935	30441	1.00	321	t =	8.4
47	64-935	30441	1.00	124	p	<.01
48	64-935	30441	1.00	281	%CHG =	-65.8
49	64-935	30441	.300	776	MEAN =	472.2
50	64-935	30441	.300	282	STD =	179.5
51	64-935	30441	.300	520	SE =	73.3
52	64-935	30441	.300	413	t =	5.1
53	64-935	30441	.300	344	p	N.S.
54	64-935	30441	.300	439	%CHG =	-29.7
55	64-935	30441	.100	411	MEAN =	428.2
56	64-935	30441	.100	320	STD =	119.1
57	64-935	30441	.100	295	SE =	46.8
58	64-935	30441	.100	425	t =	9.1
59	64-935	30441	.100	821	p	<.02
60	64-935	30441	.100	495	%CHG =	-38.3
61	62-320	30559	.300	50	MEAN =	165.6
62	62-320	30559	.300	107	STD =	107.1
63	62-320	30559	.300	222	SE =	43.7
64	62-320	30559	.300	60	t =	8.8
65	62-320	30559	.300	217	p	<.01
66	62-320	30559	.300	327	%CHG =	-75.3
67	62-320	30559	.100	262	MEAN =	331.7
68	62-320	30559	.100	434	STD =	186.7
70	62-320	30559	.100	559	SE =	74.1
71	62-320	30559	.100	188	t =	3.5
69	62-320	30559	.100	225	p	<.01
72	62-320	30559	.100	804	%CHG =	-50.8
73	62-320	30559	.030	431	MEAN =	445.1
74	62-320	30559	.030	472	STD =	94.1
75	62-320	30559	.030	571	SE =	36.4
76	62-320	30559	.030	874	t =	3.1
77	62-320	30559	.030	517	p	<.01
78	62-320	30559	.030	815	%CHG =	-33.8

Computed 12-09-87

Performed by-

Witness- R Stephenson

Cont'd to-

64586	29851	280-85	>	1	09-JUN-87	917-065
64589	29852	280-85	=	.16	15-JUN-87	917-081
64602	29743	101-85	>	.3	05-MAY-87	917-050
64602	29743	101-85	>	.3	05-MAY-87	917-050
64604	29744	101-85	>	.3	05-MAY-87	917-051
64604	29744	101-85	>	.3	05-MAY-87	917-051
64604	29745	101-85	=	.48	14-JUL-87	917-086
64608	29756	298-85	>	7.5	15-MAY-87	917-056
64638	29835	570-83		.34	09-DEC-87	917-140
64639	29836	570-83	>	1	09-JUN-87	917-066
64640	29839	367-86	>	1	09-JUN-87	917-068
64641	29840	367-86	>	1	09-JUN-87	917-068
64642	29841	367-86	>	1	09-JUN-87	917-089
64673	29904	280-85	=	2.6	18-SEP-87	917-111
64686	29927	387-85	>	10	18-SEP-87	917-113
64691	29942	366-86		.58	16-DEC-87	917-141
64722	30004	280-85	=	.2	23-OCT-87	917-126
64723	30627	100-85	=	.16	19-FEB-88	917-159
64723	30877	100-85	=	.09	19-FEB-88	917-159

SAHNUM	REGNO	PATENT	R	ED50	EDATE	REF
64723	30766	100-85	=	.22	19-FEB-88	917-159
64723	30009	100-85	=	.36	18-SEP-87	917-107
64744	30059	295-84	>	.1	14-JUL-87	917-090
64745	30765	295-84	=	.016	19-FEB-88	917-154
64745	30060	295-84	=	.016	20-OCT-87	917-127
64747	30067	298-84	=	.11	01-JUL-87	917-087
64748	30068	298-84	=	.04	19-FEB-88	917-155
64792	30146	260-85	=	.74	13-OCT-87	917-123
64816	30199	295-84	=	.1	12-OCT-87	917-119
64844	30280	384-85	=	.07	09-DEC-87	917-135
64844	30769	384-85	=	.08	19-FEB-88	917-167
64896	30378	366-87	>	.3	06-OCT-87	917-119
64897	30379	366-87	>	.3	06-OCT-87	917-120
64906	30393	280-85	=	.045	05-JAN-88	917-150
64906	30772	280-85	=	.1	15-JAN-88	917-155
64933	30441	299-84	>	1	09-DEC-87	917-138
64935	30447	299-84	=	.49	09-DEC-87	917-138
64936	30482	299-84	>	1	09-DEC-87	917-135
64999	30623	298-84	=	.1	19-FEB-88	917-168
65002	30629	101-85	=	.76	05-JAN-88	917-144
65003	30630	101-85	=	.09	19-FEB-88	917-159

SAHNUM	REGNO	PATENT	R	ED50	EDATE	REF
65003	30902	101-85	=	.06	19-FEB-88	917-170
86665	25887	102-82	>	10	06-MAY-87	917-056
87469	26362	101-82	>	10	06-MAY-87	917-056
89826	29587	101-82	>	10	06-MAY-87	917-057
317223	24022		>	16	20-MAR-84	812-183
880349	29591	102-82	>	10	18-AUG-87	917-098
880586	29586	102-82	>	10	18-AUG-87	917-098
880820	29589	102-82	>	10	18-AUG-87	917-099

140 records selected.

SQL>

Case No. 600-7101/CONT/INT.(5)
Patent -

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

WATTANASIN
v.
FUJIKAWA et al.

Interference Nos. 102,648, 102,975
Examiner-in-Chief: M. Sofocleous

SUPPLEMENTAL DECLARATION OF ROBERT G.ENGSTROM PURSUANT TO 37 CFR §1.672

I, Robert G. Engstrom, do hereby declare as follows:

All of the below-indicated activities took place in the United States.

Exhibit Q comprises a true copy of a Biological Activity Data Report dated May 24, 1988 which I sent to the Patent Department concerning the compounds of PD 299/84, together with a computer printout of the Sandoz database dated May 23, 1988. The printout contains IC_{50} and some ED_{50} values for compounds of Patent Disclosure 295/84 and compounds of the subject Patent Disclosure 299/84.

(I note that I became aware of a computer entry error comprising the inadvertent "switching" of the ED_{50} data for compounds 64-933 and 64-935. The corrections on the printout are in my handwriting and would have been made on or about May 23, 1988.)

The undersigned declares further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful

false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

I hereby subscribe my name to the foregoing Declaration this 19 day of February, 1993.

Robert Engstrom

Robert Engstrom

Q

BIOLOGICAL ACTIVITY DATA REPORT (FOR PATENT DEPT.)

INVENTOR: S. Wattanasin DISCL. NO.: 299-84 418

ATTORNEY: M. Kassenoff DATE: May 24, 1988

1. ACTIVITY TO BE DISCLOSED:
Inhibition of cholesterol biosynthesis, antihypercholesteremic, antiatherosclerotic

2. IF ANY COMPOUNDS COVERED BY ABOVE-NOTED DISCLOSURE HAVE MORE THAI ONE ACTIVITY, INDICATE TOTAL NUMBER OF ACTIVITIES AND PREPARE A SEPARATE B.A.D.R. SHEET FOR EACH. TOTAL NO. OF ACTIVITIES: 1

3.a) TEST METHODS USED TO ESTABLISH ACTIVITY:
HMG-CoA reductase inhibition in rat liver microsomes (DT 64)
Cholesterol synthesis inhibition invivo in rats (DT 65)

b) DOSAGE RANGES BASED ON ACTUAL DOSES USED IN TEST PROCEDURE:
0.050 - 1.5 mg/kg

4. COMPOUNDS TESTED WITHIN DISCLOSURE WHICH EXHIBIT WEAK OR GREATER ACTIVITY:
64-935, 54-933

5. DOSAGE SCHEDULE - Broad Ranges:

a) Large / small animals:	.10	to	1.0	mg/kg.
b) Large animals:	20	to	200	mg/day.

6. MOST PREFERED COMPOUND FOR ACTIVITY DESIGNATED:

64-935

7. OTHER PREFERRED OR POTENTIALLY PREFERRED COMPOUNDS FOR DESIGNATEI ACTIVITY:
64-936, 63-366, 64-933, 64-934

8. ED50 FOR THE PREFERRED COMPOUND IN EACH OF THE TEST METHODS INDICATED IN 3a) FOR THE DESIGNATED ACTIVITY:

COMPOUND	IC50 uM DT64	ED50 mg.kg DT65	Potency x Mevinolin*
Compactin	1.01	3.5	0.11
Mevinolin	0.14	0.41	1 (standard)
64-935	0.41	0.49	0.3
64-936	0.53	>1.0	
64-933	2.37	2.40	

* Clinical dose of mevinolin (Lovasatin) = 20-80 mg/day

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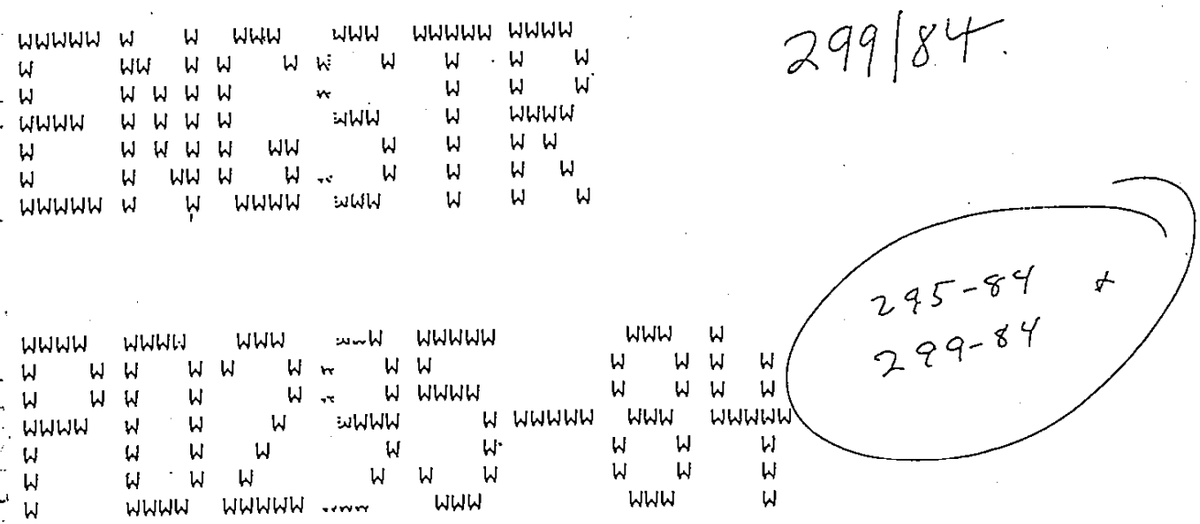
419

299/84



295-84 &
299-84

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File last modified: 88-05-23. 08:25:36. Mon

Spooled: 88-05-23 08:50:36. Mon [Spooler rev 19.4.6]
Started: 88-05-23 08:50:40. Mon on: PR0 by: PR0

IC50 TABLE RAT MICROSOMAL ASSAY (CSI-DT64)

THIS FILE IS A CALCULATED ESTIMATE OF THE IC50 (CONCENTRATION WHICH REDUCES THE CONVERSION OF HMG-CoA TO MEVALONATE BY 50%) USING ALL THE STUDIES ON THE RELEVANT COMPOUNDS UP TO THE SORT DATE.

LAST UPDATE: 02-04-88 SORT BY: DISCLNO

COMPOUND	REGNO	DISCL	IC50 uM	DATE	REF	COMMENTS
SAH-062977	24162	295-84	25.0000	02-07-84	1014-248	
SAH-062978	24163	295-84	0.0180	02-07-84	1014-249	
SAH-063033	24315	295-84	0.0450	04-18-84	1014-257	SAPONIFIED
SAH-063033	24315	295-84	0.5250	02-29-84	1014-257	
SAH-063034	24316	295-84	0.3630	02-22-84	1014-258	
SAH-063035	24317	295-84	0.0400	02-22-84	1014-259	
SAH-063074	24446	295-84	0.4000	05-23-84	1014-277	
SAH-063074	24446	295-84	0.6900	03-26-84	1014-277	
SAH-063075	24448	295-84	0.5300	04-18-84	1014-278	SAPONIFIED
SAH-063075	24448	295-84	0.9040	03-26-84	1014-278	
SAH-063076	24449	295-84	0.5800	06-12-84	1014-279	
SAH-063076	24449	295-84	0.6400	05-23-84	1014-279	
SAH-063076	24449	295-84	0.9000	03-26-84	1014-279	
SAH-063083	24511	295-84	1.9100	03-28-84	1014-281	
SAH-063083	24511	295-84	2.3200	03-28-84	1014-281	
SAH-063084	24512	295-84	3.1600	06-12-84	1014-282	
SAH-063084	24512	295-84	6.3200	03-28-84	1014-282	
SAH-063144	24750	295-84	1.1600	05-10-84	1014-294	SAPONIFIED
SAH-063144	24750	295-84	2.0200	05-10-84	1014-294	
SAH-063145	24755	295-84	>10.0000	05-07-84	1014-295	SAPONIFIED
SAH-063145	24755	295-84	>10.0000	05-10-84	1014-295	
SAH-063146	24756	295-84	>10.0000	05-07-84	1014-296	
SAH-063158	24809	295-84	0.1000	06-04-84	1069-002	SAPONIFIED
SAH-063158	24809	295-84	0.3430	06-04-84	1069-002	
SAH-063159	24810	295-84	0.2250	06-12-84	1069-003	
SAH-063159	24810	295-84	0.2630	06-04-84	1069-003	
SAH-063160	24811	295-84	0.1110	06-04-84	1069-004	SAPONIFIED
SAH-063160	24811	295-84	1.5600	06-04-84	1069-004	
SAH-063161	24821	295-84	0.0020	06-04-84	1069-005	
SAH-063161	24821	295-84	0.0020	06-12-84	1069-005	
SAH-063162	24822	295-84	0.0030	06-04-84	1069-006	
SAH-063162	24822	295-84	0.0035	06-12-84	1069-006	
SAH-063174	24865	295-84	0.0140	06-06-84	1069-013	SAPONIFIED
SAH-063174	24865	295-84	0.0190	06-06-84	1069-013	
SAH-063175	24866	295-84	0.0260	06-06-84	1069-014	
SAH-063229	25075	295-84	>10.0000	08-04-84	1069-036	
SAH-063230	25078	295-84	0.0042	08-01-84	1069-037	
SAH-063231	25079	295-84	0.0058	08-04-84	1069-038	
SAH-063269	25205	295-84	0.0030	09-10-84	1069-053	SAPONIFIED
SAH-063269	25205	295-84	0.0440	09-12-84	1069-053	
SAH-063270	25206	295-84	0.0080	09-05-84	1069-054	SAPONIFIED
SAH-063271	25208	295-84	0.0320	09-10-84	1069-055	
SAH-063271	25208	295-84	0.1450	09-12-84	1069-055	

SAH-064484	F	29413	95-84	0.0320	11-24-86	1149-227
SAH-064744	E	30059	95-84	0.0320	05-01-87	1149-293
SAH-064745	S	30060	95-84	0.0030	05-01-87	1149-294
SAH-064745	S	30060	95-84	0.0030	07-07-87	1149-297
SAH-064815	E	30198	95-84	0.0220	07-07-87	1238-001
SAH-064816	S	30199	95-84	0.0450	07-07-87	1238-002
SAH-063162	S	30203	95-84	0.0080	07-07-87	1238-003
SAH-064745		30765	95-84	0.0020	01-12-88	1238-030
SAH-063366		25496	99-84	1.5800	12-13-84	1069-113
SAH-063549		26082	99-84	7.3100	06-13-84	1069-197
SAH-063548		26080	99-84	3.7750	06-13-84	1069-198 —
SAH-064933	E	30441	99-84	2.3700	10-08-87	1238-013
SAH-064934	S	30442	99-84	2.6100	10-08-87	1238-014
SAH-064935	E	30447	99-84	0.4130	10-08-87	1238-015 —
SAH-064936	S	30448	99-84	0.5300	10-13-87	1238-016 —

ED50 TABLE RAT INVIVO ACETATE INCORPORATION (CSIV-DT65)

THIS FILE IS A CALCULATED ESTIMATE OF THE ED50 (DOSE WHICH REDUCES THE INCORPORATION OF 14C-ACETATE INTO CHOLESTEROL BY 50%) USING ALL THE STUDIES ON THE RELEVANT COMPOUNDS UP TO THE SORT DATE.

LAST UPDATE: 1-06-88 SORT BY: REGNO

COMPOUND	REGNO	CISCL	ED50 mg/kg	DATE mm-dd-yy	REF bk-pg	COMMENTS
SAH-064745	30060	95-84 =	0.016	10-20-87	917-127	N=9
SAH-064745	30765	95-84 =	0.016	02-19-88	917-154	N=3 BS BATCH
SAH-064745	ALL	95-84 =	0.016	02-19-88	917-154	N=12 2BATCHES
SAH-063162	25500	95-84 =	0.019	09-18-87	917-101	N=10
SAH-063162	ALL	95-84 =	0.040	09-18-87		N=19 3BATCHES
SAH-063162	25085	95-84 =	0.079	10-11-84	812-266	N=8
SAH-064119	27563	95-84 =	0.08	05-16-86	869-228	N=6
SAH-064744	30059	95-84 >	0.10	07-14-87	917-090	N=3 -21% @.10
SAH-064816	30199	95-84 =	0.10	10-12-87	917-119	N=6
SAH-064483	29412	95-84 =	0.13	02-06-87	917-024	N=3
SAH-064063	27424	95-84 =	0.19	04-17-86	869-211	N=3
SAH-064309	28718	95-84 =	0.19	11-03-86	869-283	N=3
SAH-063231	25079	95-84 >	0.25	08-30-84	812-250	
SAH-064393	29163	95-84 =	0.25	02-25-87	917-031	N=6
SAH-063161	24821	95-84 >	0.250	11-29-84	812-293	-12@0.25
SAH-063989	27237	95-84 =	0.28	04-04-86	869-195	N=6
SAH-063425	25687	95-84 >	0.3	03-20-85	869-046	N=3
SAH-064305	28701	95-84 >	0.3	11-03-86	869-280	N=3 -34% @.3
SAH-064480	29404	95-84 >	0.3	02-06-87	917-023	N=3 +3% @.3
SAH-063270	ALL	95-84 =	0.308	02-07-85		N=11 2BATCHES
SAH-063270	25206	95-84 =	0.33	10-11-84	812-267	
SAH-063270	25501	95-84 =	0.362	01-21-85	869-018	
SAH-064307	28705	95-84 =	0.47	02-06-87	917-020	N=6
SAH-063159	24810	95-84 >	0.5	06-19-84	812-219	

422

SAH-063162	24822	95-84	<	0.5	06-19-84	812-219	N=1 -87@0.5
SAH-063175	24866	95-84	<	0.5	06-19-84	812-220	
SAH-063230	25078	95-84	>	0.500	11-29-84	812-294	
SAH-064391	29161	95-84	=	0.51	10-30-86	917-011	N=3
SAH-063035	24317	95-84	>	0.6	05-07-84	812-201	
SAH-063145	24755	95-84	>	0.6	05-18-84	812-208	
SAH-063146	24756	95-84	>	0.6	05-18-84	812-208	
SAH-063174	24865	95-84	=	0.706	06-19-84	812-220	
SAH-064481	29406	95-84	>	1.0	02-06-87	917-024	N=3 -28% @1.0
SAH-064482	29411	95-84	>	1.0	03-18-87	917-041	N=3 -41% @1.0
SAH-064064	27433	95-84	=	1.05	07-17-86	869-263	N=6
SAH-064204	27793	95-84	=	1.21	10-02-86	869-298	N=6
SAH-064141	27630	95-84	>	1.25	02-24-87	917-029	N=6 -24% @1.25
SAH-064308	28717	95-84	>	1.5	11-03-86	869-283	N=3 -16% @1.5
SAH-064193	27760	95-84	>	2.4	07-24-86	869-269	N=3 -24% @2.4
SAH-063076	24449	95-84	<	2.5	05-14-84	812-204	
SAH-063084	24512	95-84	>	2.5	05-07-84	812-201	
SAH-064933	30441	99-84	=	~~0.49~~ 1	12-09-87	917-138	N=3 -3% @1.0
SAH-064935	30447	99-84	≈	~~1.0~~ .99	12-09-87	917-138	N=3

600 - 6951

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 114 027**
A1

(12) **EUROPEAN PATENT APPLICATION**

(21) Application number: 83810548.4

(22) Date of filing: 22.11.83

(51) Int. Cl.³: C 07 D 209/18, C 07 D 405/04, A 61 K 31/405

(30) Priority: 22.11.82 US 443668
04.11.83 US 548850

(43) Date of publication of application: 25.07.84
Bulletin 84/30

(84) Designated Contracting States: AT BE CH DE FR GB IT LI LU NL SE

(71) Applicant: SANDOZ AG, Lichtstrasse 35, CH-4002 Basel (CH)
(84) Designated Contracting States: BE CH FR GB IT LI LU NL SE

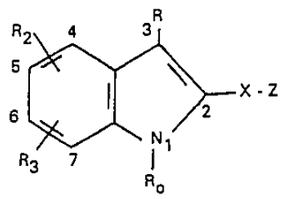
(71) Applicant: SANDOZ-PATENT-GMBH, Humboldtstrasse 3, D-7850 Lörrach (DE)
(84) Designated Contracting States: DE

(71) Applicant: SANDOZ-ERFINDUNGEN Verwaltungsgesellschaft m.b.H., Brunner Strasse 59, A-1235 Vienna (AT)
(84) Designated Contracting States: AT

(72) Inventor: Kathawala, Faizulla Gulamhusein, 39 Woodland Avenue, Mountain Lakes, N.J., 07946 (US)

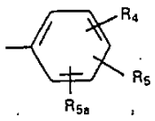
(54) **Analogs of mevalolactone and derivatives thereof, processes for their production, pharmaceutical compositions containing them and their use as pharmaceuticals.**

(57) Compounds of formula I



(I)

wherein one of R and R_0 is



and the other is primary or secondary C_{1-6}alkyl, C_{3-6}-cycloalkyl or phenyl-$(CH_2)_m$-,
wherein

R_4 is hydrogen, C_{1-4}alkyl, C_{1-4}alkoxy, (except t-butoxy), trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy,

R_5 is hydrogen, C_{1-3}alkyl, C_{1-3}alkoxy, trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy,

R_{5a} is hydrogen, C_{1-2}alkyl, C_{1-2}alkoxy, fluoro or chloro, and

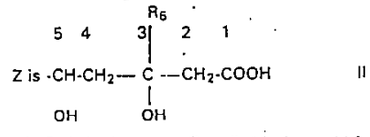
m is 1, 2, or 3,

with the provisos that both R_5 and R_{5a} must be hydrogen when R_4 is hydrogen, R_{5a} must be hydrogen when R_5 is hydrogen, not more than one of R_4 and R_5 is trifluoromethyl, not more than one of R_4 and R_5 is phenoxy and not more than one of R_4 and R_5 is benzyloxy,

R_2 is hydrogen, C_{1-4}alkyl, C_{3-6}cycloalkyl, C_{1-4}alkoxy, (except t-butoxy), trofluoromethyl, fluoro, chloro, phenoxy or benzyloxy,

R_3 is hydrogen, C_{1-3}alkyl, C_{1-3}alkoxy, trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy, with the provisos that R_3 must be hydrogen when R_2 is hydrogen, not more than one of R_2 and R_3 is trifluoromethyl, not more than one of R_2 and R_3 is phenoxy, and not more than one of R_2 and R_3 is benzyloxy,

X is $-(CH_2)_n-$ or $-CH=CH-$ (n = 0, 1, 2 or 3),



(II)

wherein R_6 is hydrogen or C_{1-3}alkyl in free acid form or in the form of a physiologically-hydrolysable and -acceptable ester or a lactone thereof or in salt form.

These compounds are indicated for use as pharmaceuticals particularly for inhibiting cholesterol biosynthesis and treating atherosclesoris.

EP 0 114 027 A1

formulae V, X-XII, XX and XXIXB-XXIXD) and Groups (xiv)-(xx), (xxxiii)-(xxxviii) and (lxxxix)-(cxiv) for formulae XXVI-XXVIII) to the extent consistent therewith.

The compounds of formula I possess pharmacological activity in particular they are inhibitors of 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase and as a consequence inhibitors of cholesterol biosynthesis as demonstrated in the following three tests.

Test A: In Vitro Microsomal Assay of HMG-CoA Reductase Inhibition:

200 ul. aliquots (1.08-1.50 mg./ml.) of rat liver microsomal suspensions, freshly prepard from male Spargue-Dawley rats (150-225 g. body weight), in Buffer A with 10 mmol. dithiothreitol are incubated with 10 ul. test substance dissolved in dimethylacetamide and assayed for HMG-CoA reductase activity as described by Ackerman et al., J. Lipid Res. 18, 408-413 (1977). In the assay the microsomes are the source of the HMG-CoA reductase enzyme which catalyses the reduction of HMG-CoA to mevalonate. The assay employs a chloroform extraction to separate the product, [^{14}C]mevalonolactone, formed by the HMG-CoA reductase reaction from the substrate, [^{14}C]HMG-CoA. [^{3}H]mevalono-lactone is added as an internal reference. Inhibition of HMG-CoA reductase is calculated from the decrease in specific activity [^{14}C/^{3}H]mevalonate) of test groups compared to controls.

Test B: In Vitro Cell Culture Cholesterol Biosynthesis Screen:

The cell culture is prepared as follows: Stock monolayer cultures of the Fu5AH rat hepatoma cell line (originally obtained from G. Rothblat; see Rothblat, Lipids 9, 526-535 (1974) are routinely maintained in Eagle's Minimum Essential Medium (EMEM) supplemented with 10% fetal bovine serum (FBS) in 75 cm^2 tissue culture flasks. For these studies, when the cultures reach

The isomer of Yang et al. and the isomer disclosed in Reaction Scheme III yield lactones having the 4R,6S configuration and, as a result of epimerization in Reaction X, such compounds having the 4R,6R configuration. Lactones having the 4S,6R and 4S,6S configuration may be obtained from the other isomer whose synthesis is disclosed in Rection Scheme III.

The availability of these intermediates enables synthesis of optically pure end products.

Reaction products both intermediale and final can be isolated and purified in conventional mannr whereby intermediates can where appropriately be employed directly in a subsequent reaction

Mixtures of stereoisomers (cis, trans and optical) may be separated by conventional means at whatever stage of synthesis is appropriate. Such methods include re-crystalisation, chromatography, formation of esters with optically pure acids and alcohols or of amides and salts (cf also Sommer et al. J.A.C. S 80, 3271 (1958)) with subsequent reconversion under retention of optical purity. For example diastereoisomeric (-)-α-naphthyl-phenylmethylsilyl derivatives of a lactone type end product of formula I may be separated on a silica solumn having covalently bound L-phenylglycine (eluant n-hexane/acetate : 1/1).

Salts may be prepared in conventional manner from free acids, lactones and esters and vice-versa. Whilst all salts are covered by the invention pharmaceutically acceptable salts especially sodium, potassium and ammonium particularly sodium salts are preferred.

The various forms of the compounds of formula I are by virtue of their interconvertability useful as intermediates in addition to the use set out below.

Also within the scope of this invention are the intermediates of formulae V, X, XI, XII, XX, XXIV, XXVI-XXVIII and XXIXB-XXIXD. The preferences for each variable are the same as those set forth for the compounds of formula I, with the preferred groups of such compounds including those that correspond to Groups (i)-(xiii) and (xxxix)-lxxxviii) (for

formulae V, X-XII, XX and XXIXB-XXIXD) and Groups (xiv)-(xx), (xxxiii)-(xxxviii) and (lxxxix)-(cxiv) for formulae XXVI-XXVIII) to the extent consistent therewith.

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confluence, they are removed by mild enzymatic treatment with 0.25% trypsin in Hanks' balanced salt solution (without calcium and magnesium). After centrifugation of the cell suspension and aspiration of the enzymatic solution, a cell pellet is resuspended in an appropriate volume of media for seeding into 60 mm. tissue culture dishes. The cultures are incubated at 37°C in an atmosphere of high humidity and 5% carbon dioxide. When the cultures are confluent (approximately 5 days), they are ready for use. The culture media is aspirated from the dishes and replaced with 3 ml of EMEM suplemented with 5 mg/ml of dilipidized serum protein (DLSP) prepared by the method of Rothblat et al., In Vitro 12, 554-557 (1976). Replacement of the FBS with DLSP has been shown to stimulate the incorporation of [^{14}C]acetate into sterol by removing the exogenous sterol supplied by the FBS, thereby requiring the cells to synthesized sterol. Enthanced 3-hydroxy-3-methylglutaryl Coenzyme A reductase (HMG-CoA reductase) activity is measurable in the cells in response to the lack of exogenous sterol. Following approximately 24 hours incubation at 37°C in the DLSP supplemented media, the assay is initiated by the addition of 3μCi of [^{14}C]acetate and the test substances solubilized in dimethylsulfoxide (DMSO) or distilled water. Solvent controls and compactin-treated controls are always prepared. Triplicate 60mm. tissue culture dishes are run for each group. After 3 hours incubation at 37°C, the cultures are examined microscopically using an inverted phase contrast microscope. Notations are made of any morphological changes which may have occurred in the cultures. The media is aspirated and the cell layer is gently washed twice with 0.9% sodium chloride solution (saline). The cell layer is then harvested in 3 ml. of 0.9% saline by gentle scraping with a rubber policeman and transferred to a clean glass tube with Teflon lined cap. The dishes are rinsed with 3 ml. of 0.9% saline and rescraped, and the cells are combined with the first harvest. The tubes are centrifuged at 1500 r.p.m. for 10 minutes

in an IEC PR-J centrifuge, and the supernatant is asperated.

The cells are then extracted as follows: One ml. of 100% ethanol is added to the cell pellet followed by sonication for 10 seconds with a "LO" setting of 50 on a Bronwell Biosonik IV. One hundred ul. are taken for protein determination. One ml. of 15% potassium hydroxide (KOH) is added, and the samples are thoroughly vortexed. Saponification is accomplished by heating the ethanol-KOH treated samples at 60°C for 60 minutes in a water bath. Following dilution of the samples with 2ml. of distilled water, they are extracted three times with 7 ml. of petroleum ether. The petroleum ether extracts are then washed three times with 2 ml. of distilled water and finally taken to dryness under a stream of nitrogen.

The obtained samples are then analyzed by thin layer chromatography (TLC) as follows: Residues from the petroleum ether extraction are taken up in a small volume of hexane and spotted on silica gel 60 TLC plates (E. Merck). Development of the plates is carried out in a 150 parts by volume hexane: 50 parts by volume diethyl ether: 5 parts by volume galcial acetic acid solvent system using a three phase development procedure. Visualization is accomplished in an iodine vapor chamber. The plates are divided into five sections such that each section contains the molecules having the following approximate Rf values: section 1- 0-0.4, section 2- 0.4-0.55, section 3- 0.55-0.7, section 4- 0.7-0.9 and section 5- 0.9-1.0. Section 2 contains the non-saponifiable sterols. The five sections of the TLC plates are scraped into scintillation vials. Blanks are also prepared from scrapings of chromatographed non-labelled standards. ACS® scintillation cocktail is added, and the radioactivity is determined in a liquid scintillation spectrometer. [^{14}C]hexadecane standards are used to determine counting efficiencies. The total protein content of the samples is determined employing the Bio-Rad Protein Assay System.

The results are reported as disintegrations per minute per mg protein (d.p.m./mg protein) for each of the live TLC sections. Mean d.p.m./mg protein ± standard error of the mean are compared for percentage change (%Δ) and statistical significance with solvent control means. TLC section 2 data is taken as a measure of HMG-CoA reductase activity inhibition.

Test C: In Vivo Cholesterol Biosynthesis Inhibition Tests: In vivo studies utilize male Wistar Royal Hart rats weighing 150±20 g which have been kept for 7-10 days on an altered light cycle (6:30 a.m. - 6:30 p.m. dark) housed two per cage and fed powdered Purina Rat Chow and water ad libitum. Three hours before the diurnal maximum of cholesterol synthesis at mid-dark, the rats are administered the test substances dissolved or as a suspension in 0.5% carboxymethylcellulose in a volume of 1 ml/100 g body weight. Controls receive vehicle alone. One hour after receiving the test substance, the rats are injected intraperitoneally with about 25 μCi/100 g body weight of sodium [1-^{14}C]acetate 1-3 mCi/mmol. Two hours after mid-dark, blood samples are obtained under sodium hexobarbitol anesthesia and the serum separated by centrifugation.

Serum samples are saponified and neutralized, and the 3β-hydroxy sterols are precipiated with digitonin basically as described by Sperry et al., J. Biol. Chem. 187, 97 (1950). The [^{14}C]digitonides are then counted by liquid scintillation spectrometry. After correcting for efficiencies, the results are calculated in nCi (nanocuries) of sterol formed per 100 ml of serum. Inhibition of sterol synthesis is calculated from the reduction in the nCi of sterols formed from test groups compared to controls.

The compounds are thus indicated for use as hypolipoproteinemic and anti-atherosclerotic agents.

An indicated suitable daily dosage for use in the treatment of hyperlipoproteinemia and athersclerosis is from about

1 to 2000 mg preferably 1.5 to 100 mg suitably administered in divided dosages of 0.25 to 1000 mg preferably 0.4 to 50 mg two to four times daily or in retard form.

They may be administered in free acid form or in the form of a physiologically-hydrolysable and -acceptable ester or a lactone thereof or in pharmaceutically acceptable salt form whereby the various forms have activities in the same range.

The invention therefore also concerns a method of treating hyperlipoproteinemia or atherosclerosis by administration of a compound of formula I in free acid form or in the form of a physiologically-hydrolysable and -acceptable ester or a lactone thereof or in pharmaceutically acceptable salt form as well as such compounds for use as pharmaceuticals e.g. as hypolipoproteinemic and anti-atherosclerotic agents.

The compounds may be administered alone, or in admixture with a pharmaceutically acceptable diluent or carrier, and, optionally other excipients, and administered orally in such forms as tablets, elixirs, capsules or suspensions or parenterally in such forms as injectable solutions or suspensions.

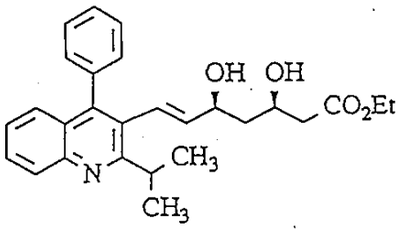
The preferred pharmaceutical compositions from the standpoint of ease of preparation and administration are solid compositions, particularly tablets and hard-filled or liquid-filled capsules.

Such compositions also form part of the invention.

The following examples, in which all temperatures are in °C illustrate the invention.

form 5-1

INHIBITORY EFFECT ON CHOLESTEROL SYNTHESIS (RATS) ED_{50} (mg/Kg)



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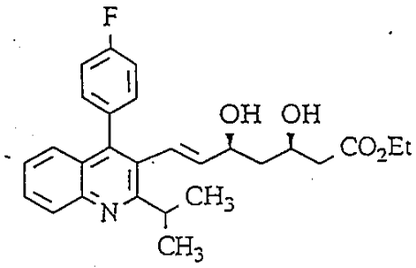

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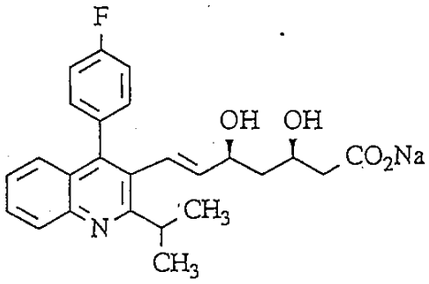

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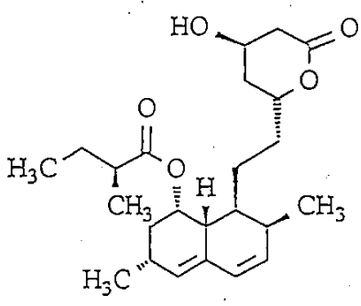

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

#114

WATTANASIN

V. Interference No. 102,648

FUJIKAWA et al. Examiner-in-Chief: M. Sofocleous

**WATTANASIN REPLY TO
FUJIKAWA OPPOSITION TO
WATTANASIN PROPOSED FINDINGS OF FACT**

Honorable Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Sir:

Fujikawa have opposed the Wattanasin Proposed Findings of Fact filed with the Wattanasin opening brief on July 16, 1993.

First of all, Wattanasin notes that under 37 CFR 1.656(g), proposed findings of fact and/or conclusions of law are not mandatory, and it is solely within the discretion of the Board to adopt them in whole or in part or not to adopt them at all irrespective of whether or not they fully comply with the rules.

With respect to the grounds of the Fujikawa opposition, Wattanasin responds as follows:

1. There was no abandonment, supression or concealment of the Wattanasin invention between June 1985 (by which time he had reduced to practice by testing in vitro the "initial phase" compounds 63-366, 63-548 and 63-549), and March 1987, when work was resumed on the "second phase" compounds, because during this period Wattanasin was involved in continuing synthesis work within

the generic invention of HMG-CoA inhibitors and furthermore suffered from a manpower shortage in his laboratory which prevented him from completing the quinoline series, although it remained his intention to do so (WB[1] at 28-30, 67-68).

2. Additional testing was not needed for a reduction to practice of the "second phase" compounds 64-933, 64-934/NA, 64-935, and 64-936/NA, because their practical utility was already known to Wattanasin from the prior testing of the "initial phase" compounds (WB at 27-28).

3. Even if testing of the second phase compounds was required for a reduction to practice, diligence in making and testing the second phase compounds is shown by Wattanasin from just prior to the Fujikawa benefit date of August 20, 1987 to the in vitro testing carried out on October 8 and 13, 1987 by Dr. Scallen (WRB at 35-43).

4. The in vitro testing constituted a renewed reduction to practice within the count because it confirmed the practical utility of the "second phase" compounds, and because the activity in vitro could be reasonably correlated with activity in vivo. If arguendo the Board finds that the Wattanasin in vitro testing of Wattanasin does not prove a reduction to practice and requires in vivo testing, then the Board should sua sponte also restrict Fujikawa to, at the earliest, their priority date of August 3, 1988, when they first introduced in vivo test results in their priority filing (WRB at 11-19).

1."WB" is the Wattanasin opening brief; "WRB" is the Wattanasin reply brief; "WR" is the Wattanasin record.

5. In vivo testing of compounds 64-933, 64-935 and 64-936/NA was also pursued with diligence down to October 22 and 29, 1987; and culminated in further activity for the count comprising entry of ED_{50}'s for 64-933, 64-935 and 64-936/NA into the Sandoz database on December 9, 1987 (WB at 43-45; WRB at 19-29). In vivo administration to rats of carboxymethylcellulose solutions or suspensions of test compounds (WR at 204) met the limitations of the count (WRB at 24, WR at 204).

6. Wattanasin did not at any time abandon, suppress or conceal the invention, and nothing in the record supports such an inference. On the contrary, in view of the January 1988 recommendation of the Sandoz Patent Committee to file a patent application on the Watttanasin invention, there was an outstanding obligation to file, and attorney activity toward that objective, through to the filing date of March 3, 1989, which was 14 months after the last activity for the count (WB at 45-57; WRB at 24-25).

7. Accordingly, it is submitted that Wattanasin has proved priority by a preponderance of the evidence, or by clear and convincing evidence, over Fujikawa.

Respectfully submitted,

Diane Furman

Diane E. Furman
Attorney for the Party Wattanasin
Registration No. 31,104
201-503-7332

SANDOZ CORPORATION
59 Route 10
E. Hanover, NJ 07936

DEF:rmf
September 7, 1993

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231, on Sept. 7, 1993
(Date of Deposit)
Diane E. Furman
Name of applicant, assignee, or Registered Representative
Diane Furman
Signature
9/7/93
Date of Signature

CERTIFICATE OF SERVICE

It is hereby certified that a true copy of the paper entitled:

WATTANASIN REPLY TO
FUJIKAWA OPPOSITION TO
WATTANASIN PROPOSED FINDINGS OF FACT

was served on counsel for the party Fujikawa et al., this 7th day of September 1993, by postage pre-paid first-class mail addressed to the following:

Oblon, Spivak, McClelland, Maier & Neustadt, P.C.
Attn: Steven B. Kelber, Esq.
1755 South Jefferson Davis Highway
Crystal Square 5, Ste. 400
Arlington, VA 22202

Diane E. Furman

#115

49-111-0

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

WATTANASIN	:	
	:	INTERFERENCE NO.: 102,648
V.	:	EXAMINER-IN-CHIEF:
FUJIKAWA ET AL	:	MICHAEL SOFOCLEOUS

FUJIKAWA REPLY TO THE WATTANASIN
OPPOSITION TO FUJIKAWA'S MOTION TO SUPPRESS EVIDENCE

HONORABLE COMMISSIONER OF PATENTS AND TRADEMARKS
WASHINGTON, D.C. 20231
BOX INTERFERENCE

SIR:

On September 7, 1993, Wattanasin filed and served its Opposition to Fujikawa's Motion to Suppress the Declaration of Robert E. Engstrom and Supplemental Declaration of Robert E. Engstrom, WR 203-206 and WR 207-208, respectively.[1] The Opposition

[1] Wattanasin's Opposition was properly due in conjunction with the filing of Wattanasin Reply Brief, which was due September 4, 1993. 37 CFR §1.657(h) and the Wattanasin Request for Extension of Time approved June 7, 1993, Paper No. 98 in Interference 102,648. Wattanasin did not seek an Extension of Time in which to file its Opposition, and did not explain why the Opposition could not have been timely filed. If the Opposition is not considered as untimely, this Reply may be similarly disregarded.

neither contests the applicable Federal Rules of Evidence nor the case law cited by Fujikawa, but rather attempts to avoid suppression of the evidence by alleging a new series of facts no where supported in the Record.

Wattanasin alleges, for instance, that the actual raw data obtained from the experiments referred to in the Engstrom Declarations appears in the fifth column of WX K-1. Where is the testimony to support this? Wattanasin urges that "various computations were made including a percent change in nanoCurie count". Where is the evidence to support this? Wattanasin urges that:

> A percent change greater than 50% would indicate activity in the assay.

This is no where supported in the Record. Wattanasin urges that the assay:

> Is a quite stringent assay, where the industry standard, compactin, itself had an ED50 of 3.5, as described by Wattanasin in the Reply Brief at 21-22.

Not only is there no evidence in the Record to support this, but Wattanasin is now citing arguments in its own Reply Brief as authority for facts not in evidence! The Wattanasin unsupported assertion of facts in the form of attorney argument goes on and on. No where does the Record support the conclusion that the biological activity data report is the meaning of the entry in Exhibit Q, page 418 explained, nor is the manner of its calculation set forth anywhere. The testing procedure referred to at page 3 of the Wattanasin Opposition is not the issue, rather, the issue is the raw material, the computer mathematical manipulations applied to that data, and the support for the same by authoritative testimony, all of which Wattanasin concedes are lacking from the Record.

Wattanasin urges this Board has discretion in applying the Rules of Evidence. No support by case law is cited. The Board applies the Rules as the law commands. The Board, it is believed, does not have discretion to ignore the Rules, which Wattanasin apparently concedes has not been complied with herein with regard to Engstrom Declarations. Most bizarre of all is the assertion that:

> The resulting ED_{50} calculation was generated thereon by Sandoz in the ordinary course of

business.

Page 3 of the Opposition. Not only is this not supported anywhere in the Record, but it is wholly irrelevant. It is not things done in the ordinary course of business that are admitted under the Hearsay Rule, but rather, reports and documents produced in the ordinary course of business. This is neither. Moreover, the Fujikawa Opposition is not premised on the Hearsay Rule, and the question of course of business is irrelevant. Many of the remaining Wattanasin arguments are of pure fabric to avoid the arguments leveled at the Engstrom Declarations. For instance, Wattanasin does not explain why the error in the original Engstrom Declaration was not earlier detected, and why permission was not requested for its correction, nor does it indicate how the error was determined to be reliably indicated to be in error. The assertion that the term NA can be added or deleted to the compound identification without consequence is not only contradictory to Holmlund's testimony cited in Fujikawa's Motion to Suppress, but is totally unsupported by any testimony anywhere.

Wattanasin concedes, by silence, the applicability of the Rules of Evidence and case law cited by Fujikawa. Attorney argument is no substitute for fact. The Engstrom Declarations must

be suppressed.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.

Steven B. Kelber
Registration No.: 30,073
Attorney for Fujikawa et al

CERTIFICATE OF SERVICE

I hereby certify that true copies of:

1. **FUJIKAWA REPLY TO THE WATTANASIN OPPOSITION TO FUJIKAWA'S MOTION TO SUPPRESS EVIDENCE**

2. **CERTIFICATE OF SERVICE**

were served upon Counsel for Wattanasin as follows:

Diane E. Furman
SANDOZ CORP.
59 Route 10
E. Hanover, New Jersey 07936

via FACSIMILE and FEDERAL EXPRESS, this 22ND day of SEPTEMBER, 1993.

STEVEN B. KELBER

Interference 102,648
Interference 102,975

#115

49-111-0

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

WATTANASIN	:	
	:	INTERFERENCE NO.: 102,648
V.	:	
	:	EXAMINER-IN-CHIEF:
FUJIKAWA ET AL	:	MICHAEL SOFOCLEOUS

FUJIKAWA REPLY TO THE WATTANASIN OPPOSITION TO FUJIKAWA'S MOTION TO SUPPRESS EVIDENCE

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Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.

Steven B. Kelber
Registration No.: 30,073
Attorney for Fujikawa et al

CERTIFICATE OF SERVICE

I hereby certify that true copies of:

1. FUJIKAWA REPLY TO THE WATTANASIN OPPOSITION TO FUJIKAWA'S MOTION TO SUPPRESS EVIDENCE

2. CERTIFICATE OF SERVICE

were served upon Counsel for Wattanasin as follows:

Diane E. Furman
SANDOZ CORP.
59 Route 10
E. Hanover, New Jersey 07936

via FACSIMILE and FEDERAL EXPRESS, this 22ND day of SEPTEMBER, 1993.

STEVEN B. KELBER

Interference 102,648
Interference 102,975

#115

49-111-0

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

WATTANASIN	:	
V.	:	INTERFERENCE NO.: 102,648
	:	EXAMINER-IN-CHIEF:
FUJIKAWA ET AL	:	MICHAEL SOFOCLEOUS

FUJIKAWA REPLY TO THE WATTANASIN
OPPOSITION TO FUJIKAWA'S MOTION TO SUPPRESS EVIDENCE

HONORABLE COMMISSIONER OF PATENTS AND TRADEMARKS
WASHINGTON, D.C. 20231
BOX INTERFERENCE

SIR:

On September 7, 1993, Wattanasin filed and served its Opposition to Fujikawa's Motion to Suppress the Declaration of Robert E. Engstrom and Supplemental Declaration of Robert E. Engstrom, WR 203-206 and WR 207-208, respectively.[1] The Opposition

[1] Wattanasin's Opposition was properly due in conjunction with the filing of Wattanasin Reply Brief, which was due September 4, 1993. 37 CFR §1.657(h) and the Wattanasin Request for Extension of Time approved June 7, 1993, Paper No. 98 in Interference 102,648. Wattanasin did not seek an Extension of Time in which to file its Opposition, and did not explain why the Opposition could not have been timely filed. If the Opposition is not considered as untimely, this Reply may be similarly disregarded.

neither contests the applicable Federal Rules of Evidence nor the case law cited by Fujikawa, but rather attempts to avoid suppression of the evidence by alleging a new series of facts no where supported in the Record.

Wattanasin alleges, for instance, that the actual raw data obtained from the experiments referred to in the Engstrom Declarations appears in the fifth column of WX K-1. Where is the testimony to support this? Wattanasin urges that "various computations were made including a percent change in nanoCurie count". Where is the evidence to support this? Wattanasin urges that:

> A percent change greater than 50% would indicate activity in the assay.

This is no where supported in the Record. Wattanasin urges that the assay:

> Is a quite stringent assay, where the industry standard, compactin, itself had an ED50 of 3.5, as described by Wattanasin in the Reply Brief at 21-22.

Not only is there no evidence in the Record to support this, but Wattanasin is now citing arguments in its own Reply Brief as authority for facts not in evidence! The Wattanasin unsupported assertion of facts in the form of attorney argument goes on and on. No where does the Record support the conclusion that the biological activity data report is the meaning of the entry in Exhibit Q, page 418 explained, nor is the manner of its calculation set forth anywhere. The testing procedure referred to at page 3 of the Wattanasin Opposition is not the issue, rather, the issue is the raw material, the computer mathematical manipulations applied to that data, and the support for the same by authoritative testimony, all of which Wattanasin concedes are lacking from the Record.

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	:	INTERFERENCE NO.: 102,648
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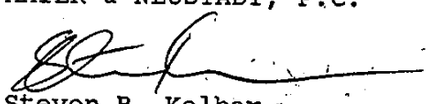

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STEVEN B. KELBER

Interference 102,648
Interference 102,975

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

#11(

WATTANASIN

Interference No. 102,648

V.

Examiner-in-Chief: M. Sofocleous

FUJIKAWA et al.

COMMUNICATION

Attention: Mrs. Hall

Pursuant to your telephone request today, enclosed are three (3) additional copies of each of the following papers mailed by the party Wattanasin on September 7, 1993 for the above-identified interference:

(1) Wattanasin Filing of Reply Brief

(2) Wattanasin Reply to Fujikawa Opposition to Wattanasin Proposed findings of Fact

(3) Wattanasin Opposition to Fujikawa Motion to Suppress Evidence

Respectfully submitted,

Diane Furman 9/21/93

Diane E. Furman
Attorney for the Party Wattanasin
Registration No. 31,104
201-503-7332

Enclosures as noted

#116

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

WATTANASIN

V. Interference No. 102,648

FUJIKAWA et al. Examiner-in-Chief: M. Sofocleous

WATTANASIN REPLY TO
FUJIKAWA OPPOSITION TO
WATTANASIN PROPOSED FINDINGS OF FACT

FYI

Honorable Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Sir:

Fujikawa have opposed the Wattanasin Proposed Findings of Fact filed with the Wattanasin opening brief on July 16, 1993.

First of all, Wattanasin notes that under 37 CFR 1.656(g), proposed findings of fact and/or conclusions of law are not mandatory, and it is solely within the discretion of the Board to adopt them in whole or in part or not to adopt them at all irrespective of whether or not they fully comply with the rules.

With respect to the grounds of the Fujikawa opposition, Wattanasin responds as follows:

1. There was no abandonment, supression or concealment of the Wattanasin invention between June 1985 (by which time he had reduced to practice by testing in vitro the "initial phase" compounds 63-366, 63-548 and 63-549), and March 1987, when work was resumed on the "second phase" compounds, because during this period Wattanasin was involved in continuing synthesis work within

the generic invention of HMG-CoA inhibitors and furthermore suffered from a manpower shortage in his laboratory which prevented him from completing the quinoline series, although it remained his intention to do so (WB[1] at 28-30, 67-68).

2. Additional testing was not needed for a reduction to practice of the "second phase" compounds 64-933, 64-934/NA, 64-935, and 64-936/NA, because their practical utility was already known to Wattanasin from the prior testing of the "initial phase" compounds (WB at 27-28).

3. Even if testing of the second phase compounds was required for a reduction to practice, diligence in making and testing the second phase compounds is shown by Wattanasin from just prior to the Fujikawa benefit date of August 20, 1987 to the in vitro testing carried out on October 8 and 13, 1987 by Dr. Scallen (WRB at 35-43).

4. The in vitro testing constituted a renewed reduction to practice within the count because it confirmed the practical utility of the "second phase" compounds, and because the activity in vitro could be reasonably correlated with activity in vivo. If arguendo the Board finds that the Wattanasin in vitro testing of Wattanasin does not prove a reduction to practice and requires in vivo testing, then the Board should sua sponte also restrict Fujikawa to, at the earliest, their priority date of August 3, 1988, when they first introduced in vivo test results in their priority filing (WRB at 11-19).

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7. Accordingly, it is submitted that Wattanasin has proved priority by a preponderance of the evidence, or by clear and convincing evidence, over Fujikawa.

Respectfully submitted,

Diane Furman

Diane E. Furman
Attorney for the Party Wattanasin
Registration No. 31,104
201-503-7332

SANDOZ CORPORATION
59 Route 10
E. Hanover, NJ 07936

DEF:rmf
September 7, 1993

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to Commissioner of Patents and Trademarks, Washington, D.C. 20231, on Sept. 7, 1993
(Date of Deposit)
Diane E. Furman
Name of applicant, assignee, or registered representative
Diane Furman
Signature
9/7/93
Date of Signature

CERTIFICATE OF SERVICE

It is hereby certified that a true copy of the paper entitled:

WATTANASIN REPLY TO
FUJIKAWA OPPOSITION TO
WATTANASIN PROPOSED FINDINGS OF FACT

was served on counsel for the party Fujikawa et al., this 7th day of September 1993, by postage pre-paid first-class mail addressed to the following:

Oblon, Spivak, McClelland, Maier & Neustadt, P.C.
Attn: Steven B. Kelber, Esq.
1755 South Jefferson Davis Highway
Crystal Square 5, Ste. 400
Arlington, VA 22202

Diane E. Furman

#116

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

WATTANASIN

Interference No. 102,648

FUJIKAWA et al.

Examiner-in-Chief: M. Sofocleous

WATTANASIN REPLY TO
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DEF:rmf
September 7, 1993

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#116

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Interference No. 102,648

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Examiner-in-Chief: M. Sofocleous

WATTANASIN REPLY TO
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FYI

SEP 22 1993

RECEIVED IN
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V. Interference No. 102,648

FUJIKAWA et al. Examiner-in-Chief: M. Sofocleous

WATTANASIN OPPOSITION
TO FUJIKAWA MOTION TO SUPPRESS EVIDENCE

FYI

Honorable Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Sir:

Fujikawa have moved to supress the Declaration and Supplemental Declaration of Robert E. Engstrom, the Sandoz researcher who conducted in vivo testing of the Wattanasin compounds in rats, together with Exhibits K-1 and Q which accompany his respective declarations. For the convenience of the Board, copies of these declarations and exhibits (as well as the companion Rodney Slaughter declaration) are appended hereto.

Fujikawa are apparently objecting to the ED_{50} data in the Engstrom declaration (WR 206) because they "constitute the results of not one but two computer manipulations."

Whatever, Fujikawa intend by this, the following things are evident from these declaration and exhibit pages:

1. Pages 334 and 337 (see upper right hand corner of exhibit page) are summary pages generated for each of the screenings carried out starting October 22 and October 29, 1987, respectively, and simply record the type of test solutions utilized;

2. Pages 335-336 and 338-339 show the actual counts in nanocuries per 100 ml. of rat serum obtained for each in vivo testing.

As described more fully by Engstrom at WR 204, the rats were administered the test substance dissolved or as a suspension in a formulation comprising carboxymethylcellulose. The rats were therafter injected with a given amount of radiolabeled sodium acetate. Serum samples were then obtained, the sterols were precipitated, and their radioactivity detected by liquid scintillation spectrometry.

The count in nanoCuries per 100 ml. rat serum is listed down the fifth column of the WX K-1 computer printout. This is the actual raw data obtained from the experiments. From the nanoCurie values received for the six rats in each testing, various computations were made including a "% change" in nanoCurie count. A % change greater than 50% would indicate activity in the assay. (This is a quite stringent assay, where the industry standard, compactin, itself had an ED50 of 3.5, as described by Wattanasin in the Reply Brief at 21-22.)

This data were then inputed into a computer program which generated an ED_{50} number for each compound tested, and the ED_{50} was downloaded in the Sandoz database maintained in the ordinary course of business. (Notice that the database accepted only ED_{50} values which were smaller than 1.) However, in Exhibit Q (at page 418), a Biological Activity Data Report on the Wattanasin compounds shows that compound 64-933 was also calculated to have a specific ED_{50} value of 2.40.

Calculation of ED_{50} in this manner was hardly new to the art as of December 1987. In fact, the whole Engstom in vivo testing procedure appears almost verbatim at page 33 of the Kathawala 1984 European patent publication on fluvastatin, EP 114,027 which was cited as "technological background" against the involved Fujikawa '930 patent (copy of relevant pages also appended).

Even the Fujikawa rebuttal witness, Dr. Homlund, acknowledged that he had "no quarrel with the techniques for determining statistical activity" used by Wattanasin (FR at 204).

Given the art-recognized status of this in vivo assay, it is hard to understand why Fujikawa insist on being provided with computer programs or logorithms so that they can trace the exact progress of each byte of information.

The Board has discretion in applying the rules of evidence, and there is submitted to be no convincing argument that a "rule of reason" should not apply here where the raw data is attested to by the individuals who actually performed the experiments, and the resulting ED_{50} calculation was generated thereon by Sandoz in the ordinary course of business.

Fujikawa affect discomfort that the ED_{50} data for one of 64-933 and 64-936/NA was inadvertently "switched" at page 206 of the original Engstrom declaration. Regardless of whether this typographical error is related in any way to an acknowledged Engstrom "goof" showing up in Exhibit Q, all of the other Wattanasin Exhibits are uniform in assigning an ED_{50} value to

compound 64-935, alone, of 0.49 (see, e.g., Exhibit S-1 (relevant page also appended))[1].

Like any other business or technical information maintained in the ordinary course of business by Sandoz, the ED_{50} data in a sense speaks for itself, and should not be invalidated by a purported lack of foundation, particularly since the underlying computer programs or logorithms are not themselves likely to be comprehensible.

Accordingly, the Fujikawa motion to suppress should be denied.

SANDOZ CORP.
50 route 10
E. Hanover, NJ 07936
Attachments as noted
September 7, 1993

Respectfully submitted,

Diane E. Furman
Attorney for the Party Wattanasin
Registration No. 31,104
201-503-7332

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231, on Sept. 7, 1993
(Date of Deposit)
Diane E. Furman
Name of applicant, assignee, or Registered Representative
Signature
Sept 7, 1993
Date of Signature

1. Fujikawa also attempt an argument surrounding the absence of a sodium salt indication, i.e. "NA", from the Sandoz database printout for 64-936(NA) included in Wattanasin Exhibit K-1 (at 336). However, notice that on pages 203, 205 and 209 of the Wattanasin record "64-936" is used interchangeably with the designation "64-936/NA", just as the Sandoz fluvastatin compound, a sodium salt (technically, "62-320/NA"), is typically referred to as, simply, 62-320 (WR at 484), without the added sodium designation. It is hard to see how Fujikawa could allege difficulty with practices that are customary in the art, and manifested throughout the Wattanasin record in relation to compounds of known strucutre such as fluvastatin.

CERTIFICATE OF SERVICE

It is hereby certified that a true copy of the paper entitled:

WATTANASIN OPPOSITION
TO FUJIKAWA MOTION TO SUPPRESS EVIDENCE

and the attachments thereto were served on counsel for the party Fujikawa et al., this 7th day of September 1993, by postage pre-paid first-class mail addressed to the following:

Oblon, Spivak, McClelland, Maier & Neustadt, P.C.
Attn: Steven B. Kelber, Esq.
1755 South Jefferson Davis Highway
Crystal Square 5, Ste. 400
Arlington, VA 22202

Diane Furman

Diane E. Furman

600 - 6951

(19) Europäisches Patentamt
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A1

(12) # EUROPEAN PATENT APPLICATION

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(71) Applicant: SANDOZ AG, Lichtstrasse 35, CH-4002 Basel (CH)
(84) Designated Contracting States: BE CH FR GB IT LI LU NL SE

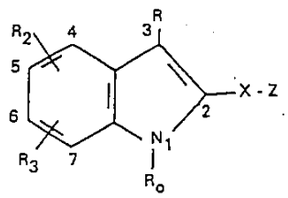
(71) Applicant: SANDOZ-PATENT-GMBH, Humboldtstrasse 3, D-7850 Lörrach (DE)
(84) Designated Contracting States: DE

(71) Applicant: SANDOZ-ERFINDUNGEN Verwaltungsgesellschaft m.b.H., Brunner Strasse 59, A-1235 Vienna (AT)
(84) Designated Contracting States: AT

(72) Inventor: Kathawala, Faizulla Gulamhusein, 39 Woodland Avenue, Mountain Lakes, N.J., 07946 (US)

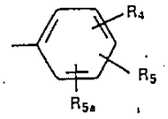
(54) **Analogs of mevalolactone and derivatives thereof, processes for their production, pharmaceutical compositions containing them and their use as pharmaceuticals.**

(57) Compounds of formula I

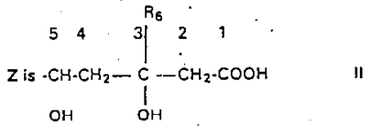


(I)

wherein one of R and R_6 is



and the other is primary or secondary C_{1-6}alkyl, C_{3-6}cycloalkyl or phenyl-$(CH_2)_m$-,
wherein
R_4 is hydrogen, C_{1-4}alkyl, C_{1-4}alkoxy, (except t-butoxy), trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy,
R_5 is hydrogen, C_{1-3}alkyl, C_{1-3}alkoxy, trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy,
R_{5a} is hydrogen, C_{1-2}alkyl, C_{1-2}alkoxy, fluoro or chloro, and
m is 1, 2, or 3,
with the provisos that both R_5 and R_{5a} must be hydrogen when R_4 is hydrogen, R_{5a} must be hydrogen when R_5 is hydrogen, not more than one of R_4 and R_5 is trifluoromethyl, not more than one of R_4 and R_5 is phenoxy and not more than one of R_4 and R_5 is benzyloxy,
R_2 is hydrogen, C_{1-4}alkyl, C_{3-6}cycloalkyl, C_{1-4}alkoxy, (except t-butoxy), trofluoromethyl, fluoro, chloro, phenoxy or benzyloxy,
R_3 is hydrogen, C_{1-3}alkyl, C_{1-3}alkoxy, trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy, with the provisos that R_3 must be hydrogen when R_2 is hydrogen, not more than one of R_2 and R_3 is trifluoromethyl, not more than one of R_2 and R_3 is phenoxy, and not more than one of R_2 and R_3 is benzyloxy,
X is $-(CH_2)_n-$ or $-CH=CH-$ (n = 0, 1, 2 or 3),



(II)

wherein R_6 is hydrogen or C_{1-3}alkyl in free acid form or in the form of a physiologically-hydrolysable and -acceptable ester or a lactone thereof or in salt form.
These compounds are indicated for use as pharmaceuticals particularly for inhibiting cholesterol biosynthesis and treating atherosclerosis.

EP 0 114 027 A1

The isomer of Yang et al. and the isomer disclosed in Reaction Scheme III yield lactones having the 4R,6S configuration and, as a result of epimerization in Reaction X, such compounds having the 4R,6R configuration. Lactones having the 4S,6R and 4S,6S configuration may be obtained from the other isomer whose synthesis is disclosed in Rection Scheme III.

The availability of these intermediates enables synthesis of optically pure end products.

Reaction products both intermediale and final can be isolated and purified in conventional mannr whereby intermediates can where appropriately be employed directly in a subsequent reaction.

Mixtures of stereoisomers (cis, trans and optical) may be separated by conventional means at whatever stage of synthesis is appropriate. Such methods include re-crystalisation, chromatography, formation of esters with optically pure acids and alcohols or of amides and salts (cf also Sommer et al. J.A.C. S 80, 3271 (1958)) with subsequent reconversion under retention of optical purity. For example diastereoisomeric (-)-α-naphthyl-phenylmethylsilyl derivatives of a lactone type end product of formula I may be separated on a silica solumn having covalently bound L-phenylglycine (eluant n-hexane/acetate : 1/1).

Salts may be prepared in conventional manner from free acids, lactones and esters and vice-versa. Whilst all salts are covered by the invention pharmaceutically acceptable salts especially sodium, potassium and ammonium particularly sodium salts are preferred.

The various forms of the compounds of formula I are by virtue of their interconvertability useful as intermediates in addition to the use set out below.

Also within the scope of this invention are the intermediates of formulae V, X, XI, XII, XX, XXIV, XXVI-XXVIII and XXIX8-XXIXD. The preferences for each variable are the same as those set forth for the compounds of formula I, with the preferred groups of such compounds including those that correspond to Groups (i)-(xiii) and (xxxix)-lxxxviii) (for

formulae V, X-XII, XX and XXIXB-XXIXD) and Groups (xiv)-(xx), (xxxiii)-(xxxviii) and (lxxxix)-(cxiv) for formulae XXVI-XXVIII) to the extent consistent therewith.

The compounds of formula I possess pharmacological activity in particular they are inhibitors of 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase and as a consequence inhibitors of cholesterol biosynthesis as demonstrated in the following three tests.

Test A: In Vitro Microsomal Assay of HMG-CoA Reductase Inhibition:

200 ul. aliquots (1.08-1.50 mg./ml.) of rat liver microsomal suspensions, freshly prepard from male Spargue-Dawley rats (150-225 g. body weight), in Buffer A with 10 mmol. dithiothreitol are incubated with 10 ul. test substance dissolved in dimethylacetamide and assayed for HMG-CoA reductase activity as described by Ackerman et al., J. Lipid Res. 18, 408-413 (1977). In the assay the microsomes are the source of the HMG-CoA reductase enzyme which catalyses the reduction of HMG-CoA to mevalonate. The assay employs a chloroform extraction to separate the product, [^{14}C]mevalonolactone, formed by the HMG-CoA reductase reaction from the substrate, [^{14}C]HMG-CoA. [^{3}H]mevalono-lactone is added as an internal reference. Inhibition of HMG-CoA reductase is calculated from the decrease in specific activity [^{14}C/^{3}H]mevalonate) of test groups compared to controls.

Test B: In Vitro Cell Culture Cholesterol Biosynthesis Screen:

The cell culture is prepared as follows: Stock monolayer cultures of the Fu5AH rat hepatoma cell line (originally obtained from G. Rothblat; see Rothblat, Lipids 9, 526-535 (1974) are routinely maintained in Eagle's Minimum Essential Medium (EMEM) supplemented with 10% fetal bovine serum (FBS) in 75 cm^2 tissue culture flasks. For these studies, when the cultures reach

confluence, they are removed by mild enzymatic treatment with 0.25% trypsin in Hanks' balanced salt solution (without calcium and magnesium). After centrifugation of the cell suspension and aspiration of the enzymatic solution, a cell pellet is resuspended in an appropriate volume of media for seeding into 60 mm. tissue culture dishes. The cultures are incubated at 37°C in an atmosphere of high humidity and 5% carbon dioxide. When the cultures are confluent (approximately 5 days), they are ready for use. The culture media is aspirated from the dishes and replaced with 3 ml of EMEM suplemented with 5 mg/ml of dilipidized serum protein (DLSP) prepared by the method of Rothblat et al., In Vitro 12, 554-557 (1976). Replacement of the FBS with DLSP has been shown to stimulate the incorporation of [^{14}C]acetate into sterol by removing the exogenous sterol supplied by the FBS, thereby requiring the cells to synthesized sterol. Enthanced 3-hydroxy-3-methylglutaryl Coenzyme A reductase (HMG-CoA reductase) activity is measurable in the cells in response to the lack of exogenous sterol. Following approximately 24 hours incubation at 37°C in the DLSP supplemented media, the assay is initiated by the addition of 3μCi of [^{14}C]acetate and the test substances solubilized in dimethylsulfoxide (DMSO) or distilled water. Solvent controls and compactin-treated controls are always prepared. Triplicate 60mm. tissue culture dishes are run for each group. After 3 hours incubation at 37°C, the cultures are examined microscopically using an inverted phase contrast microscope. Notations are made of any morphological changes which may have occurred in the cultures. The media is aspirated and the cell layer is gently washed twice with 0.9% sodium chloride solution (saline). The cell layer is then harvested in 3 ml. of 0.9% saline by gentle scraping with a rubber policeman and transferred to a clean glass tube with Teflon lined cap. The dishes are rinsed with 3 ml. of 0.9% saline and rescraped, and the cells are combined with the first harvest. The tubes are centrifuged at 1500 r.p.m. for 10 minutes

in an IEC PR-J centrifuge, and the supernatant is asperated.

The cells are then extracted as follows: One ml. of 100% ethanol is added to the cell pellet followed by sonication for 10 seconds with a "LO" setting of 50 on a Bronwell Biosonik IV. One hundred ul. are taken for protein determination. One ml. of 15% potassium hydroxide (KOH) is added, and the samples are thoroughly vortexed. Saponification is accomplished by heating the ethanol-KOH treated samples at 60°C for 60 minutes in a water bath. Following dilution of the samples with 2ml. of distilled water, they are extracted three times with 7 ml. of petroleum ether. The petroleum ether extracts are then washed three times with 2 ml. of distilled water and finally taken to dryness under a stream of nitrogen.

The obtained samples are then analyzed by thin layer chromatography (TLC) as follows: Residues from the petroleum ether extraction are taken up in a small volume of hexane and spotted on silica gel 60 TLC plates (E. Merck). Development of the plates is carried out in a 150 parts by volume hexane: 50 parts by volume diethyl ether: 5 parts by volume galcial acetic acid solvent system using a three phase development procedure. Visualization is accomplished in an iodine vapor chamber. The plates are divided into five sections such that each section contains the molecules having the following approximate Rf values: section 1- 0-0.4, section 2- 0.4-0.55, section 3- 0.55-0.7, section 4- 0.7-0.9 and section 5- 0.9-1.0. Section 2 contains the non-saponifiable sterols. The five sections of the TLC plates are scraped into scintillation vials. Blanks are also prepared from scrapings of chromatographed non-labelled standards. ACS® scintillation cocktail is added, and the radioactivity is determined in a liquid scintillation spectrometer. [^{14}C]hexadecane standards are used to determine counting efficiencies. The total protein content of the samples is determined employing the Bio-Rad Protein Assay System.

The results are reported as disintegrations per minute per mg protein (d.p.m./mg protein) for each of the five TLC sections. Mean d.p.m./mg protein ± standard error of the mean are compared for percentage change (%Δ) and statistical significance with solvent control means. TLC section 2 data is taken as a measure of HMG-CoA reductase activity inhibition.

Test C: In Vivo Cholesterol Biosynthesis Inhibition Tests: In vivo studies utilize male Wistar Royal Hart rats weighing 150±20 g which have been kept for 7-10 days on an altered light cycle (6:30 a.m. - 6:30 p.m. dark) housed two per cage and fed powdered Purina Rat Chow and water ad libitum. Three hours before the diurnal maximum of cholesterol synthesis at mid-dark, the rats are administered the test substances dissolved or as a suspension in 0.5% carboxymethylcellulose in a volume of 1 ml/100 g body weight. Controls receive vehicle alone. One hour after receiving the test substance, the rats are injected intraperitoneally with about 25 μCi/100 g body weight of sodium [1-^{14}C]acetate 1-3 mCi/mmol. Two hours after mid-dark, blood samples are obtained under sodium hexobarbitol anesthesia and the serum separated by centrifugation.

Serum samples are saponified and neutralized, and the 3β-hydroxy sterols are precipiated with digitonin basically as described by Sperry et al., J. Biol. Chem. 187, 97 (1950). The [^{14}C]digitonides are then counted by liquid scintillation spectrometry. After correcting for efficiencies, the results are calculated in nCi (nanocuries) of sterol formed per 100 ml of serum. Inhibition of sterol synthesis is calculated from the reduction in the nCi of sterols formed from test groups compared to controls.

The compounds are thus indicated for use as hypolipoproteinemic and anti-atherosclerotic agents.

An indicated suitable daily dosage for use in the treatment of hyperlipoproteinemia and athersclerosis is from about

1 to 2000 mg preferably 1.5 to 100 mg suitably administered in divided dosages of 0.25 to 1000 mg preferably 0.4 to 50 mg two to four times daily or in retard form.

They may be administered in free acid form or in the form of a physiologically-hydrolysable and -acceptable ester or a lactone thereof or in pharmaceutically acceptable salt form whereby the various forms have activities in the same range.

The invention therefore also concerns a method of treating hyperlipoproteinemia or atherosclerosis by administration of a compound of formula I in free acid form or in the form of a physiologically-hydrolysable and -acceptable ester or a lactone thereof or in pharmaceutically acceptable salt form as well as such compounds for use as pharmaceuticals e.g. as hypolipoproteinemic and anti-atherosclerotic agents.

The compounds may be administered alone, or in admixture with a pharmaceutically acceptable diluent or carrier, and, optionally other excipients, and administered orally in such forms as tablets, elixirs, capsules or suspensions or parenterally in such forms as injectable solutions or suspensions.

The preferred pharmaceutical compositions from the standpoint of ease of preparation and administration are solid compositions, particularly tablets and hard-filled or liquid-filled capsules.

Such compositions also form part of the invention.

The following examples, in which all temperatures are in °C illustrate the invention.

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

WATTANASIN
v.
Fujikawa et al.

Interference No. 102,648, 102,975
Examiner-in-Chief: M. Sofocleous

DECLARATION OF ROBERT G. ENGSTROM PURSUANT TO 37 CFR §1.672

I, Robert G. Engstrom, do hereby declare as follows:

(1) That I have been employed by Sandoz Pharmaceuticals Corporation since 1964 as a Research Scientist. Among my responsibilities has been supervising the testing of new HMG Co-A reductase inhibiting compounds synthesized by Sandoz chemists.

(2) That all activities referred to in this Declaration took place in the United States.

IN VIVO TESTING OF
WATTANASIN COMPOUNDS 64-933, 64-935 and 64-936/Na

1. On or before October 29, 1987, in my laboratory under my supervision, Rodney Slaughter began performing the below-indicated protocol on compounds 64-933, 64-935 and 64-936/Na:

In vivo studies utilized male Wistar Royal Hart rats weighing 150 ± 20 g. which have been kept for 7-10 days on an altered light cycle (6:30 A.M. - 6:30 P.M. dark) housed two per cage and fed powdered Purina Rat Chow and water ad libitum. Three hours before the diurnal maximum of cholesterol systhesis at mid-day the rats were administered the test substances dissolved or as a suspension in 0.5% carboxymethylcellulose in a volume of 1 ml./100 g. body weight. Controls received vehicle alone. One hour after receiving the test substance, the rats were injected intraperitoneally with about 25 μCi/100 g. body weight of sodium [1-^{14}C]acetate 1-3 mCi/mmol. Two hours after mid-dark, blood samples were obtained under sodium hexobarbitol anesthesia, and the serum was separated by centrifugation. The resulting serum samples were saponified and neutralized, and the 3β-hydroxy sterols were precipitated with digitonin basically as described by Sperry et al., J. Biol. Chem. 187,97(1950). The [^{14}C]digitonides were counted by liquid scintillation spectrometry. The assay is based on the conversion of ^{14}C-acetate to ^{14}C-cholesterol in vivo.

2. The counts in DPM of digitonin precipitable sterol (β-hydroxy sterol, mostly cholesterol in the rat) were entered by Rodney Slaughter into my computer program, which converted them to nCi of sterol found per 100 ml. of serum at 4 hours after the injection of the ^{14}C-acetate.

3. I have reviewed Exhibit K-1 hereto, which comprises true copies of pages 133, 134, and 135, 136, 137 and 138 of R. Slaughter's Laboratory Notebook #917. I witnessed Rodney Slaughter's signature on each of these pages, and each page bears my true signature as a witness.

4. Notebook pages 133-135 contain true copies of a computer printout for the protocol and results in nCi/dl of Study #H318, which was commenced on October 22, 1987. I initialed the first page of this computer printout on or before October 22, 1987. This computer printout on page 135 indicates that an in vivo assay of compound 64-936 was started on October 22, 1987.

5. Notebook pages 136-138 contain true copies of a computer printout for the protocol and results in nCi/dl of Study #H319, which was commenced on October 29, 1987. I initialed the first page of this computer printout on page 136 on or prior to October 29, 1987. This computer printout on page 137-138 indicates that an in vivo assay of compound 64-933 and 64-935 was started on October 29, 1987.

6. Both studies were completed on or prior to December 9, 1987, the date indicated at the bottom of pages 135 and 138.

7. It was my responsibility to enter the nCi/dl data into a separate computer program which calculates the ED_{50} values of a compound tested in vivo from the reduction in the nCi of sterols formed from test groups compared to controls for each assay, and forms a database of the ED_{50} values. On or before December 9, 1987, I entered the data for compounds 64-933, 64-935 and 64-936/Na.

8. The 1st page of Exhibit K-1 comprises a true copy of part of the ED_{50} database. This page indicates that the ED_{50} for compounds 64-933, 64-935 and 64-936/Na was in the system as of December 9, 1987. Therefore, the information was available to other Sandoz employees having access to the computer database as of December 9, 1987.

The ED50 for these compounds are:

COMPOUND	ED_{50} (mg/kg)
64-933	0.49
64-935	>1.0
64-936	>1.0

. . .

The undersigned declares further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

I hereby subscribe my name to the foregoing DECLARATION this 13 day of November 1992.

Robert G. Engstrom

Robert G. Engstrom

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

WATTANASIN
v. Interference Nos. 102,648, 102,975
FUJIKAWA et al. Examiner-in-Chief: M. Sofocleous

DECLARATION OF RODNEY SLAUGHTER PURSUANT TO 37 CFR §1.672

I, Rodney Slaughter, do hereby declare as follows:

(1) That I have been employed by Sandoz Pharmaceuticals Corporation since 1982, and during the time periods referred to herein, I worked in the Department of Lipid Metabolism.

(2) That it has been my responsibility to carry out an in vivo testing program of various HMG-CoA reductase inhibitor compounds, including Wattanasin compounds 64-933, 64-935 and 64-936.

(3) That all of the below-indicated activities took place in the United States.

IN VIVO TESTING OF
WATTANASIN COMPOUNDS 64-933, 64-935 and 64-936

1. On or before October 29, 1987, I carried out the below-indicated protocol on compounds 64-933, 64-935 and 64-936:

In vivo studies utilized male Wistar Royal Hart rats weighing 150 ± 20 g. which have been kept for 7-10 days on an altered light cycle (6:30 A.M. - 6:30 P.M. dark) housed two per cage and fed powdered Purina Rat Chow and water ad libitum. Three hours before the diurnal maximum of cholesterol systhesis at mid-day the rats were administered the test substances dissolved or as a suspension in 0.5% carboxymethylcellulose in a volume of 1 ml./100 g. body weight. Controls received vehicle alone. One hour after receiving the test substance, the rats were injected intraperitoneally with about 25 μCi/100 g. body weight of sodium [1-^{14}C]acetate 1-3 mCi/mmol. Two hours after mid-dark, blood samples were obtained under sodium hexobarbitol anesthesia, and the serum was separated by centrifugation. The resulting serum samples were saponified and neutralized, and the 3β-hydroxy sterols were precipitated with digitonin basically as described by Sperry et al., J. Biol. Chem. 187,97(1950). The [^{14}C]digitonides were counted by liquid scintillation spectrometry. The assay is based on the conversion of ^{14}C-acetate to ^{14}C-cholesterol in vivo.

2. I entered the counts in DPM of digitonin precipitable sterol (β-hydroxy sterol, mostly cholesterol in the rat) into a computer program, which converted them to nCi of sterol found per 100 ml. of serum at 4 hours after the injection of the ^{14}C-acetate.

3. I have reviewed Exhibit K-1 hereto, which comprises true copies of pages 133, 134, 135, 136, 137 and 138 of my Laboratory Notebook #917.

4. Notebook pages 133-135 contain true copies of a computer printout for the protocol and results in nCi/dl of Study #H318, which I started on October 22, 1987. These pages contain the date of 10/22/87 at the top in my handwriting.

5. Notebook pages 136-138 contain true copies of a computer printout for the protocol and results in nCi/dl of Study #H319, which I started on October 29, 1987. These pages contain the date of 10/29/87 at the top in my handwriting.

6. Both studies were completed on or prior to December 9, 1987, the date indicated at the bottom of the computer printouts on pages 135 and 138.

7. It was my practice to paste the computer printouts into my notebook and to sign the notebook page when I did this.

The undersigned declares further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

I hereby subscribe my name to the foregoing DECLARATION this 13 day of November 1992.

Rodney Slaughter

Title- Cholesterol Synthesis Inhibition Screen

Date- 10/22/87 Proj. # 3137

From- 134

185

334

CHOLESTEROL BIOSYNTHESIS IN VIVO

LIPID METABOLISM DEPARTMENT
HMGR SCREENING UNIT
Sandoz Research Institute
To: Dr. D. Weinstein, Departmenthead
Mr. R. Slaughter, Responsible Technician
From: Mr. R. Engstrom, Responsible Investigator
CC: D.N., M.L.R., ARC

STUDY # H518
STUDY ON 10/22/87
SK.REF. 917-33
APPROVAL
DATE 10/21/87
GEN. ARC88S-006

Title: In vivo single dose assay to test for inhibition of biosynthesis by compounds: 63-748, 64-844, 64-988

Purpose: Determine the invivo effects of test compounds in rats on cholesterol biosynthesis.

Experimental design: IN VIVO CHOLESTEROL BIOSYNTHESIS INHIBITION DT0065 Invivo single dose assay of inhibition of Reference/method: 740/001. Stock solutions and dilutions prepared in 0.5% CMC, administered p.o. at 1ml/100gm weight. Rats bled via carotid incision using hexobarbital anesthesia. Animal use will be in compliance with ARC regulations. Duration = 1 hr. No/group = 6. No of groups = 14. WCR rats.

Rats	COMPOUND	REGNO	DOSE mg/kg	STOCK mg/20ml	WORKING SOLUTION ml stock q.s. to 15ml
1-6	Control	------	------	------	------
7-12	63-748	26688	1	2	UNDILUTED
13-18	"	"	0.3	-	4.5
19-24	"	"	0.1	-	1.5
25-30	64-844	30280	0.3	2	4.5
31-36	"	"	0.1	-	1.5
37-42	"	"	0.03	-	0.45
43-48	64-988	30488	1	2	UNDILUTED
49-54	"	"	0.3	-	4.5
55-60	"	"	0.1	-	1.5
61-66	62-320	30304	0.3	2	4.5
67-72	"	"	0.1	-	1.5
73-78	"	"	0.03	-	0.45
79-84	Control	------	------	------	------

WATTANASIN EXHIBIT
K-1
Wattanasin v. Fujikawa et al.
Interference No. 102,648
Interference No. 102,975

Performed by- [signature]

Witness- [signature]

Cont'd to- 185

134

Title- Cholesterol Synthesis Inhibition Screen

Date 10/22/87 Pg 1 of 2

Cont'd From 133

335

IN VIVO CHOLESTEROL SYNTHESIS INHIBITION SCREEN #318

RAT COMPOUND REG# DOSE mCi/rat STATISTICS

mg/kg

BLANK

TAC-STANDARD 20178 x EFFIC= .89

1	CONTROL			492			
2	CONTROL			677	MEAN =		537.7
3	CONTROL			580	STD =		129.6
4	CONTROL			455	SE =		37.1
5	CONTROL			480			
6	CONTROL			365			
79	CONTROL			462			
80	CONTROL			316			
81	CONTROL			559			
82	CONTROL			650			
83	CONTROL			610			
84	CONTROL			745			
8	63-748	25688	1.00	170	MEAN =		155.9
9	63-748	25683	1.00	278	STD =		72.1
10	63-748	25588	1.00	113	SE =		32.7
11	63-748	25638	1.00	113	t =		7.7
12	63-748	25588	1.00	106	P		<.01
7	63-748	25568	1.00	528*	%CHG =		-71
13	63-748	25688	.300	388	MEAN =		319.8
14	63-748	25588	.300	355	STD =		66.8
15	63-748	25585	.300	391	SE =		39.5
17	63-748	25558	.300	199	t =		4.0
18	63-748	25668	.300	253	P		<.01
15	63-748	25588	.300	794*	%CHG =		-40.8
19	63-748	25568	.100	348	MEAN =		456.7
20	63-748	25686	.100	725	STD =		213.5
21	63-748	25688	.100	310	SE =		87.2
22	63-748	25585	.100	650	t =		0.8
23	63-748	25688	.100	536	P		N.S.
24	63-748	25686	.100	178	%CHG =		-14.7
25	64-844	30280	.300	256	MEAN =		185.8
26	64-844	30280	.300	170	STD =		57.3
27	64-844	30250	.300	155	SE =		23.4
28	64-844	30280	.200	126	t =		6.5
29	64-844	30280	.300	174	P		<.01
30	64-844	30280	.200	101	%CHG =		-65.2
31	64-844	30280	.100	306	MEAN =		219.8
32	64-844	30280	.100	273	STD =		69.9
33	64-844	30280	.100	195	SE =		39.9
35	64-844	30280	.100	157	t =		6.7
36	64-844	30280	.100	155	P		<.01
34	64-844	30280	.100	696*	%CHG =		-59.1

Performed by- Todd A. Waughman

Witness- R Bethune

Cont'd to- 135

Date 10/22/87 Proj# 3,4

Title Cholesterol Synthesis Inhibition Screen

135

Cont'd From- 134

336

INVIVO CHOLESTEROL SYNTHESIS INHIBITION SCREEN HS18

RAT	COMPOUND	REGNO	DOSE mg/kg	nCi/dl	STATISTICS	
37	64-844	30280	.030	354	MEAN =	419.7
38	64-844	30280	.030	518	STD =	138.6
39	64-844	30280	.030	639	SE =	56.6
40	64-844	30280	.030	245	t =	1.7
41	64-844	30280	.030	358	p	N.S.
42	64-844	30280	.030	402	%CHG =	-21.9
43	64-936	30488	1.00	580	MEAN =	489.4
44	64-936	30488	1.00	642	STD =	132.9
45	64-936	30488	1.00	290	SE =	54.2
46	64-936	30488	1.00	388	t =	0.7
47	64-936	30488	1.00	532	p	N.S.
48	64-936	30488	1.00	513	%CHG =	-9.0
49	64-936	30488	.300	167	MEAN =	325.7
50	64-936	30488	.300	232	STD =	165.0
51	64-936	30488	.300	566	SE =	67.4
52	64-936	30488	.300	378	t =	2.7
53	64-936	30488	.300	323	p	<.02
54	64-936	30488	.300	473	%CHG =	-38.2
55	64-936	30488	.100	485	MEAN =	418.5
56	64-936	30488	.100	181	STD =	166.8
57	64-936	30488	.100	369	SE =	68.2
58	64-936	30488	.100	596	t =	1.8
59	64-936	30488	.100	367	p	N.S.
60	64-936	30488	.100	439	%CHG =	-23.5
61	62-320	30559	.300	72	MEAN =	67.5
62	62-320	30559	.300	69	STD =	13.1
63	62-320	30559	.300	72	SE =	5.4
64	62-320	30559	.300	53	t =	12.5
65	62-320	30559	.300	64	p	<.01
66	62-320	30559	.300	55	%CHG =	-87.5
67	62-320	30559	.100	135	MEAN =	165.3
68	62-320	30559	.100	238	STD =	51.1
70	62-320	30559	.100	198	SE =	32.8
71	62-320	30559	.100	109	t =	8.5
69	62-320	30559	.100	149	p	<.01
72	62-320	30559	.100	136	%CHG =	-69.3
73	62-320	30559	.030	323	MEAN =	351.2
74	62-320	30559	.030	360	STD =	173.5
75	62-320	30559	.030	77	SE =	70.8
76	62-320	30559	.030	576	t =	3.3
77	62-320	30559	.030	463	p	<.05
78	62-320	30559	.030	277	%CHG =	-34.7

* = rejected by "Q" test
= LACK OF SAMPLE

Computed 12-09-87

Performed by- [signature]

Witness- [signature]

Cont'd to-

136 Title- Cholesterol Synthesis Inhibition Screen

Date 10/29/87 Proj: 3,9

Cont'd From-

337

CHOLESTEROL BIOSYNTHESIS INHIBITION SCREEN

LIPID METABOLISM DEPARTMENT
MNOR SCREENING UNIT
Sandoz Research Institute
To: Dr. D. Weinstein, Departmenthead
Mr. R. Slauchter, Responsible Technician
From: Mr. R. Engstrom, Responsible Investigator
CC: D.N., M.L.B., ARC

STUDY # H319
STUDY ON 10/29/87
BK.REF. 917-136
APPROVAL
DATE 10/29/87
GEN. ARC#86-004

Title: In vivo single dose assay to test for inhibition of biosynthesis by compounds: 84-296, 84-938, 83-935

Purpose: Determine the invivo effects of test compounds in rats on cholesterol biosynthesis.

Experimental design: IN VIVO CHOLESTEROL BIOSYNTHESIS INHIBITION STUDY Invivo single dose assay of inhibition of Reference method: 740/001. Stock solutions and dilutions prepared in 0.5% CMC, administered p.o. at 1ml/100gm weight. Rats bled via carotid incision using hexobarbital anesthesia. Animal use will be in compliance with ARC regulations. Duration = 1 hr. No/group = 6. No of groups = 14. MCR rats.

RATS	COMPOUND	REGNO	DOSE mg/kg	STOCK mg/20ml	WORKING SOLUTION ml stock q.s. to 15ml
1-6	Control	------	------	------	------
7-12	84-296	29377	1	2	UNDILUTED
13-18	"	"	0.3	-	4.5
19-24	"	"	0.1	-	1.5
25-30	84-938	30447	1	2	UNDILUTED
31-36	"	"	0.3	-	4.5
37-42	"	"	0.1	-	1.5
43-48	84-935	20481	1	2	UNDILUTED
49-54	"	"	0.3	-	4.5
55-60	"	"	0.1	-	1.5
61-66	83-920	30555	0.3	2	4.5
67-72	"	"	0.1	-	1.5
73-78	"	"	0.03	-	0.45
79-84	Control	------	------	------	------

Performed by-

Witness-

Cont'd to- 337

Date Proj.

Title-

137

Cont'd.From-

338

IN VIVO CHOLESTEROL SYNTHESIS INHIBITION SCREEN RESULTS

RAT	COMPOUND	REGNO	DOSE mg/kg		nCi/dl	STATISTICS	
	BLANK				7		
	14C-STANDARD				20176 x EFFIC=		SE
1	CONTROL				983		
2	CONTROL				515	MEAN =	671.8
3	CONTROL				648	STD =	211.0
4	CONTROL				578	SE =	80.9
5	CONTROL				934		
6	CONTROL				354		
78	CONTROL				756		
80	CONTROL				847		
81	CONTROL				814		
82	CONTROL				545		
83	CONTROL				872		
84	CONTROL				714		
7	84-298	28277	1.00		203	MEAN =	151.7
8	84-298	28277	1.00		381	STD =	118.8
9	84-298	28277	1.00		82	SE =	48.4
10	84-298	28277	1.00		78	t =	6.8
11	84-298	28277	1.00		71	p	<.01
12	84-298	28277	1.00		115	%CHG =	-77
13	84-298	28277	.300		311	MEAN =	235.1
14	84-298	28277	.300		264	STD =	81.4
15	84-298	28277	.300		257	SE =	33.2
16	84-298	28277	.300		307	t =	8.3
17	84-298	28277	.300		114	p	<.01
18	84-298	28277	.300		157	%CHG =	-65.0
19	84-298	28277	.100		581	MEAN =	386.7
20	84-298	28277	.100		387	STD =	81.5
21	84-298	28277	.100		248	SE =	33.3
22	84-298	28277	.100		392	t =	4.1
23	84-298	28277	.100		499	p	<.01
24	84-298	28277	.100		425	%CHG =	-42.1
25	84-933	30447	1.00		836	MEAN =	838.1
26	84-933	30447	1.00		275	STD =	253.4
27	84-933	30447	1.00		136	SE =	103.5
28	84-933	30447	1.00		584	t =	2.0
29	84-933	30447	1.00		288	p	N.S.
30	84-933	30447	1.00		447	%CHG =	-38.3
31	84-933	30447	.300		830	MEAN =	557.4
32	84-933	30447	.300		646	STD =	100.5
33	84-933	30447	.300		525	SE =	41.0
34	84-933	30447	.300		598	t =	1.8
35	84-933	30447	.300		356	p	N.S.
36	84-933	30447	.300		815	%CHG =	-17.0

Performed by-

138

Title-

Date 12/24/87 Proj.

Cont'd From 137

INVIVO CHOLESTEROL SYNTHESIS INHIBITION SCREEN NO19

RAT	COMPOUND	REGNO	DOSE mg/kg	nCi/dl	STATISTICS	
37	64-933	30447	.100	555	MEAN =	547.0
38	64-933	30447	.100	735	STD =	147.2
39	64-933	30447	.100	370	SE =	60.1
40	64-933	30447	.100	378	t =	1.5
41	64-933	30447	.100	581	P	N.S.
42	64-933	30447	.100	652	%CHG =	-16.6
43	64-935	30441	1.00	182	MEAN =	230.0
44	64-935	30441	1.00	307	STD =	78.2
45	64-935	30441	1.00	198	SE =	31.9
46	64-935	30441	1.00	321	t =	6.4
47	64-935	30441	1.00	124	P	<.01
48	64-935	30441	1.00	281	%CHG =	-65.8
49	64-935	30441	.300	776	MEAN =	673.2
50	64-935	30441	.300	282	STD =	179.5
51	64-935	30441	.300	580	SE =	73.3
52	64-935	30441	.300	413	t =	2.1
53	64-935	30441	.300	344	P	N.S.
54	64-935	30441	.300	438	%CHG =	-29.7
55	64-935	30441	.100	411	MEAN =	428.2
56	64-935	30441	.100	320	STD =	119.1
57	64-935	30441	.100	396	SE =	48.6
58	64-935	30441	.100	425	t =	8.1
59	64-935	30441	.100	621	P	<.02
60	64-935	30441	.100	495	%CHG =	-38.3
61	62-320	30559	.300	90	MEAN =	185.6
62	62-320	30559	.300	107	STD =	107.1
63	62-320	30559	.300	222	SE =	43.7
64	62-320	30559	.300	60	t =	8.8
65	62-320	30559	.300	217	P	<.01
66	62-320	30559	.300	327	%CHG =	-75.5
67	62-320	30559	.100	262	MEAN =	331.7
68	62-320	30559	.100	432	STD =	165.7
70	62-320	30559	.100	559	SE =	74.1
71	62-320	30559	.100	198	t =	3.5
69	62-320	30559	.100	228	P	<.01
72	62-320	30559	.100	604	%CHG =	-50.9
73	62-320	30559	.030	421	MEAN =	448.1
74	62-320	30559	.030	472	STD =	54.1
75	62-320	30559	.030	571	SE =	38.4
76	62-320	30559	.030	674	t =	3.1
77	62-320	30559	.030	517	P	<.01
78	62-320	30559	.030	815	%CHG =	-38.8

Computed 12-09-87

Performed by-

Witness- R Stephens

Cont'd to-

340

64568	29551	280-85	>	1	09-JUN-87	917-085
64569	29552	280-85	=	.16	15-JUN-87	917-081
64602	29743	101-85	>	.3	05-MAY-87	917-050
64602	29743	101-85	>	.3	05-MAY-87	917-050
64604	29744	101-85	>	.3	05-MAY-87	917-051
64604	29744	101-85	>	.3	05-MAY-87	917-051
64604	29745	101-85	=	.48	14-JUL-87	917-086
64608	29756	298-85	>	7.5	15-MAY-87	917-056
64638	29835	570-83		.34	09-DEC-87	917-140
64639	29836	570-83	>	1	09-JUN-87	917-066
64640	29839	367-86	>	1	09-JUN-87	917-068
64641	29840	367-86	>	1	09-JUN-87	917-068
64642	29841	367-86	>	1	09-JUN-87	917-089
64673	29904	280-85	=	2.6	18-SEP-87	917-111
64686	29927	387-85	>	10	18-SEP-87	917-113
64691	29942	366-86		.58	16-DEC-87	917-141
64722	30004	280-85	=	.2	23-OCT-87	917-126
64723	30627	100-85	=	.16	19-FEB-88	917-159
64723	30877	100-85	=	.09	19-FEB-88	917-159

SAINUM	REGNO	PATENT	R	ED50	EDATE	REF
64723	30766	100-85	=	.22	19-FEB-88	917-159
64723	30009	100-85	=	.36	18-SEP-87	917-107
64744	30059	295-84	>	.1	14-JUL-87	917-090
64745	30765	295-84	=	.016	19-FEB-88	917-154
64745	30060	295-84	=	.016	20-OCT-87	917-127
64747	30067	298-84	=	.11	01-JUL-87	917-087
64748	30068	298-84	=	.04	19-FEB-88	917-155
64792	30146	280-85	=	.74	13-OCT-87	917-123
64816	30199	295-84	=	.1	12-OCT-87	917-119
64844	30280	384-85	=	.07	09-DEC-87	917-135
64844	30769	384-85	=	.08	19-FEB-88	917-167
64896	30378	366-87	>	.3	06-OCT-87	917-119
64897	30379	366-87	>	.3	06-OCT-87	917-120
64906	30393	280-85	=	.045	05-JAN-88	917-150
64906	30772	280-85	=	.1	15-JAN-88	917-155
64933	30441	299-84	>	1	09-DEC-87	917-138
64935	30447	299-84	=	.49	09-DEC-87	917-138
64936	30488	299-84	>	1	09-DEC-87	917-135
64999	30623	298-84	=	.1	19-FEB-88	917-168
65002	30629	101-85	=	.76	05-JAN-88	917-144
65003	30630	101-85	=	.09	19-FEB-88	917-159

SAINUM	REGNO	PATENT	R	ED50	EDATE	REF
65003	30902	101-85	=	.06	19-FEB-88	917-170
86665	25887	102-82	>	10	06-MAY-87	917-056
87469	26362	101-82	>	10	06-MAY-87	917-056
89826	29587	101-82	>	10	05-MAY-87	917-057
317223	24022		>	16	20-MAR-84	312-183
380349	29591	102-82	>	10	18-AUG-87	917-098
380586	29588	102-82	>	10	18-AUG-87	917-098
380820	29589	102-82	>	10	18-AUG-87	917-098

140 records selected.

SQL>

Case No. 600-7101/CONT/INT.(5)
Patent -

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

WATTANASIN
v.
FUJIKAWA et al.

Interference Nos. 102,648, 102,975
Examiner-in-Chief: M. Sofocleous

SUPPLEMENTAL DECLARATION OF ROBERT G.ENGSTROM PURSUANT TO 37 CFR §1.672

I, Robert G. Engstrom, do hereby declare as follows:

All of the below-indicated activities took place in the United States.

Exhibit Q comprises a true copy of a Biological Activity Data Report dated May 24, 1988 which I sent to the Patent Department concerning the compounds of PD 299/84, together with a computer printout of the Sandoz database dated May 23, 1988. The printout contains IC_{50} and some ED_{50} values for compounds of Patent Disclosure 295/84 and compounds of the subject Patent Disclosure 299/84.

(I note that I became aware of a computer entry error comprising the inadvertent "switching" of the ED_{50} data for compounds 64-933 and 64-935. The corrections on the printout are in my handwriting and would have been made on or about May 23, 1988.)

The undersigned declares further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful

false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

I hereby subscribe my name to the foregoing Declaration this 19 day of February, 1993.

Robert Engstrom

Robert Engstrom

Q

BIOLOGICAL ACTIVITY DATA REPORT (FOR PATENT DEPT.)

INVENTOR: S. Wattanasin DISCL. NO.: 299-84 4/18

ATTORNEY: M. Kassenoff DATE: May 24, 1988

1. ACTIVITY TO BE DISCLOSED:
Inhibition of cholesterol biosynthesis, antihypercholesteremic, antiatherosclerotic

2. IF ANY COMPOUNDS COVERED BY ABOVE-NOTED DISCLOSURE HAVE MORE THAI ONE ACTIVITY, INDICATE TOTAL NUMBER OF ACTIVITIES AND PREPARE A SEPARATE B.A.D.R. SHEET FOR EACH. TOTAL NO. OF ACTIVITIES: 1

3.a) TEST METHODS USED TO ESTABLISH ACTIVITY:
HMG-CoA reductase inhibition in rat liver microsomes (DT 64)
Cholesterol synthesis inhibition invivo in rats (DT 65)

b) DOSAGE RANGES BASED ON ACTUAL DOSES USED IN TEST PROCEDURE:
0.050 - 1.5 mg/kg

4. COMPOUNDS TESTED WITHIN DISCLOSURE WHICH EXHIBIT WEAK OR GREATER ACTIVITY:
64-935, 64-933

5. DOSAGE SCHEDULE - Broad Ranges:

a)	Large / small animals:	.10	to	1.0	mg/kg.
b)	Large animals:	20	to	200	mg/day.

6. MOST PREFERED COMPOUND FOR ACTIVITY DESIGNATED:

64-935

7. OTHER PREFERRED OR POTENTIALLY PREFERRED COMPOUNDS FOR DESIGNATEI ACTIVITY:
64-936, 63-366, 64-933, 64-934

8. ED50 FOR THE PREFERRED COMPOUND IN EACH OF THE TEST METHODS INDICATED IN 3a) FOR THE DESIGNATED ACTIVITY:

COMPOUND	IC50 uM DT64	ED50 mg.kg DT65	Potency x Mevinolin*
Compactin	1.01	3.5	0.11
Mevinolin	0.14	0.41	1 (standard)
64-935	0.41	0.49	0.3
64-936	0.53	>1.0	
64-933	2.37	2.40	

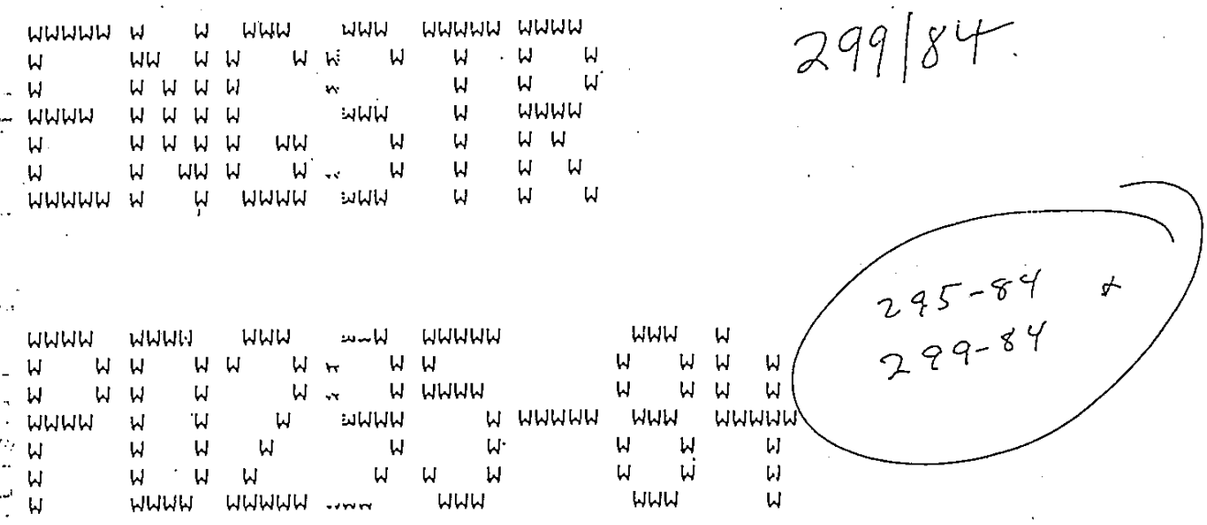
* Clinical dose of mevinolin (Lovasatin) = 20-80 mg/day

User: STR -at pr0

<USER02>ENGSTR>IC5 TA>PD295-84

419

299/84



295-84 &
299-84

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File last modified: 88-05-23.08:25:36.Mon

Spooled: 88-05-23 08:50:36.Mon [Spooler rev 19.4.6]
Started: 88-05-23 08:50:40.Mon on: PR0 by: PR0

IC50 TABLE RAT MICROSOMAL ASSAY (CSI-DT64)

THIS FILE IS A CALCULATED ESTIMATE OF THE IC50 (CONCENTRATION WHICH REDUCES THE CONVERSION OF HMG-CoA TO MEVALONATE BY 50%) USING ALL THE STUDIES ON THE RELEVANT COMPOUNDS UP TO THE SORT DATE.

LAST UPDATE: 02-04-88 SORT BY: DISCLNO

COMPOUND	REGNO	DISCL	IC50 uM	DATE	REF	COMMENTS
SAH-062977	24162	295-84	25.0000	02-07-84	1014-248	
SAH-062978	24163	295-84	0.0180	02-07-84	1014-249	
SAH-063033	24315	295-84	0.0450	04-18-84	1014-257	SAPONIFIED
SAH-063033	24315	295-84	0.5250	02-29-84	1014-257	
SAH-063034	24316	295-84	0.3630	02-22-84	1014-258	
SAH-063035	24317	295-84	0.0400	02-22-84	1014-259	
SAH-063074	24446	295-84	0.4000	05-23-84	1014-277	
SAH-063074	24446	295-84	0.6900	03-26-84	1014-277	
SAH-063075	24448	295-84	0.5300	04-18-84	1014-278	SAPONIFIED
SAH-063075	24448	295-84	0.9040	03-26-84	1014-278	
SAH-063076	24449	295-84	0.5800	06-12-84	1014-279	
SAH-063076	24449	295-84	0.6400	05-23-84	1014-279	
SAH-063076	24449	295-84	0.9000	03-26-84	1014-279	
SAH-063083	24511	295-84	1.9100	03-28-84	1014-281	
SAH-063083	24511	295-84	2.3200	03-28-84	1014-281	
SAH-063084	24512	295-84	3.1600	06-12-84	1014-282	
SAH-063084	24512	295-84	6.3200	03-28-84	1014-282	
SAH-063144	24750	295-84	1.1600	05-10-84	1014-294	SAPONIFIED
SAH-063144	24750	295-84	2.0200	05-10-84	1014-294	
SAH-063145	24755	295-84	>10.0000	05-07-84	1014-295	SAPONIFIED
SAH-063145	24755	295-84	>10.0000	05-10-84	1014-295	
SAH-063146	24756	295-84	>10.0000	05-07-84	1014-296	
SAH-063158	24809	295-84	0.1000	06-04-84	1069-002	SAPONIFIED
SAH-063158	24809	295-84	0.3430	06-04-84	1069-002	
SAH-063159	24810	295-84	0.2250	06-12-84	1069-003	
SAH-063159	24810	295-84	0.2630	06-04-84	1069-003	
SAH-063160	24811	295-84	0.1110	06-04-84	1069-004	SAPONIFIED
SAH-063160	24811	295-84	1.5600	06-04-84	1069-004	
SAH-063161	24821	295-84	0.0020	06-04-84	1069-005	
SAH-063161	24821	295-84	0.0020	06-12-84	1069-005	
SAH-063162	24822	295-84	0.0030	06-04-84	1069-006	
SAH-063162	24822	295-84	0.0035	06-12-84	1069-006	
SAH-063174	24865	295-84	0.0140	06-06-84	1069-013	SAPONIFIED
SAH-063174	24865	295-84	0.0190	06-06-84	1069-013	
SAH-063175	24866	295-84	0.0260	06-06-84	1069-014	
SAH-063229	25075	295-84	>10.0000	08-04-84	1069-036	
SAH-063230	25078	295-84	0.0042	08-01-84	1069-037	
SAH-063231	25079	295-84	0.0058	08-04-84	1069-038	
SAH-063269	25205	295-84	0.0030	09-10-84	1069-053	SAPONIFIED
SAH-063269	25205	295-84	0.0440	09-12-84	1069-053	
SAH-063270	25206	295-84	0.0080	09-05-84	1069-054	SAPONIFIED
SAH-063271	25208	295-84	0.0320	09-10-84	1069-055	
SAH-063271	25208	295-84	0.1450	09-12-84	1069-055	

SAH-064484	F	29413	95-84	0.0320	11-24-86	1149-227
SAH-064744	E	30059	95-84	0.0320	05-01-87	1149-293
SAH-064745	S	30060	95-84	0.0030	05-01-87	1149-294
SAH-064745	S	30060	95-84	0.0030	07-07-87	1149-297
SAH-064815	E	30198	95-84	0.0220	07-07-87	1238-001
SAH-064816	S	30199	95-84	0.0450	07-07-87	1238-002
SAH-063162	S	30203	95-84	0.0080	07-07-87	1238-003
SAH-064745		30765	95-84	0.0020	01-12-88	1238-030
SAH-063366		25496	99-84	1.5800	12-13-84	1069-113
SAH-063549		26082	99-84	7.3100	06-13-84	1069-197
SAH-063548		26080	99-84	3.7750	06-13-84	1069-198
SAH-064933	E	30441	99-84	2.3700	10-08-87	1238-013
SAH-064934	S	30442	99-84	2.6100	10-08-87	1238-014
SAH-064935	E	30447	99-84	0.4130	10-08-87	1238-015
SAH-064936	S	30448	99-84	0.5300	10-13-87	1238-016

ED50 TABLE RAT INVIVO ACETATE INCORPORATION (CSIV-DT65)

THIS FILE IS A CALCULATED ESTIMATE OF THE ED50 (DOSE WHICH REDUCES THE INCORPORATION OF 14C-ACETATE INTO CHOLESTEROL BY 50%) USING ALL THE STUDIES ON THE RELEVANT COMPOUNDS UP TO THE SORT DATE.

LAST UPDATE: 1-06-88 SORT BY: REGNO

COMPOUND	REGNO	DISCL	ED50 mg/kg	DATE mm-dd-yy	REF bk-pg	COMMENTS
SAH-064745	30060	95-84 =	0.016	10-20-87	917-127	N=9
SAH-064745	30765	95-84 =	0.016	02-19-88	917-154	N=3 BS BATCH
SAH-064745	ALL	95-84 =	0.016	02-19-88	917-154	N=12 2BATCHES
SAH-063162	25500	95-84 =	0.019	09-18-87	917-101	N=10
SAH-063162	ALL	95-84 =	0.040	09-18-87		N=19 3BATCHES
SAH-063162	25085	95-84 =	0.079	10-11-84	812-266	N=8
SAH-064119	27563	95-84 =	0.08	05-16-86	869-228	N=6
SAH-064744	30059	95-84 >	0.10	07-14-87	917-090	N=3 -21% @.10
SAH-064816	30199	95-84 =	0.10	10-12-87	917-119	N=6
SAH-064483	29412	95-84 =	0.13	02-06-87	917-024	N=3
SAH-064063	27424	95-84 =	0.19	04-17-86	869-211	N=3
SAH-064309	28718	95-84 =	0.19	11-03-86	869-283	N=3
SAH-063231	25079	95-84 >	0.25	08-30-84	812-250	
SAH-064393	29163	95-84 =	0.25	02-25-87	917-031	N=6
SAH-063161	24821	95-84 >	0.250	11-29-84	812-293	-12@0.25
SAH-063989	27237	95-84 =	0.28	04-04-86	869-195	N=6
SAH-063425	25687	95-84 >	0.3	03-20-85	869-046	N=3
SAH-064305	28701	95-84 >	0.3	11-03-86	869-280	N=3 -34% @.3
SAH-064480	29404	95-84 >	0.3	02-06-87	917-023	N=3 +3% @.3
SAH-063270	ALL	95-84 =	0.308	02-07-85		N=11 2BATCHES
SAH-063270	25206	95-84 =	0.33	10-11-84	812-267	
SAH-063270	25501	95-84 =	0.362	01-21-85	869-018	
SAH-064307	28705	95-84 =	0.47	02-06-87	917-020	N=6
SAH-063159	24810	95-84 >	0.5	06-19-84	812-219	

422

SAH-063162	24822	E95-84	<	0.5	06-19-84	812-219	N=1 -87@0.5
SAH-063175	24866	E95-84	<	0.5	06-19-84	812-220	
SAH-063230	25078	E95-84	>	0.500	11-29-84	812-294	
SAH-064391	29161	E95-84	=	0.51	10-30-86	917-011	N=3
SAH-063035	24317	E95-84	>	0.6	05-07-84	812-201	
SAH-063145	24755	E95-84	>	0.6	05-18-84	812-208	
SAH-063146	24756	E95-84	>	0.6	05-18-84	812-208	
SAH-063174	24865	E95-84	=	0.706	06-19-84	812-220	
SAH-064481	29406	E95-84	>	1.0	02-06-87	917-024	N=3 -28% @1.0
SAH-064482	29411	E95-84	>	1.0	03-18-87	917-041	N=3 -41% @1.0
SAH-064064	27433	E95-84	=	1.05	07-17-86	869-263	N=6
SAH-064204	27793	E95-84	=	1.21	10-02-86	869-298	N=6
SAH-064141	27630	E95-84	>	1.25	02-24-87	917-029	N=6 -24% @1.25
SAH-064308	28717	E95-84	>	1.5	11-03-86	869-283	N=3 -16% @1.5
SAH-064193	27760	E95-84	>	2.4	07-24-86	869-269	N=3 -24% @2.4
SAH-063076	24449	E95-84	<	2.5	05-14-84	812-204	
SAH-063084	24512	E95-84	>	2.5	05-07-84	812-201	
SAH-064933	30441	E99-84	=	~~0.49~~ 1	12-09-87	917-138	N=3 -3% @1.0
SAH-064935	30447	E99-84	≈	~~1.0~~ .99	12-09-87	917-138	N=3

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

#116

WATTANASIN

v. Interference No. 102,648

FUJIKAWA et al. Examiner-in-Chief: M. Sofocleous

WATTANASIN OPPOSITION
TO FUJIKAWA MOTION TO SUPPRESS EVIDENCE

FYI

Honorable Commissioner of Patents
and Trademarks
Washington, D.C. 20231

SEP 22 1993
RECEIVED IN
BOX INTERFERENCE

Sir:

Fujikawa have moved to supress the Declaration and Supplemental Declaration of Robert E. Engstrom, the Sandoz researcher who conducted in vivo testing of the Wattanasin compounds in rats, together with Exhibits K-1 and Q which accompany his respective declarations. For the convenience of the Board, copies of these declarations and exhibits (as well as the companion Rodney Slaughter declaration) are appended hereto.

Fujikawa are apparently objecting to the ED_{50} data in the Engstrom declaration (WR 206) because they "constitute the results of not one but two computer manipulations."

Whatever, Fujikawa intend by this, the following things are evident from these declaration and exhibit pages:

1. Pages 334 and 337 (see upper right hand corner of exhibit page) are summary pages generated for each of the screenings carried out starting October 22 and October 29, 1987, respectively, and simply record the type of test solutions utilized;

2. Pages 335-336 and 338-339 show the actual counts in nanocuries per 100 ml. of rat serum obtained for each in vivo testing.

As described more fully by Engstrom at WR 204, the rats were administered the test substance dissolved or as a suspension in a formulation comprising carboxymethylcellulose. The rats were therafter injected with a given amount of radiolabeled sodium acetate. Serum samples were then obtained, the sterols were precipitated, and their radioactivity detected by liquid scintillation spectrometry.

The count in nanoCuries per 100 ml. rat serum is listed down the fifth column of the WX K-1 computer printout. This is the actual raw data obtained from the experiments. From the nanoCurie values received for the six rats in each testing, various computations were made including a "% change" in nanoCurie count. A % change greater than 50% would indicate activity in the assay. (This is a quite stringent assay, where the industry standard, compactin, itself had an ED50 of 3.5, as described by Wattanasin in the Reply Brief at 21-22.)

This data were then inputed into a computer program which generated an ED_{50} number for each compound tested, and the ED_{50} was downloaded in the Sandoz database maintained in the ordinary course of business. (Notice that the database accepted only ED_{50} values which were smaller than 1.) However, in Exhibit Q (at page 418), a Biological Activity Data Report on the Wattanasin compounds shows that compound 64-933 was also calculated to have a specific ED_{50} value of 2.40.

Calculation of ED_{50} in this manner was hardly new to the art as of December 1987. In fact, the whole Engstom in vivo testing procedure appears almost verbatim at page 33 of the Kathawala 1984 European patent publication on fluvastatin, EP 114,027 which was cited as "technological background" against the involved Fujikawa '930 patent (copy of relevant pages also appended).

Even the Fujikawa rebuttal witness, Dr. Homlund, acknowledged that he had "no quarrel with the techniques for determining statistical activity" used by Wattanasin (FR at 204).

Given the art-recognized status of this in vivo assay, it is hard to understand why Fujikawa insist on being provided with computer programs or logorithms so that they can trace the exact progress of each byte of information.

The Board has discretion in applying the rules of evidence, and there is submitted to be no convincing argument that a "rule of reason" should not apply here where the raw data is attested to by the individuals who actually performed the experiments, and the resulting ED_{50} calculation was generated thereon by Sandoz in the ordinary course of business.

Fujikawa affect discomfort that the ED_{50} data for one of 64-933 and 64-936/NA was inadvertently "switched" at page 206 of the original Engstrom declaration. Regardless of whether this typographical error is related in any way to an acknowledged Engstrom "goof" showing up in Exhibit Q, all of the other Wattanasin Exhibits are uniform in assigning an ED_{50} value to

compound 64-935, alone, of 0.49 (see, e.g., Exhibit S-1 (relevant page also appended))[1].

Like any other business or technical information maintained in the ordinary course of business by Sandoz, the ED_{50} data in a sense speaks for itself, and should not be invalidated by a purported lack of foundation, particularly since the underlying computer programs or logorithms are not themselves likely to be comprehensible.

Accordingly, the Fujikawa motion to suppress should be denied.

Respectfully submitted,

Diane E. Furman
Attorney for the Party Wattanasin
Registration No. 31,104
201-503-7332

SANDOZ CORP.
50 route 10
E. Hanover, NJ 07936
Attachments as noted
September 7, 1993

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231, on Sept. 7, 1993
(Date of Deposit)
Diane E. Furman
Name of applicant, assignee, or Registered Representative
Signature
Sept 7, 1993
Date of Signature

1. Fujikawa also attempt an argument surrounding the absence of a sodium salt indication, i.e. "NA", from the Sandoz database printout for 64-936(NA) included in Wattanasin Exhibit K-1 (at 336). However, notice that on pages 203, 205 and 209 of the Wattanasin record "64-936" is used interchangeably with the designation "64-936/NA", just as the Sandoz fluvastatin compound, a sodium salt (technically, "62-320/NA"), is typically referred to as, simply, 62-320 (WR at 484), without the added sodium designation. It is hard to see how Fujikawa could allege difficulty with practices that are customary in the art, and manifested throughout the Wattanasin record in relation to compounds of known strucutre such as fluvastatin.

CERTIFICATE OF SERVICE

It is hereby certified that a true copy of the paper entitled:

WATTANASIN OPPOSITION
TO FUJIKAWA MOTION TO SUPPRESS EVIDENCE

and the attachments thereto were served on counsel for the party Fujikawa et al., this 7th day of September 1993, by postage pre-paid first-class mail addressed to the following:

Oblon, Spivak, McClelland, Maier & Neustadt, P.C.
Attn: Steven B. Kelber, Esq.
1755 South Jefferson Davis Highway
Crystal Square 5, Ste. 400
Arlington, VA 22202

Diane Furman

Diane E. Furman

600 - 6951

(19) Europäisches Patentamt
European Patent Office
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(11) Publication number: **0 114 027**
A1

EUROPEAN PATENT APPLICATION

(12)

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(71) Applicant: SANDOZ AG, Lichtstrasse 35, CH-4002 Basel (CH)
(84) Designated Contracting States: BE CH FR GB IT LI LU NL SE

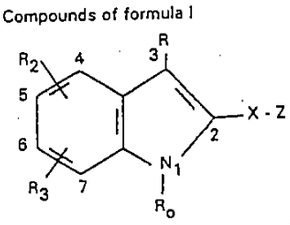
(71) Applicant: SANDOZ-PATENT-GMBH, Humboldtstrasse 3, D-7850 Lörrach (DE)
(84) Designated Contracting States: DE

(71) Applicant: SANDOZ-ERFINDUNGEN Verwaltungsgesellschaft m.b.H., Brunner Strasse 59, A-1235 Vienna (AT)
(84) Designated Contracting States: AT

(72) Inventor: Kathawala, Faizulla Gulamhusein, 39 Woodland Avenue, Mountain Lakes, N.J., 07946 (US)

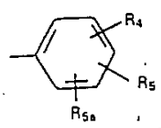
(54) **Analogs of mevalolactone and derivatives thereof, processes for their production, pharmaceutical compositions containing them and their use as pharmaceuticals.**

(57) Compounds of formula I

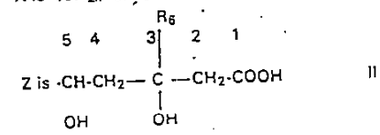


(I)

wherein one of R and R_6 is



and the other is primary or secondary C_{1-6}alkyl, C_{3-6}cycloalkyl or phenyl-$(CH_2)_m$-,
wherein
R_4 is hydrogen, C_{1-4}alkyl, C_{1-4}alkoxy, (except t-butoxy), trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy,
R_5 is hydrogen, C_{1-3}alkyl, C_{1-3}alkoxy, trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy,
R_{5a} is hydrogen, C_{1-2}alkyl, C_{1-2}alkoxy, fluoro or chloro, and
m is 1, 2, or 3,
with the provisos that both R_5 and R_{5a} must be hydrogen when R_4 is hydrogen, R_{5a} must be hydrogen when R_5 is hydrogen, not more than one of R_4 and R_5 is trifluoromethyl, not more than one of R_4 and R_5 is phenoxy and not more than one of R_4 and R_5 is benzyloxy,
R_2 is hydrogen, C_{1-4}alkyl, C_{3-6}cycloalkyl, C_{1-4}alkoxy, (except t-butoxy), trofluoromethyl, fluoro, chloro, phenoxy or benzyloxy,
R_3 is hydrogen, C_{1-3}alkyl, C_{1-3}alkoxy, trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy, with the provisos that R_3 must be hydrogen when R_2 is hydrogen, not more than one of R_2 and R_3 is trifluoromethyl, not more than one of R_2 and R_3 is phenoxy, and not more than one of R_2 and R_3 is benzyloxy,
X is $-(CH_2)_n-$ or $-CH=CH-$ (n = 0, 1, 2 or 3),



(II)

wherein R_6 is hydrogen or C_{1-3}alkyl in free acid form or in the form of a physiologically-hydrolysable and -acceptable ester or a lactone thereof or in salt form.
These compounds are indicated for use as pharmaceuticals particularly for inhibiting cholesterol biosynthesis and treating atherosclesoris.

EP 0 114 027 A1

The isomer of Yang et al. and the isomer disclosed in Reaction Scheme III yield lactones having the 4R,6S configuration and, as a result of epimerization in Reaction X, such compounds having the 4R,6R configuration. Lactones having the 4S,6R and 4S,6S configuration may be obtained from the other isomer whose synthesis is disclosed in Rection Scheme III.

The availability of these intermediates enables synthesis of optically pure end products.

Reaction products both intermediale and final can be isolated and purified in conventional mannr whereby intermediates can where appropriately be employed directly in a subsequent reaction

Mixtures of stereoisomers (cis, trans and optical) may be separated by conventional means at whatever stage of synthesis is appropriate. Such methods include re-crystalisation, chromatography, formation of esters with optically pure acids and alcohols or of amides and salts (cf also Sommer et al. J.A.C. S 80, 3271 (1958)) with subsequent reconversion under retention of optical purity. For example diastereoisomeric (-)-α-naphthyl-phenylmethylsilyl derivatives of a lactone type end product of formula I may be separated on a silica solumn having covalently bound L-phenylglycine (eluant n-hexane/acetate : 1/1).

Salts may be prepared in conventional manner from free acids, lactones and esters and vice-versa. Whilst all salts are covered by the invention pharmaceutically acceptable salts especially sodium, potassium and ammonium particularly sodium salts are preferred.

The various forms of the compounds of formula I are by virtue of their interconvertability useful as intermediates in addition to the use set out below.

Also within the scope of this invention are the intermediates of formulae V, X, XI, XII, XX, XXIV, XXVI-XXVIII and XXIXB-XXIXD. The preferences for each variable are the same as those set forth for the compounds of formula I, with the preferred groups of such compounds including those that correspond to Groups (i)-(xiii) and (xxxix)-lxxxviii) (for

formulae V, X-XII, XX and XXIXB-XXIXD) and Groups (xiv)-(xx), (xxxiii)-(xxxviii) and (lxxxix)-(cxiv) for formulae XXVI-XXVIII) to the extent consistent therewith.

The compounds of formula I possess pharmacological activity in particular they are inhibitors of 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase and as a consequence inhibitors of cholesterol biosynthesis as demonstrated in the following three tests.

Test A: In Vitro Microsomal Assay of HMG-CoA Reductase Inhibition:

200 ul. aliquots (1.08-1.50 mg./ml.) of rat liver microsomal suspensions, freshly prepard from male Spargue-Dawley rats (150-225 g. body weight), in Buffer A with 10 mmol. dithiothreitol are incubated with 10 ul. test substance dissolved in dimethylacetamide and assayed for HMG-CoA reductase activity as described by Ackerman et al., J. Lipid Res. 18, 408-413 (1977). In the assay the microsomes are the source of the HMG-CoA reductase enzyme which catalyses the reduction of HMG-CoA to mevalonate. The assay employs a chloroform extraction to separate the product, [^{14}C]mevalonolactone, formed by the HMG-CoA reductase reaction from the substrate, [^{14}C]HMG-CoA. [^{3}H]mevalono-lactone is added as an internal reference. Inhibition of HMG-CoA reductase is calculated from the decrease in specific activity [^{14}C/^{3}H]mevalonate) of test groups compared to controls.

Test B: In Vitro Cell Culture Cholesterol Biosynthesis Screen:

The cell culture is prepared as follows: Stock monolayer cultures of the Fu5AH rat hepatoma cell line (originally obtained from G. Rothblat; see Rothblat, Lipids 9, 526-535 (1974) are routinely maintained in Eagle's Minimum Essential Medium (EMEM) supplemented with 10% fetal bovine serum (FBS) in 75 cm^2 tissue culture flasks. For these studies, when the cultures reach

confluence, they are removed by mild enzymatic treatment with 0.25% trypsin in Hanks' balanced salt solution (without calcium and magnesium). After centrifugation of the cell suspension and aspiration of the enzymatic solution, a cell pellet is resuspended in an appropriate volume of media for seeding into 60 mm. tissue culture dishes. The cultures are incubated at 37°C in an atmosphere of high humidity and 5% carbon dioxide. When the cultures are confluent (approximately 5 days), they are ready for use. The culture media is aspirated from the dishes and replaced with 3 ml of EMEM suplemented with 5 mg/ml of dilipidized serum protein (DLSP) prepared by the method of Rothblat et al., In Vitro 12, 554-557 (1976). Replacement of the FBS with DLSP has been shown to stimulate the incorporation of [^{14}C]acetate into sterol by removing the exogenous sterol supplied by the FBS, thereby requiring the cells to synthesized sterol. Enthanced 3-hydroxy-3-methylglutaryl Coenzyme A reductase (HMG-CoA reductase) activity is measurable in the cells in response to the lack of exogenous sterol. Following approximately 24 hours incubation at 37°C in the DLSP supplemented media, the assay is initiated by the addition of 3μCi of [^{14}C]acetate and the test substances solubilized in dimethylsulfoxide (DMSO) or distilled water. Solvent controls and compactin-treated controls are always prepared. Triplicate 60mm. tissue culture dishes are run for each group. After 3 hours incubation at 37°C, the cultures are examined microscopically using an inverted phase contrast microscope. Notations are made of any morphological changes which may have occurred in the cultures. The media is aspirated and the cell layer is gently washed twice with 0.9% sodium chloride solution (saline). The cell layer is then harvested in 3 ml. of 0.9% saline by gentle scraping with a rubber policeman and transferred to a clean glass tube with Teflon lined cap. The dishes are rinsed with 3 ml. of 0.9% saline and rescraped, and the cells are combined with the first harvest. The tubes are centrifuged at 1500 r.p.m. for 10 minutes

in an IEC PR-J centrifuge, and the supernatant is asperated.

The cells are then extracted as follows: One ml. of 100% ethanol is added to the cell pellet followed by sonication for 10 seconds with a "LO" setting of 50 on a Bronwell Biosonik IV. One hundred ul. are taken for protein determination. One ml. of 15% potassium hydroxide (KOH) is added, and the samples are thoroughly vortexed. Saponification is accomplished by heating the ethanol-KOH treated samples at 60°C for 60 minutes in a water bath. Following dilution of the samples with 2ml. of distilled water, they are extracted three times with 7 ml. of petroleum ether. The petroleum ether extracts are then washed three times with 2 ml. of distilled water and finally taken to dryness under a stream of nitrogen.

The obtained samples are then analyzed by thin layer chromatography (TLC) as follows: Residues from the petroleum ether extraction are taken up in a small volume of hexane and spotted on silica gel 60 TLC plates (E. Merck). Development of the plates is carried out in a 150 parts by volume hexane: 50 parts by volume diethyl ether: 5 parts by volume galcial acetic acid solvent system using a three phase development procedure. Visualization is accomplished in an iodine vapor chamber. The plates are divided into five sections such that each section contains the molecules having the following approximate Rf values: section 1- 0-0.4, section 2- 0.4-0.55, section 3- 0.55-0.7, section 4- 0.7-0.9 and section 5- 0.9-1.0. Section 2 contains the non-saponifiable sterols. The five sections of the TLC plates are scraped into scintillation vials. Blanks are also prepared from scrapings of chromatographed non-labelled standards. ACS® scintillation cocktail is added, and the radioactivity is determined in a liquid scintillation spectrometer. [^{14}C]hexadecane standards are used to determine counting efficiencies. The total protein content of the samples is determined employing the Bio-Rad Protein Assay System.

The results are reported as disintegrations per minute per mg protein (d.p.m./mg protein) for each of the five TLC sections. Mean d.p.m./mg protein ± standard error of the mean are compared for percentage change (%Δ) and statistical significance with solvent control means. TLC section 2 data is taken as a measure of HMG-CoA reductase activity inhibition.

Test C: In Vivo Cholesterol Biosynthesis Inhibition Tests: In vivo studies utilize male Wistar Royal Hart rats weighing 150±20 g which have been kept for 7-10 days on an altered light cycle (6:30 a.m. - 6:30 p.m. dark) housed two per cage and fed powdered Purina Rat Chow and water ad libitum. Three hours before the diurnal maximum of cholesterol synthesis at mid-dark, the rats are administered the test substances dissolved or as a suspension in 0.5% carboxymethylcellulose in a volume of 1 ml/100 g body weight. Controls receive vehicle alone. One hour after receiving the test substance, the rats are injected intraperitoneally with about 25 μCi/100 g body weight of sodium [1-^{14}C]acetate 1-3 mCi/mmol. Two hours after mid-dark, blood samples are obtained under sodium hexobarbitol anesthesia and the serum separated by centrifugation.

Serum samples are saponified and neutralized, and the 3β-hydroxy sterols are precipiated with digitonin basically as described by Sperry et al., J. Biol. Chem. 187, 97 (1950). The [^{14}C]digitonides are then counted by liquid scintillation spectrometry. After correcting for efficiencies, the results are calculated in nCi (nanocuries) of sterol formed per 100 ml of serum. Inhibition of sterol synthesis is calculated from the reduction in the nCi of sterols formed from test groups compared to controls.

The compounds are thus indicated for use as hypolipoproteinemic and anti-atherosclerotic agents.

An indicated suitable daily dosage for use in the treatment of hyperlipoproteinemia and athersclerosis is from about

1 to 2000 mg preferably 1.5 to 100 mg suitably administered in divided dosages of 0.25 to 1000 mg preferably 0.4 to 50 mg two to four times daily or in retard form.

They may be administered in free acid form or in the form of a physiologically-hydrolysable and -acceptable ester or a lactone thereof or in pharmaceutically acceptable salt form whereby the various forms have activities in the same range.

The invention therefore also concerns a method of treating hyperlipoproteinemia or atherosclerosis by administration of a compound of formula I in free acid form or in the form of a physiologically-hydrolysable and -acceptable ester or a lactone thereof or in pharmaceutically acceptable salt form as well as such compounds for use as pharmaceuticals e.g. as hypolipoproteinemic and anti-atherosclerotic agents.

The compounds may be administered alone, or in admixture with a pharmaceutically acceptable diluent or carrier, and, optionally other excipients, and administered orally in such forms as tablets, elixirs, capsules or suspensions or parenterally in such forms as injectable solutions or suspensions.

The preferred pharmaceutical compositions from the standpoint of ease of preparation and administration are solid compositions, particularly tablets and hard-filled or liquid-filled capsules.

Such compositions also form part of the invention.

The following examples, in which all temperatures are in °C illustrate the invention.

107

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

WATTANASIN
v.
Fujikawa et al.

Interference No. 102,648, 102,975
Examiner-in-Chief: M. Sofocleous

DECLARATION OF ROBERT G. ENGSTROM PURSUANT TO 37 CFR §1.672

I, Robert G. Engstrom, do hereby declare as follows:

(1) That I have been employed by Sandoz Pharmaceuticals Corporation since 1964 as a Research Scientist. Among my responsibilities has been supervising the testing of new HMG Co-A reductase inhibiting compounds synthesized by Sandoz chemists.

(2) That all activities referred to in this Declaration took place in the United States.

IN VIVO TESTING OF
WATTANASIN COMPOUNDS 64-933, 64-935 and 64-936/Na

1. On or before October 29, 1987, in my laboratory under my supervision, Rodney Slaughter began performing the below-indicated protocol on compounds 64-933, 64-935 and 64-936/Na:

In vivo studies utilized male Wistar Royal Hart rats weighing 150 ± 20 g. which have been kept for 7-10 days on an altered light cycle (6:30 A.M. - 6:30 P.M. dark) housed two per cage and fed powdered Purina Rat Chow and water ad libitum. Three hours before the diurnal maximum of cholesterol systhesis at mid-day the rats were administered the test substances dissolved or as a suspension in 0.5% carboxymethylcellulose in a volume of 1 ml./100 g. body weight. Controls received vehicle alone. One hour after receiving the test substance, the rats were injected intraperitoneally with about 25 μCi/100 g. body weight of sodium [1-^{14}C]acetate 1-3 mCi/mmol. Two hours after mid-dark, blood samples were obtained under sodium hexobarbitol anesthesia, and the serum was separated by centrifugation. The resulting serum samples were saponified and neutralized, and the 3β-hydroxy sterols were precipitated with digitonin basically as described by Sperry et al., J. Biol. Chem. 187,97(1950). The [^{14}C]digitonides were counted by liquid scintillation spectrometry. The assay is based on the conversion of ^{14}C-acetate to ^{14}C-cholesterol in vivo.

2. The counts in DPM of digitonin precipitable sterol (β-hydroxy sterol, mostly cholesterol in the rat) were entered by Rodney Slaughter into my computer program, which converted them to nCi of sterol found per 100 ml. of serum at 4 hours after the injection of the ^{14}C-acetate.

3. I have reviewed Exhibit K-1 hereto, which comprises true copies of pages 133, 134, and 135, 136, 137 and 138 of R. Slaughter's Laboratory Notebook #917. I witnessed Rodney Slaughter's signature on each of these pages, and each page bears my true signature as a witness.

4. Notebook pages 133-135 contain true copies of a computer printout for the protocol and results in nCi/dl of Study #H318, which was commenced on October 22, 1987. I initialed the first page of this computer printout on or before October 22, 1987. This computer printout on page 135 indicates that an in vivo assay of compound 64-936 was started on October 22, 1987.

5. Notebook pages 136-138 contain true copies of a computer printout for the protocol and results in nCi/dl of Study #H319, which was commenced on October 29, 1987. I initialed the first page of this computer printout on page 136 on or prior to October 29, 1987. This computer printout on page 137-138 indicates that an in vivo assay of compound 64-933 and 64-935 was started on October 29, 1987.

6. Both studies were completed on or prior to December 9, 1987, the date indicated at the bottom of pages 135 and 138.

7. It was my responsibility to enter the nCi/dl data into a separate computer program which calculates the ED_{50} values of a compound tested in vivo from the reduction in the nCi of sterols formed from test groups compared to controls for each assay, and forms a database of the ED_{50} values. On or before December 9, 1987, I entered the data for compounds 64-933, 64-935 and 64-936/Na.

8. The 1st page of Exhibit K-1 comprises a true copy of part of the ED_{50} database. This page indicates that the ED_{50} for compounds 64-933, 64-935 and 64-936/Na was in the system as of December 9, 1987. Therefore, the information was available to other Sandoz employees having access to the computer database as of December 9, 1987.

The ED50 for these compounds are:

COMPOUND	ED_{50} (mg/kg)
64-933	0.49
64-935	>1.0
64-936	>1.0

. . .

The undersigned declares further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

I hereby subscribe my name to the foregoing DECLARATION this 13 day of November 1992.

Robert G. Engstrom

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

WATTANASIN
v.
FUJIKAWA et al.

Interference Nos. 102,648, 102,975
Examiner-in-Chief: M. Sofocleous

DECLARATION OF RODNEY SLAUGHTER PURSUANT TO 37 CFR §1.672

I, Rodney Slaughter, do hereby declare as follows:

(1) That I have been employed by Sandoz Pharmaceuticals Corporation since 1982, and during the time periods referred to herein, I worked in the Department of Lipid Metabolism.

(2) That it has been my responsibility to carry out an in vivo testing program of various HMG-CoA reductase inhibitor compounds, including Wattanasin compounds 64-933, 64-935 and 64-936.

(3) That all of the below-indicated activities took place in the United States.

IN VIVO TESTING OF
WATTANASIN COMPOUNDS 64-933, 64-935 and 64-936

1. On or before October 29, 1987, I carried out the below-indicated protocol on compounds 64-933, 64-935 and 64-936:

In vivo studies utilized male Wistar Royal Hart rats weighing 150 ± 20 g. which have been kept for 7-10 days on an altered light cycle (6:30 A.M. - 6:30 P.M. dark) housed two per cage and fed powdered Purina Rat Chow and water ad libitum. Three hours before the diurnal maximum of cholesterol systhesis at mid-day the rats were administered the test substances dissolved or as a suspension in 0.5% carboxymethylcellulose in a volume of 1 ml./100 g. body weight. Controls received vehicle alone. One hour after receiving the test substance, the rats were injected intraperitoneally with about 25 µCi/100 g. body weight of sodium [1-^{14}C]acetate 1-3 mCi/mmol. Two hours after mid-dark, blood samples were obtained under sodium hexobarbitol anesthesia, and the serum was separated by centrifugation. The resulting serum samples were saponified and neutralized, and the 3β-hydroxy sterols were precipitated with digitonin basically as described by Sperry et al., J. Biol. Chem. 187,97(1950). The [^{14}C]digitonides were counted by liquid scintillation spectrometry. The assay is based on the conversion of ^{14}C-acetate to ^{14}C-cholesterol in vivo.

2. I entered the counts in DPM of digitonin precipitable sterol (β-hydroxy sterol, mostly cholesterol in the rat) into a computer program, which converted them to nCi of sterol found per 100 ml. of serum at 4 hours after the injection of the ^{14}C-acetate.

3. I have reviewed Exhibit K-1 hereto, which comprises true copies of pages 133, 134, 135, 136, 137 and 138 of my Laboratory Notebook #917.

4. Notebook pages 133-135 contain true copies of a computer printout for the protocol and results in nCi/dl of Study #H318, which I started on October 22, 1987. These pages contain the date of 10/22/87 at the top in my handwriting.

5. Notebook pages 136-138 contain true copies of a computer printout for the protocol and results in nCi/dl of Study #H319, which I started on October 29, 1987. These pages contain the date of 10/29/87 at the top in my handwriting.

6. Both studies were completed on or prior to December 9, 1987, the date indicated at the bottom of the computer printouts on pages 135 and 138.

7. It was my practice to paste the computer printouts into my notebook and to sign the notebook page when I did this.

The undersigned declares further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

I hereby subscribe my name to the foregoing DECLARATION this 13 day of November 1992.

Rodney Slaughter

Date 10/22/87 Proj. 11317

Title Cholesterol Synthesis Inhibition Screen

Book from- 134

135

334

CHOLESTEROL BIOSYNTHESIS (LIV)

LIPID METABOLISM DEPARTMENT
HMGR SCREENING UNIT
Sandoz Research Institute
To: Dr. D. Weinstein, Departmenthead
Mr. R. Slaughter, Responsible Technician
From: Mr. R. Engstrom, Responsible Investigator
CC: D.N., M.L.R., ARC

STUDY #: H518
STUDY ON 10/22/87
BK.REF. 917 33
APPROVAL
DATE 10/21/87
GEN. ARC86S-006

Title: In vivo single dose assay to test for inhibition of biosynthesis by compounds: 63-748, 64-B4a, 64-938

Purpose: Determine the invivo effects of test compounds in rats on cholesterol biosynthesis.

Experimental design: IN VIVO CHOLESTEROL BIOSYNTHESIS INHIBITION DT0065 Invivo single dose assay of inhibition of Reference method: 740/001. Stock solutions and dilutions prepared in 0.5% CMC, administered p.o. at 1ml/100gm weight. Rats bled via carotid incision using hexobarbital anesthesia. Animal use will be in compliance with ARC regulations. Duration = 1 hr. No/group = 5. No of groups = 14. UCR rats.

Rats	COMPOUND	REGNO	DOSE mg/kg	STOCK mg/20ml	WORKING SOLUTION ml stock q.s. to 15ml
1-5	Control	------	------	------	----------
7-12	63-748	26688	1	2	UNDILUTED
13-18	"	"	0.3	-	4.5
19-24	"	"	0.1	-	1.5
25-30	64-B4a	30280	0.3	2	4.5
31-36	"	"	0.1	-	1.5
37-42	"	"	0.03	-	0.45
43-48	64-938	30488	1	2	UNDILUTED
49-54	"	"	0.3	-	4.5
55-60	"	"	0.1	-	1.5
61-66	62-810	30859	0.3	2	4.5
67-72	"	"	0.1	-	1.5
73-78	"	"	0.03	-	0.45
79-84	Control	------	------	------	----------

WATTANASIN EXHIBIT
K-1
Wattanasin v. Fujikawa et al.
Interference No. 102,648
Interference No. 102,975

Performed by- Todd A. Mauchlin

Witness- R D

Cont'd to- 15Y

134

Title- Cholesterol Synthesis Inhibition Screen

Date 10/22/68 Proj 123

Cont'd From 133

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IN VIVO CHOLESTEROL SYNTHESIS INHIBITION SCREEN #318

RAT	COMPOUND	REGNO	DOSE mg/kg	PO/IP	STATISTICS		
BLANK							
SAC-STANDARD			20178	X EFFIC=		.99	
1	CONTROL			493			
2	CONTROL			677	MEAN =	537.7	
3	CONTROL			580	STD =	128.6	
4	CONTROL			455	SE =	37.1	
5	CONTROL			490			
6	CONTROL			365			
79	CONTROL			462			
80	CONTROL			316			
81	CONTROL			599			
82	CONTROL			650			
83	CONTROL			610			
84	CONTROL			745			
8	63-748	25688	1.00	170	MEAN =	155.9	
9	63-748	25688	1.00	278	STD =	73.1	
10	63-748	25688	1.00	113	SE =	32.7	
11	63-748	25688	1.00	113	t =	7.7	
12	63-748	25688	1.00	106	P	<.01	
7	63-748	25688	1.00	528*	%CHG =	-71	
13	63-748	25688	.300	356	MEAN =	319.8	
14	63-748	25688	.300	355	STD =	66.3	
15	63-748	25688	.300	391	SE =	39.5	
17	63-748	25688	.300	199	t =	4.0	
18	63-748	25688	.300	253	P	<.01	
16	63-748	25688	.300	794*	%CHG =	+40.6	
19	63-748	25688	.100	348	MEAN =	456.7	
20	63-748	25688	.100	726	STD =	213.5	
21	63-748	25688	.100	310	SE =	87.2	
22	63-748	25688	.100	650	t =	0.8	
23	63-748	25688	.100	536	P	N.S.	
24	63-748	25688	.100	178	%CHG =	-14.7	
25	64-844	30280	.300	256	MEAN =	185.8	
26	64-844	30280	.300	170	STD =	57.3	
27	64-844	30280	.300	165	SE =	23.4	
28	64-844	30280	.300	125	t =	8.5	
29	64-844	30280	.300	174	P	<.01	
30	64-844	30280	.300	101	%CHG =	-66.2	
31	64-844	30280	.100	306	MEAN =	219.8	
32	64-844	30280	.100	273	STD =	69.9	
33	64-844	30280	.100	195	SE =	28.9	
35	64-844	30280	.100	157	t =	8.7	
36	64-844	30280	.100	166	P	<.01	
34	64-844	30280	.100	695*	%CHG =	-58.1	

Performed by- Ted R. Slaughter

Witness- R Eglinton

Cont'd to- 135

Date 10/22/97 Proj# 3,4

Title- Cholesterol Synthesis Inhibition Screen

135

Cont'd From- 134

336

INVIVO CHOLESTEROL SYNTHESIS INHIBITION SCREEN HG18

RAT	COMPOUND REGNO	DOSE mg/kg	nCi/dl	STATISTICS	
37	64-844	30280	.030	354	MEAN = 419.7
38	64-844	30280	.030	518	STD = 136.6
39	64-844	30280	.030	639	SE = 56.6
40	64-844	30280	.030	248	t = 1.7
41	64-844	30280	.030	358	p N.S.
42	64-844	30280	.030	402	%CHG = -21.9
43	64-936	30486	1.00	580	MEAN = 489.4
44	64-936	30486	1.00	642	STD = 132.9
45	64-936	30486	1.00	290	SE = 54.2
46	64-936	30486	1.00	328	t = 0.7
47	64-936	30486	1.00	532	p N.S.
48	64-936	30486	1.00	513	%CHG = -9.0
49	64-936	30486	.300	167	MEAN = 325.7
50	64-936	30486	.300	232	STD = 165.0
51	64-936	30486	.300	566	SE = 87.4
52	64-936	30486	.300	278	t = 2.7
53	64-936	30486	.300	323	p <.02
54	64-936	30486	.300	473	%CHG = -38.2
55	64-936	30486	.100	485	MEAN = 416.5
56	64-936	30486	.100	181	STD = 166.8
57	64-936	30486	.100	639	SE = 62.9
58	64-936	30486	.100	696	t = 1.6
59	64-936	30486	.100	367	p N.S.
60	64-936	30486	.100	439	%CHG = -32.5
61	62-320	30559	.300	72	MEAN = 67.5
62	62-320	30559	.300	89	STD = 12.1
63	62-320	30559	.300	73	SE = 5.4
64	62-320	30559	.300	53	t = 12.9
65	62-320	30559	.300	64	p <.01
66	62-320	30559	.300	55	%CHG = -87.5
67	62-320	30559	.100	135	MEAN = 165.3
68	62-320	30559	.100	238	STD = 51.1
70	62-320	30559	.100	198	SE = 32.6
71	62-320	30559	.100	109	t = 8.5
69	62-320	30559	.100	149	p <.01
72	62-320	30559	.100	158	%CHG = -69.3
73	62-320	30559	.030	323	MEAN = 351.2
74	62-320	30559	.030	380	STD = 173.8
75	62-320	30559	.030	77	SE = 70.8
76	62-320	30559	.030	579	t = 2.3
77	62-320	30559	.030	493	p <.05
78	62-320	30559	.030	277	%CHG = -84.7

* = rejected by "Q" test
- =LACK OF SAMPLE

Computed 12-09-97

Performed by- [signature]

Witness- [signature]

Cont'd to-

136 Title- Cholesterol Synthesis Inhibition Screen

Date 10/29/87 Proj: 3.9

Cont'd from-

337 -

CHOLESTEROL BIOSYNTHESIS INHIBITION SCREEN

LIPID METABOLISM DEPARTMENT
HNOR SCREENING UNIT
Sandoz Research Institute
To: Dr. D. Weinstein, Departmenthead
Mr. R. Slaughter, Responsible Technician
From: Mr. R. Engstrom, Responsible Investigator
CC: D.N., M.L.R., ARC

STUDY # HS19
STUDY ON 10/29/87
BK.REF. 917-136
APPROVAL
DATE 10/29/87
GEN. ARC#86-004

Title: In vivo single dose assay to test for inhibition of biosynthesis by compounds: 84-298, 84-938, 83-935

Purpose: Determine the invivo effects of test compounds in rats on cholesterol biosynthesis.

Experimental design: IN VIVO CHOLESTEROL BIOSYNTHESIS INHIBITION ST0005 Invivo single dose assay of inhibition of Reference method: 740/001. Stock solutions and dilutions prepared in 0.5% CMC, administered p.o. at 1ml/100gm weight. Rats bled via carotid incision using hexobarbital anesthesia. Animal use will be in compliance with ARC regulations. Duration = 1 hr. No/group = 6. No of groups = 14. HSR rats.

RATS	COMPOUND	BSGNO	DOSE mg/kg	STOCK mg/20ml	WORKING SOLUTION ml stock q.s. to 15ml
1-6	Control	------	------	------	------
7-12	84-298	29277	1	1	UNDILUTED
13-18	"	"	0.3	-	4.5
19-24	"	"	0.1	-	1.5
25-30	84-938	30447	1	1	UNDILUTED
31-36	"	"	0.3	-	4.5
37-42	"	"	0.1	-	1.5
43-48	84-935	30441	1	1	UNDILUTED
49-54	"	"	0.3	-	4.5
55-60	"	"	0.1	-	1.5
61-66	83-920	30556	0.3	1	4.5
67-72	"	"	0.1	-	1.5
73-78	"	"	0.03	-	0.45
79-84	Control	------	------	------	------

Performed by-

Witness-

Cont'd to- 337

Date 10/2/73 Proj.

Cont'd.From-

Title- [illegible]

137

338

INVIVO CHOLESTEROL SYNTHESIS INHIBITION SCREEN R315

RAT	COMPOUND	REGNO	DOSE mg/kg	nCi/dl	STATISTICS	
	BLANK			7		
	14C-STANDARD			20176	% EFFIC=	99
1	CONTROL			953		
2	CONTROL			515	MEAN =	671.8
3	CONTROL			646	STD =	211.0
4	CONTROL			578	SE =	80.9
5	CONTROL			934		
6	CONTROL			354		
79	CONTROL			755		
80	CONTROL			847		
81	CONTROL			814		
82	CONTROL			549		
83	CONTROL			872		
84	CONTROL			714		
7	64-298	28277	1.00	203	MEAN =	151.7
8	64-298	28277	1.00	381	STD =	118.8
9	64-298	28277	1.00	82	SE =	48.4
10	64-298	28277	1.00	78	t =	6.8
11	64-298	28277	1.00	71	P	<.01
12	64-298	28277	1.00	115	%CHG =	-77
13	64-298	28277	.300	311	MEAN =	235.1
14	64-298	28277	.300	284	STD =	81.4
15	64-298	28277	.300	257	SE =	33.2
16	64-298	28277	.300	307	t =	8.3
17	64-298	28277	.300	114	P	<.01
18	64-298	28277	.300	157	%CHG =	-65.0
19	64-298	28277	.100	581	MEAN =	385.7
20	64-298	28277	.100	387	STD =	81.5
21	64-298	28277	.100	245	SE =	33.3
22	64-298	28277	.100	382	t =	4.1
23	64-298	28277	.100	499	P	<.01
24	64-298	28277	.100	426	%CHG =	-42.1
25	64-933	30447	1.00	636	MEAN =	436.1
26	64-933	30447	1.00	275	STD =	253.4
27	64-933	30447	1.00	136	SE =	103.5
28	64-933	30447	1.00	584	t =	2.0
29	64-933	30447	1.00	258	P	N.S.
30	64-933	30447	1.00	447	%CHG =	-36.5
31	64-933	30447	.300	830	MEAN =	557.4
32	64-933	30447	.300	646	STD =	100.5
33	64-933	30447	.300	385	SE =	41.0
34	64-933	30447	.300	598	t =	1.6
35	64-933	30447	.300	366	P	N.S.
36	64-933	30447	.300	615	%CHG =	-17.0

Performed by-

138 Title-

Date 12/[illegible]/87 Proj...

Cont'd From...137

IN VIVO CHOLESTEROL SYNTHESIS INHIBITION SCREEN H319-...

RAT	COMPOUND	REGNO	DOSE mg/kg	nCi/Ci	STATISTICS	
37	64-933	30447	.100	555	MEAN =	547.0
38	64-933	30447	.100	735	STD =	147.2
39	64-933	30447	.100	370	SE =	80.1
40	64-933	30447	.100	378	t =	1.5
41	64-933	30447	.100	581	P	N.S.
42	64-933	30447	.100	552	%CHG =	-16.6
43	64-935	30441	1.00	182	MEAN =	230.0
44	64-935	30441	1.00	307	STD =	78.2
45	64-935	30441	1.00	168	SE =	31.9
46	64-935	30441	1.00	321	t =	6.4
47	64-935	30441	1.00	124	P	<.01
48	64-935	30441	1.00	281	%CHG =	-65.6
49	64-935	30441	.300	778	MEAN =	472.2
50	64-935	30441	.300	282	STD =	179.5
51	64-935	30441	.300	520	SE =	73.3
52	64-935	30441	.300	413	t =	2.1
53	64-935	30441	.300	344	P	N.S.
54	64-935	30441	.300	438	%CHG =	-29.7
55	64-935	30441	.100	411	MEAN =	428.2
56	64-935	30441	.100	320	STD =	119.1
57	64-935	30441	.100	296	SE =	48.6
58	64-935	30441	.100	425	t =	8.1
59	64-935	30441	.100	821	P	<.02
60	64-935	30441	.100	495	%CHG =	-38.3
61	62-320	30559	.300	60	MEAN =	185.6
62	62-320	30559	.300	107	STD =	107.1
63	62-320	30559	.300	222	SE =	43.7
64	62-320	30559	.300	60	t =	8.8
65	62-320	30559	.300	217	P	<.01
66	62-320	30559	.300	327	%CHG =	-75.3
67	62-320	30559	.100	262	MEAN =	331.7
68	62-320	30559	.100	434	STD =	188.7
70	62-320	30559	.100	589	SE =	74.1
71	62-320	30559	.100	168	t =	3.5
69	62-320	30559	.100	228	P	<.01
72	62-320	30559	.100	804	%CHG =	-50.9
73	62-320	30559	.030	621	MEAN =	445.1
74	62-320	30559	.030	472	STD =	94.1
75	62-320	30559	.030	571	SE =	38.4
76	62-320	30559	.030	374	t =	3.1
77	62-320	30559	.030	517	P	<.01
78	62-320	30559	.030	815	%CHG =	-38.8

Computed 12-09-87

Performed by-

Witness- R Stephenson

Cont'd to...

64588	29851	280-85	>	1	09-JUN-87	917-065
64589	29852	280-85	=	.16	15-JUN-87	917-081
64602	29743	101-85	>	.3	05-MAY-87	917-050
64602	29743	101-85	>	.3	05-MAY-87	917-050
64604	29744	101-85	>	.3	05-MAY-87	917-051
64604	29744	101-85	>	.3	05-MAY-87	917-051
64604	29745	101-85	=	.48	14-JUL-87	917-085
64608	29756	298-85	>	7.5	15-MAY-87	917-055
64638	29835	570-83		.34	09-DEC-87	917-140
64639	29836	570-83	>	1	09-JUN-87	917-066
64640	29839	367-86	>	1	09-JUN-87	917-068
64641	29840	367-86	>	1	09-JUN-87	917-068
64642	29841	367-86	>	1	09-JUN-87	917-068
64673	29904	280-85	=	2.6	18-SEP-87	917-089
64686	29927	387-85	>	10	18-SEP-87	917-111
64691	29942	366-86		.58	16-DEC-87	917-113
64722	30004	280-85	=	.2	23-OCT-87	917-141
64723	30627	100-85	=	.16	19-FEB-88	917-126
64723	30877	100-85	=	.09	19-FEB-88	917-159

SAHNUM	REGNO	PATENT	R	ED50	EDATE	REF
64723	30766	100-85	=	.22	19-FEB-88	917-159
64723	30009	100-85	=	.36	18-SEP-87	917-107
64744	30059	295-84	>	.1	14-JUL-87	917-090
64745	30765	295-84	=	.016	19-FEB-88	917-154
64745	30060	295-84	=	.016	20-OCT-87	917-127
64747	30067	298-84	=	.11	01-JUL-87	917-087
64748	30068	298-84	=	.04	19-FEB-88	917-155
64792	30146	260-85	=	.74	13-OCT-87	917-123
64816	30199	295-84	=	.1	12-OCT-87	917-119
64844	30280	384-85	=	.07	09-DEC-87	917-135
64844	30769	384-85	=	.08	19-FEB-88	917-167
64896	30378	366-87	>	.3	06-OCT-87	917-119
64897	30379	366-87	>	.3	06-OCT-87	917-120
64906	30393	280-85	=	.045	05-JAN-88	917-150
64906	30772	280-85	=	.1	15-JAN-88	917-155
64933	30441	299-84	>	1	09-DEC-87	917-138
64935	30447	299-84	=	.49	09-DEC-87	917-138
64936	30488	299-84	>	1	09-DEC-87	917-135
64999	30623	298-84	=	.1	19-FEB-88	917-168
65002	30629	101-85	=	.76	05-JAN-88	917-144
65003	30630	101-85	=	.09	19-FEB-88	917-159

SAHNUM	REGNO	PATENT	R	ED50	EDATE	REF
65003	30902	101-85	=	.06	19-FEB-88	917-170
86665	25887	102-82	>	10	06-MAY-87	917-056
87469	26362	101-82	>	10	06-MAY-87	917-056
89826	29587	101-82	>	10	06-MAY-87	917-057
317223	24022		>	16	20-MAR-84	812-183
880349	29591	102-82	>	10	18-AUG-87	917-098
880585	29588	102-82	>	10	18-AUG-87	917-098
880820	29589	102-82	>	10	18-AUG-87	917-098

140 records selected.

SQL>

Case No. 600-7101/CONT/INT.(5)
Patent -

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

WATTANASIN
v.
FUJIKAWA et al.

Interference Nos. 102,648, 102,975
Examiner-in-Chief: M. Sofocleous

SUPPLEMENTAL DECLARATION OF ROBERT G.ENGSTROM PURSUANT TO 37 CFR §1.672

I, Robert G. Engstrom, do hereby declare as follows:

All of the below-indicated activities took place in the United States.

Exhibit Q comprises a true copy of a Biological Activity Data Report dated May 24, 1988 which I sent to the Patent Department concerning the compounds of PD 299/84, together with a computer printout of the Sandoz database dated May 23, 1988. The printout contains IC_{50} and some ED_{50} values for compounds of Patent Disclosure 295/84 and compounds of the subject Patent Disclosure 299/84.

(I note that I became aware of a computer entry error comprising the inadvertent "switching" of the ED_{50} data for compounds 64-933 and 64-935. The corrections on the printout are in my handwriting and would have been made on or about May 23, 1988.)

The undersigned declares further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful

false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

I hereby subscribe my name to the foregoing Declaration this 19 day of February, 1993.

Robert Engstrom

Robert Engstrom

Q

BIOLOGICAL ACTIVITY DATA REPORT (FOR PATENT DEPT.)

INVENTOR: S. Wattanasin DISCL. NO.: 299-84 4/8

ATTORNEY: M. Kassenoff DATE: May 24, 1988

1. ACTIVITY TO BE DISCLOSED:
Inhibition of cholesterol biosynthesis, antihypercholesteremic, antiatherosclerotic

2. IF ANY COMPOUNDS COVERED BY ABOVE-NOTED DISCLOSURE HAVE MORE THAI ONE ACTIVITY, INDICATE TOTAL NUMBER OF ACTIVITIES AND PREPARE A SEPARATE B.A.D.R. SHEET FOR EACH. TOTAL NO. OF ACTIVITIES: 1

3.a) TEST METHODS USED TO ESTABLISH ACTIVITY:
HMG-CoA reductase inhibition in rat liver microsomes (DT 64)
Cholesterol synthesis inhibition invivo in rats (DT 65)

b) DOSAGE RANGES BASED ON ACTUAL DOSES USED IN TEST PROCEDURE:
0.050 - 1.5 mg/kg

4. COMPOUNDS TESTED WITHIN DISCLOSURE WHICH EXHIBIT WEAK OR GREATER ACTIVITY:
64-935, 64-933

5. DOSAGE SCHEDULE - Broad Ranges:

a) Large / small animals:	.10	to	1.0	mg/kg.
b) Large animals:	20	to	200	mg/day.

6. MOST PREFERED COMPOUND FOR ACTIVITY DESIGNATED:

64-935

7. OTHER PREFERRED OR POTENTIALLY PREFERRED COMPOUNDS FOR DESIGNATEI ACTIVITY:
64-936, 63-366, 64-933, 64-934

8. ED50 FOR THE PREFERRED COMPOUND IN EACH OF THE TEST METHODS INDICATED IN 3a) FOR THE DESIGNATED ACTIVITY:

COMPOUND	IC50 uM DT64	ED50 mg.kg DT65	Potency x Mevinolin*
Compactin	1.01	3.5	0.11
Mevinolin	0.14	0.41	1 (standard)
64-935	0.41	0.49	0.3
64-936	0.53	>1.0	
64-933	2.37	2.40	

* Clinical dose of mevinolin (Lovasatin) = 20-80 mg/day

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419

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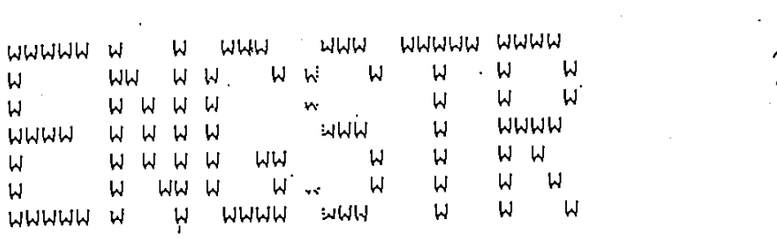
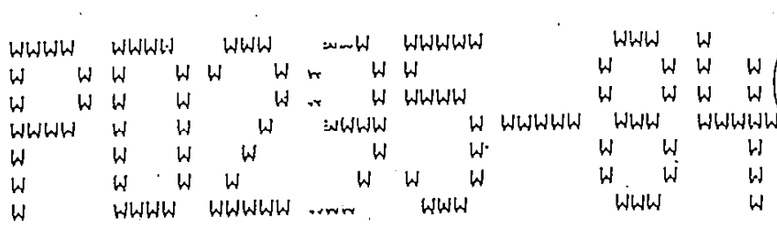
299/84.



295-84 &
299-84



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Started: 88-05-23 08:50:40. Mon on: PR0 by: PR0

IC50 TABLE RAT MICROSOMAL ASSAY (CSI-DT64)

THIS FILE IS A CALCULATED ESTIMATE OF THE IC50 (CONCENTRATION WHICH REDUCES THE CONVERSION OF HMG-CoA TO MEVALONATE BY 50%) USING ALL THE STUDIES ON THE RELEVANT COMPOUNDS UP TO THE SORT DATE.

LAST UPDATE: 02-04-88 SORT BY: DISCLNO

COMPOUND	REGNO	DISCL	IC50 uM	DATE	REF	COMMENTS
SAH-062977	24162	295-84	25.0000	02-07-84	1014-248	
SAH-062978	24163	295-84	0.0180	02-07-84	1014-249	
SAH-063033	24315	295-84	0.0450	04-18-84	1014-257	SAPONIFIED
SAH-063033	24315	295-84	0.5250	02-29-84	1014-257	
SAH-063034	24316	295-84	0.3630	02-22-84	1014-258	
SAH-063035	24317	295-84	0.0400	02-22-84	1014-259	
SAH-063074	24446	295-84	0.4000	05-23-84	1014-277	
SAH-063074	24446	295-84	0.6900	03-26-84	1014-277	
SAH-063075	24448	295-84	0.5300	04-18-84	1014-278	SAPONIFIED
SAH-063075	24448	295-84	0.9040	03-26-84	1014-278	
SAH-063076	24449	295-84	0.5800	06-12-84	1014-279	
SAH-063076	24449	295-84	0.6400	05-23-84	1014-279	
SAH-063076	24449	295-84	0.9000	03-26-84	1014-279	
SAH-063083	24511	295-84	1.9100	03-28-84	1014-281	
SAH-063083	24511	295-84	2.3200	03-28-84	1014-281	
SAH-063084	24512	295-84	3.1600	06-12-84	1014-282	
SAH-063084	24512	295-84	6.3200	03-28-84	1014-282	
SAH-063144	24750	295-84	1.1600	05-10-84	1014-294	SAPONIFIED
SAH-063144	24750	295-84	2.0200	05-10-84	1014-294	
SAH-063145	24755	295-84	>10.0000	05-07-84	1014-295	SAPONIFIED
SAH-063145	24755	295-84	>10.0000	05-10-84	1014-295	
SAH-063146	24756	295-84	>10.0000	05-07-84	1014-296	
SAH-063158	24809	295-84	0.1000	06-04-84	1069-002	SAPONIFIED
SAH-063158	24809	295-84	0.3430	06-04-84	1069-002	
SAH-063159	24810	295-84	0.2250	06-12-84	1069-003	
SAH-063159	24810	295-84	0.2630	06-04-84	1069-003	
SAH-063160	24811	295-84	0.1110	06-04-84	1069-004	SAPONIFIED
SAH-063160	24811	295-84	1.5600	06-04-84	1069-004	
SAH-063161	24821	295-84	0.0020	06-04-84	1069-005	
SAH-063161	24821	295-84	0.0020	06-12-84	1069-005	
SAH-063162	24822	295-84	0.0030	06-04-84	1069-006	
SAH-063162	24822	295-84	0.0035	06-12-84	1069-006	
SAH-063174	24865	295-84	0.0140	06-06-84	1069-013	SAPONIFIED
SAH-063174	24865	295-84	0.0190	06-06-84	1069-013	
SAH-063175	24866	295-84	0.0260	06-06-84	1069-014	
SAH-063229	25075	295-84	>10.0000	08-04-84	1069-036	
SAH-063230	25078	295-84	0.0042	08-01-84	1069-037	
SAH-063231	25079	295-84	0.0058	08-04-84	1069-038	
SAH-063269	25205	295-84	0.0030	09-10-84	1069-053	SAPONIFIED
SAH-063269	25205	295-84	0.0440	09-12-84	1069-053	
SAH-063270	25206	295-84	0.0080	09-05-84	1069-054	
SAH-063271	25208	295-84	0.0320	09-10-84	1069-055	SAPONIFIED
SAH-063271	25208	295-84	0.1450	09-12-84	1069-055	

SAH-064484	F	29413	95-84	0.0320	11-24-86	1149-227
SAH-064744	E	30059	95-84	0.0320	05-01-87	1149-293
SAH-064745	S	30060	95-84	0.0030	05-01-87	1149-294
SAH-064745	S	30060	95-84	0.0030	07-07-87	1149-297
SAH-064815	E	30198	95-84	0.0220	07-07-87	1238-001
SAH-064816	S	30199	95-84	0.0450	07-07-87	1238-002
SAH-063162	S	30203	95-84	0.0080	07-07-87	1238-003
SAH-064745		30765	95-84	0.0020	01-12-88	1238-030
SAH-063366		25496	99-84	1.5800	12-13-84	1069-113
SAH-063549		26082	99-84	7.3100	06-13-84	1069-197
SAH-063548		26080	99-84	3.7750	06-13-84	1069-198
SAH-064933	E	30441	99-84	2.3700	10-08-87	1238-013
SAH-064934	S	30442	99-84	2.6100	10-08-87	1238-014
SAH-064935	E	30447	99-84	0.4130	10-08-87	1238-015
SAH-064936	S	30448	99-84	0.5300	10-13-87	1238-016

ED50 TABLE RAT INVIVO ACETATE INCORPORATION (CSIV-DT65)

THIS FILE IS A CALCULATED ESTIMATE OF THE ED50 (DOSE WHICH REDUCES THE INCORPORATION OF 14C-ACETATE INTO CHOLESTEROL BY 50%) USING ALL THE STUDIES ON THE RELEVANT COMPOUNDS UP TO THE SORT DATE.

LAST UPDATE: 1-06-88 SORT BY: REGNO

COMPOUND	REGNO	DISCL		ED50 mg/kg	DATE mm-dd-yy	REF bk-pg	COMMENTS
SAH-064745	30060	95-84	=	0.016	10-20-87	917-127	N=9
SAH-064745	30765	95-84	=	0.016	02-19-88	917-154	N=3 BS BATCH
SAH-064745	ALL	95-84	=	0.016	02-19-88	917-154	N=12 2BATCHES
SAH-063162	25500	95-84	=	0.019	09-18-87	917-101	N=10
SAH-063162	ALL	95-84	=	0.040	09-18-87		N=19 3BATCHES
SAH-063162	25085	95-84	=	0.079	10-11-84	812-266	N=8
SAH-064119	27563	95-84	=	0.08	05-16-86	869-228	N=6
SAH-064744	30059	95-84	>	0.10	07-14-87	917-090	N=3 -21% @.10
SAH-064816	30199	95-84	=	0.10	10-12-87	917-119	N=6
SAH-064483	29412	95-84	=	0.13	02-06-87	917-024	N=3
SAH-064063	27424	95-84	=	0.19	04-17-86	869-211	N=3
SAH-064309	28718	95-84	=	0.19	11-03-86	869-283	N=3
SAH-063231	25079	95-84	>	0.25	08-30-84	812-250	
SAH-064393	29163	95-84	=	0.25	02-25-87	917-031	N=6
SAH-063161	24821	95-84	>	0.250	11-29-84	812-293	-12@0.25
SAH-063989	27237	95-84	=	0.28	04-04-86	869-195	N=6
SAH-063425	25687	95-84	>	0.3	03-20-85	869-046	N=3
SAH-064305	28701	95-84	>	0.3	11-03-86	869-280	N=3 -34% @.3
SAH-064480	29404	95-84	>	0.3	02-06-87	917-023	N=3 +3% @.3
SAH-063270	ALL	95-84	=	0.308	02-07-85		N=11 2BATCHES
SAH-063270	25206	95-84	=	0.33	10-11-84	812-267	
SAH-063270	25501	95-84	=	0.362	01-21-85	869-018	
SAH-064307	28705	95-84	=	0.47	02-06-87	917-020	N=6
SAH-063159	24810	95-84	>	0.5	06-19-84	812-219	

422

SAH-063162	24822	E95-84	<	0.5	06-19-84	812-219	N=1 -87@0.5
SAH-063175	24866	E95-84	<	0.5	06-19-84	812-220	
SAH-063230	25078	E95-84	>	0.500	11-29-84	812-294	
SAH-064391	29161	E95-84	=	0.51	10-30-86	917-011	N=3
SAH-063035	24317	E95-84	>	0.6	05-07-84	812-201	
SAH-063145	24755	E95-84	>	0.6	05-18-84	812-208	
SAH-063146	24756	E95-84	>	0.6	05-18-84	812-208	
SAH-063174	24865	E95-84	=	0.706	06-19-84	812-220	
SAH-064481	29406	E95-84	>	1.0	02-06-87	917-024	N=3 -28% @1.0
SAH-064482	29411	E95-84	>	1.0	03-18-87	917-041	N=3 -41% @1.0
SAH-064064	27433	E95-84	=	1.05	07-17-86	869-263	N=6
SAH-064204	27793	E95-84	=	1.21	10-02-86	869-298	N=6
SAH-064141	27630	E95-84	>	1.25	02-24-87	917-029	N=6 -24% @1.25
SAH-064308	28717	E95-84	>	1.5	11-03-86	869-283	N=3 -16% @1.5
SAH-064193	27760	E95-84	>	2.4	07-24-86	869-269	N=3 -24% @2.4
SAH-063076	24449	E95-84	<	2.5	05-14-84	812-204	
SAH-063084	24512	E95-84	>	2.5	05-07-84	812-201	
SAH-064933	30441	E99-84	=	~~0.49~~ >1	12-09-87	917-138	N=3 -3% @1.0
SAH-064935	30447	E99-84	≈	~~1.0~~ .49	12-09-87	917-138	N=3

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

#116

WATTANASIN

v. Interference No. 102,648

FUJIKAWA et al. Examiner-in-Chief: M. Sofocleous

WATTANASIN OPPOSITION
TO FUJIKAWA MOTION TO SUPPRESS EVIDENCE

Honorable Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Sir:

Fujikawa have moved to supress the Declaration and Supplemental Declaration of Robert E. Engstrom, the Sandoz researcher who conducted in vivo testing of the Wattanasin compounds in rats, together with Exhibits K-1 and Q which accompany his respective declarations. For the convenience of the Board, copies of these declarations and exhibits (as well as the companion Rodney Slaughter declaration) are appended hereto.

Fujikawa are apparently objecting to the ED_{50} data in the Engstrom declaration (WR 206) because they "constitute the results of not one but two computer manipulations."

Whatever, Fujikawa intend by this, the following things are evident from these declaration and exhibit pages:

1. Pages 334 and 337 (see upper right hand corner of exhibit page) are summary pages generated for each of the screenings carried out starting October 22 and October 29, 1987, respectively, and simply record the type of test solutions utilized;

2. Pages 335-336 and 338-339 show the actual counts in nanocuries per 100 ml. of rat serum obtained for each in vivo testing.

As described more fully by Engstrom at WR 204, the rats were administered the test substance dissolved or as a suspension in a formulation comprising carboxymethylcellulose. The rats were therafter injected with a given amount of radiolabeled sodium acetate. Serum samples were then obtained, the sterols were precipitated, and their radioactivity detected by liquid scintillation spectrometry.

The count in nanoCuries per 100 ml. rat serum is listed down the fifth column of the WX K-1 computer printout. This is the actual raw data obtained from the experiments. From the nanoCurie values received for the six rats in each testing, various computations were made including a "% change" in nanoCurie count. A % change greater than 50% would indicate activity in the assay. (This is a quite stringent assay, where the industry standard, compactin, itself had an ED50 of 3.5, as described by Wattanasin in the Reply Brief at 21-22.)

This data were then inputed into a computer program which generated an ED_{50} number for each compound tested, and the ED_{50} was downloaded in the Sandoz database maintained in the ordinary course of business. (Notice that the database accepted only ED_{50} values which were smaller than 1.) However, in Exhibit Q (at page 418), a Biological Activity Data Report on the Wattanasin compounds shows that compound 64-933 was also calculated to have a specific ED_{50} value of 2.40.

Calculation of ED_{50} in this manner was hardly new to the art as of December 1987. In fact, the whole Engstom in vivo testing procedure appears almost verbatim at page 33 of the Kathawala 1984 European patent publication on fluvastatin, EP 114,027 which was cited as "technological background" against the involved Fujikawa '930 patent (copy of relevant pages also appended).

Even the Fujikawa rebuttal witness, Dr. Homlund, acknowledged that he had "no quarrel with the techniques for determining statistical activity" used by Wattanasin (FR at 204).

Given the art-recognized status of this in vivo assay, it is hard to understand why Fujikawa insist on being provided with computer programs or logorithms so that they can trace the exact progress of each byte of information.

The Board has discretion in applying the rules of evidence, and there is submitted to be no convincing argument that a "rule of reason" should not apply here where the raw data is attested to by the individuals who actually performed the experiments, and the resulting ED_{50} calculation was generated thereon by Sandoz in the ordinary course of business.

Fujikawa affect discomfort that the ED_{50} data for one of 64-933 and 64-936/NA was inadvertently "switched" at page 206 of the original Engstrom declaration. Regardless of whether this typographical error is related in any way to an acknowledged Engstrom "goof" showing up in Exhibit Q, all of the other Wattanasin Exhibits are uniform in assigning an ED_{50} value to

compound 64-935, alone, of 0.49 (see, e.g., Exhibit S-1 (relevant page also appended))[1].

Like any other business or technical information maintained in the ordinary course of business by Sandoz, the ED_{50} data in a sense speaks for itself, and should not be invalidated by a purported lack of foundation, particularly since the underlying computer programs or logorithms are not themselves likely to be comprehensible.

Accordingly, the Fujikawa motion to suppress should be denied.

SANDOZ CORP.
50 route 10
E. Hanover, NJ 07936
Attachments as noted
September 7, 1993

Respectfully submitted,

Diane E. Furman
Attorney for the Party Wattanasin
Registration No. 31,104
201-503-7332

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231, on Sept. 7, 1993
(Date of Deposit)
Diane E. Furman
Name of applicant, assignee, or Registered Representative
Signature
Sept 7, 1993
Date of Signature

1. Fujikawa also attempt an argument surrounding the absence of a sodium salt indication, i.e. "NA", from the Sandoz database printout for 64-936(NA) included in Wattanasin Exhibit K-1 (at 336). However, notice that on pages 203, 205 and 209 of the Wattanasin record "64-936" is used interchangeably with the designation "64-936/NA", just as the Sandoz fluvastatin compound, a sodium salt (technically, "62-320/NA"), is typically referred to as, simply, 62-320 (WR at 484), without the added sodium designation. It is hard to see how Fujikawa could allege difficulty with practices that are customary in the art, and manifested throughout the Wattanasin record in relation to compounds of known strucutre such as fluvastatin.

CERTIFICATE OF SERVICE

It is hereby certified that a true copy of the paper entitled:

WATTANASIN OPPOSITION
TO FUJIKAWA MOTION TO SUPPRESS EVIDENCE

and the attachments thereto were served on counsel for the party Fujikawa et al., this 7th day of September 1993, by postage pre-paid first-class mail addressed to the following:

Oblon, Spivak, McClelland, Maier & Neustadt, P.C.
Attn: Steven B. Kelber, Esq.
1755 South Jefferson Davis Highway
Crystal Square 5, Ste. 400
Arlington, VA 22202

Diane Furman

Diane E. Furman

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(71) Applicant: SANDOZ AG, Lichtstrasse 35, CH-4002 Basel (CH)
(84) Designated Contracting States: BE CH FR GB IT LI LU NL SE

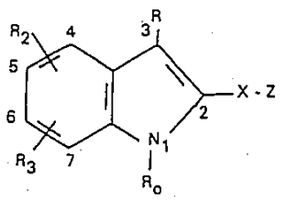
(71) Applicant: SANDOZ-PATENT-GMBH, Humboldtstrasse 3, D-7850 Lörrach (DE)
(84) Designated Contracting States: DE

(71) Applicant: SANDOZ-ERFINDUNGEN Verwaltungsgesellschaft m.b.H., Brunner Strasse 59, A-1235 Vienna (AT)
(84) Designated Contracting States: AT

(72) Inventor: Kathawala, Faizulla Gulamhusein, 39 Woodland Avenue, Mountain Lakes, N.J., 07946 (US)

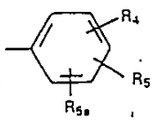
(54) **Analogs of mevalolactone and derivatives thereof, processes for their production, pharmaceutical compositions containing them and their use as pharmaceuticals.**

(57) Compounds of formula I



(I)

wherein one of R and R_6 is



and the other is primary or secondary C_{1-6}alkyl, C_{3-6}cycloalkyl or phenyl-$(CH_2)_m$-,
wherein

R_4 is hydrogen, C_{1-4}alkyl, C_{1-4}alkoxy, (except t-butoxy), trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy,

R_5 is hydrogen, C_{1-3}alkyl, C_{1-3}alkoxy, trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy,

R_{5a} is hydrogen, C_{1-2}alkyl, C_{1-2}alkoxy, fluoro or chloro, and

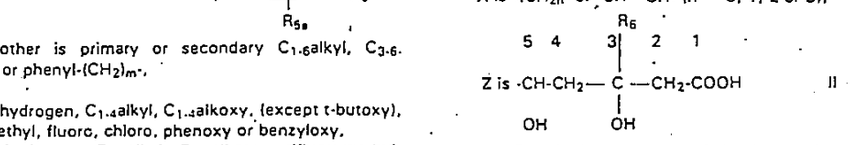
m is 1, 2, or 3,

with the provisos that both R_5 and R_{5a} must be hydrogen when R_4 is hydrogen, R_{5a} must be hydrogen when R_5 is hydrogen, not more than one of R_4 and R_5 is trifluoromethyl, not more than one of R_4 and R_5 is phenoxy and not more than one of R_4 and R_5 is benzyloxy,

R_2 is hydrogen, C_{1-4}alkyl, C_{3-6}cycloalkyl, C_{1-4}alkoxy, (except t-butoxy), trofluoromethyl, fluoro, chloro, phenoxy or benzyloxy,

R_3 is hydrogen, C_{1-3}alkyl, C_{1-3}alkoxy, trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy, with the provisos that R_3 must be hydrogen when R_2 is hydrogen, not more than one of R_2 and R_3 is trifluoromethyl, not more than one of R_2 and R_3 is phenoxy, and not more than one of R_2 and R_3 is benzyloxy,

X is $-(CH_2)_n-$ or $-CH=CH-$ (n = 0, 1, 2 or 3),



(II)

wherein R_6 is hydrogen or C_{1-3}alkyl in free acid form or in the form of a physiologically-hydrolysable and -acceptable ester or a lactone thereof or in salt form.

These compounds are indicated for use as pharmaceuticals particularly for inhibiting cholesterol biosynthesis and treating atherosclerosis.

EP 0 114 027 A1

The isomer of Yang et al. and the isomer disclosed in Reaction Scheme III yield lactones having the 4R,6S configuration and, as a result of epimerization in Reaction X, such compounds having the 4R,6R configuration. Lactones having the 4S,6R and 4S,6S configuration may be obtained from the other isomer whose synthesis is disclosed in Rection Scheme III.

The availability of these intermediates enables synthesis of optically pure end products.

Reaction products both intermediale and final can be isolated and purified in conventional mannr whereby intermediates can where appropriately be employed directly in a subsequent reaction

Mixtures of stereoisomers (cis, trans and optical) may be separated by conventional means at whatever stage of synthesis is appropriate. Such methods include re-crystalisation, chromatography, formation of esters with optically pure acids and alcohols or of amides and salts (cf also Sommer et al. J.A.C. S 80, 3271 (1958)) with subsequent reconversion under retention of optical purity. For example diastereoisomeric (-)-α-naphthyl-phenylmethylsilyl derivatives of a lactone type end product of formula I may be separated on a silica solumn having covalently bound L-phenylglycine (eluant n-hexane/acetate : 1/1).

Salts may be prepared in conventional manner from free acids, lactones and esters and vice-versa. Whilst all salts are covered by the invention pharmaceutically acceptable salts especially sodium, potassium and ammonium particularly sodium salts are preferred.

The various forms of the compounds of formula I are by virtue of their interconvertability useful as intermediates in addition to the use set out below.

Also within the scope of this invention are the intermediates of formulae V, X, XI, XII, XX, XXIV, XXVI-XXVIII and XXIXB-XXIXD. The preferences for each variable are the same as those set forth for the compounds of formula I, with the preferred groups of such compounds including those that correspond to Groups (i)-(xiii) and (xxxix)-lxxxviii) (for

formulae V, X-XII, XX and XXIXB-XXIXD) and Groups (xiv)-(xx), (xxxiii)-(xxxviii) and (lxxxix)-(cxiv) for formulae XXVI-XXVIII) to the extent consistent therewith.

The compounds of formula I possess pharmacological activity in particular they are inhibitors of 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase and as a consequence inhibitors of cholesterol biosynthesis as demonstrated in the following three tests.

Test A: In Vitro Microsomal Assay of HMG-CoA Reductase Inhibition:

200 ul. aliquots (1.08-1.50 mg./ml.) of rat liver microsomal suspensions, freshly prepard from male Spargue-Dawley rats (150-225 g. body weight), in Buffer A with 10 mmol. dithiothreitol are incubated with 10 ul. test substance dissolved in dimethylacetamide and assayed for HMG-CoA reductase activity as described by Ackerman et al., J. Lipid Res. 18, 408-413 (1977). In the assay the microsomes are the source of the HMG-CoA reductase enzyme which catalyses the reduction of HMG-CoA to mevalonate. The assay employs a chloroform extraction to separate the product, [^{14}C]mevalonolactone, formed by the HMG-CoA reductase reaction from the substrate, [^{14}C]HMG-CoA. [^{3}H]mevalono-lactone is added as an internal reference. Inhibition of HMG-CoA reductase is calculated from the decrease in specific activity [^{14}C/^{3}H]mevalonate) of test groups compared to controls.

Test B: In Vitro Cell Culture Cholesterol Biosynthesis Screen:

The cell culture is prepared as follows: Stock monolayer cultures of the Fu5AH rat hepatoma cell line (originally obtained from G. Rothblat; see Rothblat, Lipids 9, 526-535 (1974) are routinely maintained in Eagle's Minimum Essential Medium (EMEM) supplemented with 10% fetal bovine serum (FBS) in 75 cm^2 tissue culture flasks. For these studies, when the cultures reach

confluence, they are removed by mild enzymatic treatment with 0.25% trypsin in Hanks' balanced salt solution (without calcium and magnesium). After centrifugation of the cell suspension and aspiration of the enzymatic solution, a cell pellet is resuspended in an appropriate volume of media for seeding into 60 mm. tissue culture dishes. The cultures are incubated at 37°C in an atmosphere of high humidity and 5% carbon dioxide. When the cultures are confluent (approximately 5 days), they are ready for use. The culture media is aspirated from the dishes and replaced with 3 ml of EMEM suplemented with 5 mg/ml of dilipidized serum protein (DLSP) prepared by the method of Rothblat et al., In Vitro 12, 554-557 (1976). Replacement of the FBS with DLSP has been shown to stimulate the incorporation of [^{14}C]acetate into sterol by removing the exogenous sterol supplied by the FBS, thereby requiring the cells to synthesized sterol. Enthanced 3-hydroxy-3-methylglutaryl Coenzyme A reductase (HMG-CoA reductase) activity is measurable in the cells in response to the lack of exogenous sterol. Following approximately 24 hours incubation at 37°C in the DLSP supplemented media, the assay is initiated by the addition of 3μCi of [^{14}C]acetate and the test substances solubilized in dimethylsulfoxide (DMSO) or distilled water. Solvent controls and compactin-treated controls are always prepared. Triplicate 60mm. tissue culture dishes are run for each group. After 3 hours incubation at 37°C, the cultures are examined microscopically using an inverted phase contrast microscope. Notations are made of any morphological changes which may have occurred in the cultures. The media is aspirated and the cell layer is gently washed twice with 0.9% sodium chloride solution (saline). The cell layer is then harvested in 3 ml. of 0.9% saline by gentle scraping with a rubber policeman and transferred to a clean glass tube with Teflon lined cap. The dishes are rinsed with 3 ml. of 0.9% saline and rescraped, and the cells are combined with the first harvest. The tubes are centrifuged at 1500 r.p.m. for 10 minutes

in an IEC PR-J centrifuge, and the supernatant is asperated.

The cells are then extracted as follows: One ml. of 100% ethanol is added to the cell pellet followed by sonication for 10 seconds with a "LO" setting of 50 on a Bronwell Biosonik IV. One hundred ul. are taken for protein determination. One ml. of 15% potassium hydroxide (KOH) is added, and the samples are thoroughly vortexed. Saponification is accomplished by heating the ethanol-KOH treated samples at 60°C for 60 minutes in a water bath. Following dilution of the samples with 2ml. of distilled water, they are extracted three times with 7 ml. of petroleum ether. The petroleum ether extracts are then washed three times with 2 ml. of distilled water and finally taken to dryness under a stream of nitrogen.

The obtained samples are then analyzed by thin layer chromatography (TLC) as follows: Residues from the petroleum ether extraction are taken up in a small volume of hexane and spotted on silica gel 60 TLC plates (E. Merck). Development of the plates is carried out in a 150 parts by volume hexane: 50 parts by volume diethyl ether: 5 parts by volume galcial acetic acid solvent system using a three phase development procedure. Visualization is accomplished in an iodine vapor chamber. The plates are divided into five sections such that each section contains the molecules having the following approximate Rf values: section 1- 0-0.4, section 2- 0.4-0.55, section 3- 0.55-0.7, section 4- 0.7-0.9 and section 5- 0.9-1.0. Section 2 contains the non-saponifiable sterols. The five sections of the TLC plates are scraped into scintillation vials. Blanks are also prepared from scrapings of chromatographed non-labelled standards. ACS® scintillation cocktail is added, and the radioactivity is determined in a liquid scintillation spectrometer. [^{14}C]hexadecane standards are used to determine counting efficiencies. The total protein content of the samples is determined employing the Bio-Rad Protein Assay System.

The results are reported as disintegrations per minute per mg protein (d.p.m./mg protein) for each of the live TLC sections. Mean d.p.m./mg protein ± standard error of the mean are compared for percentage change (%Δ) and statistical significance with solvent control means. TLC section 2 data is taken as a measure of HMG-CoA reductase activity inhibition.

Test C: In Vivo Cholesterol Biosynthesis Inhibition Tests: In vivo studies utilize male Wistar Royal Hart rats weighing 150±20 g which have been kept for 7-10 days on an altered light cycle (6:30 a.m. - 6:30 p.m. dark) housed two per cage and fed powdered Purina Rat Chow and water ad libitum. Three hours before the diurnal maximum of cholesterol synthesis at mid-dark, the rats are administered the test substances dissolved or as a suspension in 0.5% carboxymethylcellulose in a volume of 1 ml/100 g body weight. Controls receive vehicle alone. One hour after receiving the test substance, the rats are injected intraperitoneally with about 25 μCi/100 g body weight of sodium [1-^{14}C]acetate 1-3 mCi/mmol. Two hours after mid-dark, blood samples are obtained under sodium hexobarbitol anesthesia and the serum separated by centrifugation.

Serum samples are saponified and neutralized, and the 3β-hydroxy sterols are precipiated with digitonin basically as described by Sperry et al., J. Biol. Chem. 187, 97 (1950). The [^{14}C]digitonides are then counted by liquid scintillation spectrometry. After correcting for efficiencies, the results are calculated in nCi (nanocuries) of sterol formed per 100 ml of serum. Inhibition of sterol synthesis is calculated from the reduction in the nCi of sterols formed from test groups compared to controls.

The compounds are thus indicated for use as hypolipoproteinemic and anti-atherosclerotic agents.

An indicated suitable daily dosage for use in the treatment of hyperlipoproteinemia and athersclerosis is from about

1 to 2000 mg preferably 1.5 to 100 mg suitably administered in divided dosages of 0.25 to 1000 mg preferably 0.4 to 50 mg two to four times daily or in retard form.

They may be administered in free acid form or in the form of a physiologically-hydrolysable and -acceptable ester or a lactone thereof or in pharmaceutically acceptable salt form whereby the various forms have activities in the same range.

The invention therefore also concerns a method of treating hyperlipoproteinemia or atherosclerosis by administration of a compound of formula I in free acid form or in the form of a physiologically-hydrolysable and -acceptable ester or a lactone thereof or in pharmaceutically acceptable salt form as well as such compounds for use as pharmaceuticals e.g. as hypolipoproteinemic and anti-atherosclerotic agents.

The compounds may be administered alone, or in admixture with a pharmaceutically acceptable diluent or carrier, and, optionally other excipients, and administered orally in such forms as tablets, elixirs, capsules or suspensions or parenterally in such forms as injectable solutions or suspensions.

The preferred pharmaceutical compositions from the standpoint of ease of preparation and administration are solid compositions, particularly tablets and hard-filled or liquid-filled capsules.

Such compositions also form part of the invention.

The following examples, in which all temperatures are in °C illustrate the invention.

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

WATTANASIN
v.
Fujikawa et al.

Interference No. 102,648, 102,975
Examiner-in-Chief: M. Sofocleous

DECLARATION OF ROBERT G. ENGSTROM PURSUANT TO 37 CFR §1.672

I, Robert G. Engstrom, do hereby declare as follows:

(1) That I have been employed by Sandoz Pharmaceuticals Corporation since 1964 as a Research Scientist. Among my responsibilities has been supervising the testing of new HMG Co-A reductase inhibiting compounds synthesized by Sandoz chemists.

(2) That all activities referred to in this Declaration took place in the United States.

IN VIVO TESTING OF
WATTANASIN COMPOUNDS 64-933, 64-935 and 64-936/Na

1. On or before October 29, 1987, in my laboratory under my supervision, Rodney Slaughter began performing the below-indicated protocol on compounds 64-933, 64-935 and 64-936/Na:

In vivo studies utilized male Wistar Royal Hart rats weighing 150 ± 20 g. which have been kept for 7-10 days on an altered light cycle (6:30 A.M. - 6:30 P.M. dark) housed two per cage and fed powdered Purina Rat Chow and water ad libitum. Three hours before the diurnal maximum of cholesterol systhesis at mid-day the rats were administered the test substances dissolved or as a suspension in 0.5% carboxymethylcellulose in a volume of 1 ml./100 g. body weight. Controls received vehicle alone. One hour after receiving the test substance, the rats were injected intraperitoneally with about 25 μCi/100 g. body weight of sodium [1-^{14}C]acetate 1-3 mCi/mmol. Two hours after mid-dark, blood samples were obtained under sodium hexobarbitol anesthesia, and the serum was separated by centrifugation. The resulting serum samples were saponified and neutralized, and the 3β-hydroxy sterols were precipitated with digitonin basically as described by Sperry et al., J. Biol. Chem. 187,97(1950). The [^{14}C]digitonides were counted by liquid scintillation spectrometry. The assay is based on the conversion of ^{14}C-acetate to ^{14}C-cholesterol in vivo.

2. The counts in DPM of digitonin precipitable sterol (β-hydroxy sterol, mostly cholesterol in the rat) were entered by Rodney Slaughter into my computer program, which converted them to nCi of sterol found per 100 ml. of serum at 4 hours after the injection of the ^{14}C-acetate.

3. I have reviewed Exhibit K-1 hereto, which comprises true copies of pages 133, 134, and 135, 136, 137 and 138 of R. Slaughter's Laboratory Notebook #917. I witnessed Rodney Slaughter's signature on each of these pages, and each page bears my true signature as a witness.

4. Notebook pages 133-135 contain true copies of a computer printout for the protocol and results in nCi/dl of Study #H318, which was commenced on October 22, 1987. I initialed the first page of this computer printout on or before October 22, 1987. This computer printout on page 135 indicates that an in vivo assay of compound 64-936 was started on October 22, 1987.

5. Notebook pages 136-138 contain true copies of a computer printout for the protocol and results in nCi/dl of Study #H319, which was commenced on October 29, 1987. I initialed the first page of this computer printout on page 136 on or prior to October 29, 1987. This computer printout on page 137-138 indicates that an in vivo assay of compound 64-933 and 64-935 was started on October 29, 1987.

6. Both studies were completed on or prior to December 9, 1987, the date indicated at the bottom of pages 135 and 138.

7. It was my responsibility to enter the nCi/dl data into a separate computer program which calculates the ED_{50} values of a compound tested in vivo from the reduction in the nCi of sterols formed from test groups compared to controls for each assay, and forms a database of the ED_{50} values. On or before December 9, 1987, I entered the data for compounds 64-933, 64-935 and 64-936/Na.

8. The 1st page of Exhibit K-1 comprises a true copy of part of the ED_{50} database. This page indicates that the ED_{50} for compounds 64-933, 64-935 and 64-936/Na was in the system as of December 9, 1987. Therefore, the information was available to other Sandoz employees having access to the computer database as of December 9, 1987.

The ED50 for these compounds are:

COMPOUND	ED_{50} (mg/kg)
64-933	0.49
64-935	>1.0
64-936	>1.0

. . .

The undersigned declares further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

I hereby subscribe my name to the foregoing DECLARATION this 13 day of November 1992.

Robert G. Engstrom

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

WATTANASIN
v. Interference Nos. 102,648, 102,975
FUJIKAWA et al. Examiner-in-Chief: M. Sofocleous

DECLARATION OF RODNEY SLAUGHTER PURSUANT TO 37 CFR §1.672

I, Rodney Slaughter, do hereby declare as follows:

(1) That I have been employed by Sandoz Pharmaceuticals Corporation since 1982, and during the time periods referred to herein, I worked in the Department of Lipid Metabolism.

(2) That it has been my responsibility to carry out an in vivo testing program of various HMG-CoA reductase inhibitor compounds, including Wattanasin compounds 64-933, 64-935 and 64-936.

(3) That all of the below-indicated activities took place in the United States.

IN VIVO TESTING OF
WATTANASIN COMPOUNDS 64-933, 64-935 and 64-936

1. On or before October 29, 1987, I carried out the below-indicated protocol on compounds 64-933, 64-935 and 64-936:

In vivo studies utilized male Wistar Royal Hart rats weighing 150 ± 20 g. which have been kept for 7-10 days on an altered light cycle (6:30 A.M. - 6:30 P.M. dark) housed two per cage and fed powdered Purina Rat Chow and water ad libitum. Three hours before the diurnal maximum of cholesterol systhesis at mid-day the rats were administered the test substances dissolved or as a suspension in 0.5% carboxymethylcellulose in a volume of 1 ml./100 g. body weight. Controls received vehicle alone. One hour after receiving the test substance, the rats were injected intraperitoneally with about 25 μCi/100 g. body weight of sodium [1-^{14}C]acetate 1-3 mCi/mmol. Two hours after mid-dark, blood samples were obtained under sodium hexobarbitol anesthesia, and the serum was separated by centrifugation. The resulting serum samples were saponified and neutralized, and the 3β-hydroxy sterols were precipitated with digitonin basically as described by Sperry et al., J. Biol. Chem. 187,97(1950). The [^{14}C]digitonides were counted by liquid scintillation spectrometry. The assay is based on the conversion of ^{14}C-acetate to ^{14}C-cholesterol in vivo.

2. I entered the counts in DPM of digitonin precipitable sterol (β-hydroxy sterol, mostly cholesterol in the rat) into a computer program, which converted them to nCi of sterol found per 100 ml. of serum at 4 hours after the injection of the ^{14}C-acetate.

3. I have reviewed Exhibit K-1 hereto, which comprises true copies of pages 133, 134, 135, 136, 137 and 138 of my Laboratory Notebook #917.

4. Notebook pages 133-135 contain true copies of a computer printout for the protocol and results in nCi/dl of Study #H318, which I started on October 22, 1987. These pages contain the date of 10/22/87 at the top in my handwriting.

5. Notebook pages 136-138 contain true copies of a computer printout for the protocol and results in nCi/dl of Study #H319, which I started on October 29, 1987. These pages contain the date of 10/29/87 at the top in my handwriting.

6. Both studies were completed on or prior to December 9, 1987, the date indicated at the bottom of the computer printouts on pages 135 and 138.

7. It was my practice to paste the computer printouts into my notebook and to sign the notebook page when I did this.

The undersigned declares further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

I hereby subscribe my name to the foregoing DECLARATION this 13 day of November 1992.

Rodney Slaughter

10/22/87 Proj. #3134

From- 134

Title Cholesterol Synthesis Inhibition Screen

135

334

CHOLESTEROL BIOSYNTHESIS (1)

LIPID METABOLISM DEPARTMENT
HMGR SCREENING UNIT
Sandoz Research Institute

To: Dr. D. Weinstein, Departmenthead
Mr. R. Slaughter, Responsible Technician
From: Mr. R. Engstrom, Responsible Investigator
CC: D.N., M.L.R., ARC

STUDY# HS18
STUDY ON 10/22/87
BK.REF. 917-33
APPROVAL
DATE 10/21/87
GEN. ARC86-006

Title: In vivo single dose assay to test for inhibition of biosynthesis by compounds: 63-748, 64-8AA, 64-836

Purpose: Determine the invivo effects of test compounds in rats on cholesterol biosynthesis.

Experimental design: IN VIVO CHOLESTEROL BIOSYNTHESIS INHIBITION DT0065 Invivo single dose assay or inhibition of Reference method: 340/021. Stock solutions and dilutions prepared in 0.5% CMC, administered p.o. at 1ml/100gm weight. Rats died via carotid incision using hexobarbital anesthesia. Animal use will be in compliance with ARC regulations. Duration = 1 hr. No/group = 6. No of groups = 14. UCR rats.

Rats	COMPOUND	REGNO	DOSE mg/kg	STOCK mg/20ml	WORKING SOLUTION ml stock q.s. to 15ml
1-6	Control	------	------	------	----------
7-12	63-748	26668	1	2	UNDILUTED
13-18	"	"	0.3	-	4.5
19-24	"	"	0.1	-	1.5
25-30	64-8AA	30280	0.3	2	4.5
31-36	"	"	0.1	-	1.5
37-42	"	"	0.03	-	0.45
43-48	64-836	30488	1	2	UNDILUTED
49-54	"	"	0.3	-	4.5
55-60	"	"	0.1	-	1.5
61-66	64-810	30559	0.3	2	4.5
67-72	"	"	0.1	-	1.5
73-78	"	"	0.03	-	0.45
79-84	Control	------	------	------	----------

WATTANASIN EXHIBIT
K-1
Wattanasin v. Fujikawa et al.
Interference No. 102,648
Interference No. 102,975

Performed by- [signature]

Witness- [signature]

Cont'd to- 135

134 Title- Cholesterol Synthesis Inhibition Screen

Date 10/22/87 Prof 12 3

Cont'd From 133

335

IN VIVO CHOLESTEROL SYNTHESIS INHIBITION SCREEN #316

RAT COMPOUND REGNO DOSE mG/KG SIA STATISTICS

BLANK
TAC-STANDARD 20178 X EFFIC= .99

1	CONTROL			493			
2	CONTROL			677	MEAN =		537.7
3	CONTROL			590	STD =		128.6
4	CONTROL			455	SE =		37.1
5	CONTROL			490			
6	CONTROL			365			
79	CONTROL			462			
80	CONTROL			316			
81	CONTROL			559			
82	CONTROL			650			
83	CONTROL			610			
84	CONTROL			745			
8	63-748	25688	1.00	170	MEAN =		155.9
9	63-748	25688	1.00	278	STD =		73.1
10	63-748	25688	1.00	113	SE =		32.7
11	63-748	25688	1.00	113	t =		7.7
12	63-748	25688	1.00	106	P		<.01
7	63-748	25688	1.00	528*	%CHG =		-71
13	63-748	25688	.300	386	MEAN =		319.3
14	63-748	25688	.300	355	STD =		66.3
15	63-748	25688	.300	391	SE =		39.5
17	63-748	25688	.300	159	t =		4.0
18	63-748	25688	.300	253	P		<.01
16	63-748	25688	.300	794*	%CHG =		-40.6
19	63-748	25688	.100	348	MEAN =		456.7
20	63-748	25688	.100	726	STD =		213.5
21	63-748	25688	.100	310	SE =		87.2
22	63-748	25688	.100	650	t =		0.8
23	63-748	25688	.100	536	P		N.S.
24	63-748	25688	.100	178	%CHG =		-14.7
25	64-844	30280	.300	286	MEAN =		185.8
26	64-844	30280	.300	170	STD =		57.3
27	64-844	30280	.300	155	SE =		23.4
28	64-844	30280	.300	126	t =		8.5
29	64-844	30280	.300	17A	P		<.01
30	64-844	30280	.300	101	%CHG =		-65.2
31	64-844	30280	.100	306	MEAN =		219.8
32	64-844	30280	.100	272	STD =		69.9
33	64-844	30280	.100	195	SE =		39.9
35	64-844	30280	.100	157	t =		8.7
36	64-844	30280	.100	166	P		<.01
34	64-844	30280	.100	695*	%CHG =		-58.1

Performed by- Todd A. Blankenship

Witness- R Luther

Cont'd to- 135

Date 10/22/87 Proj# 3,4

Cont'd From- 134

Title- Cholesterol Synthesis Inhibition Screen

135

336

IN VIVO CHOLESTEROL SYNTHESIS INHIBITION SCREEN HS18

RAT	COMPOUND	REGNO	DOSE mg/kg	nCi/dl	STATISTICS	
37	64-844	30280	.030	354	MEAN =	419.7
38	64-844	30280	.030	518	STD =	138.6
39	64-844	30280	.030	639	SE =	56.6
40	64-844	30280	.030	248	t =	1.7
41	64-844	30280	.030	358	p	N.S.
42	64-844	30280	.030	402	%CHG =	-21.9
43	64-936	30486	1.00	580	MEAN =	489.4
44	64-936	30486	1.00	642	STD =	132.8
45	64-936	30486	1.00	280	SE =	54.2
46	64-936	30486	1.00	328	t =	0.7
47	64-936	30486	1.00	532	p	N.S.
48	64-936	30486	1.00	513	%CHG =	-9.0
49	64-936	30486	.300	167	MEAN =	325.7
50	64-936	30486	.300	231	STD =	165.0
51	64-936	30486	.300	566	SE =	67.4
52	64-936	30486	.300	272	t =	2.7
53	64-936	30486	.300	223	p	<.02
54	64-936	30486	.300	473	%CHG =	-38.2
55	64-936	30486	.100	495	MEAN =	416.5
56	64-936	30486	.100	181	STD =	166.8
57	64-936	30486	.100	639	SE =	68.9
58	64-936	30486	.100	596	t =	1.8
59	64-936	30486	.100	357	p	N.S.
60	64-936	30486	.100	438	%CHG =	-22.5
61	62-320	30559	.300	72	MEAN =	67.5
62	62-320	30559	.300	89	STD =	12.1
63	62-320	30559	.300	72	SE =	5.4
64	62-320	30559	.300	53	t =	12.5
65	62-320	30559	.300	64	p	<.01
66	62-320	30559	.300	55	%CHG =	-87.5
67	62-320	30559	.100	135	MEAN =	185.3
68	62-320	30559	.100	232	STD =	51.1
70	62-320	30559	.100	198	SE =	22.8
71	62-320	30559	.100	109	t =	8.5
69	62-320	30559	.100	149	p	<.01
72	62-320	30559	.100	138	%CHG =	-69.3
73	62-320	30559	.030	323	MEAN =	351.2
74	62-320	30559	.030	380	STD =	173.3
75	62-320	30559	.030	77	SE =	70.8
76	62-320	30559	.030	276	t =	3.8
77	62-320	30559	.030	463	p	<.05
78	62-320	30559	.030	277	%CHG =	-34.7

* = rejected by "Q" test Computed 12-09-87

- = LACK OF SAMPLE

Performed by- [signature]

Witness- [signature]

Cont'd to-

136 Title- Cholesterol Synthesis Inhibition Screen

Date 10/29/87 Proj: 3,9

Cont'd From-

337

CHOLESTEROL BIOSYNTHESIS INHIBITION SCREEN

LIPID METABOLISM DEPARTMENT
HNGR SCREENING UNIT
Sandoz Research Institute
To: Dr. D. Weinstein, Departmenthead
Mr. R. Slauxhter, Responsible Technician
From: Mr. E. Engstrom, Responsible Investigator
CC: D.N., M.L.E., ARC

STUDY # HS19
STUDY ON 10/29/87
SK.REF. 917-136
APPROVAL
DATE 10/31/87
GEN. ARC#86-004

Title: In vivo single dose assay to test for inhibition of biosynthesis by compounds: 84-298, 84-935, 83-835

Purpose: Determine the invivo effects of test compounds in rats on cholesterol biosynthesis.

Experimental design: IN VIVO CHOLESTEROL BIOSYNTHESIS INHIBITION
DT0065 Invivo single dose assay of inhibition of
Reference method: 740/001. Stock solutions and dilutions
prepared in 0.5% CMC, administered p.o. at 1ml/100gm weight.
Rats bled via carotid incision using hexobarbital anesthesia.
Animal use will be in compliance with ARC regulations.
Duration = 1 hr. No/group = 6. No of groups = 14. UCR rats.

RATS	COMPOUND	BSGNO	DOSE mg/kg	STOCK mg/20ml	WORKING SOLUTION ml stock q.s. to 15ml
1-6	Control	------	------	------	------
7-12	84-298	29277	1	1	UNDILUTED
13-18	"	"	0.3	-	4.5
19-24	"	"	0.1	-	1.5
25-30	84-935	30447	1	1	UNDILUTED
31-36	"	"	0.3	-	4.5
37-42	"	"	0.1	-	1.5
43-48	84-935	30441	1	1	UNDILUTED
49-54	"	"	0.3	-	4.5
55-60	"	"	0.1	-	1.5
61-66	83-835	30656	0.3	1	4.5
67-72	"	"	0.1	-	1.5
73-78	"	"	0.03	-	0.45
79-84	Control	------	------	------	------

Performed by-

Witness-

Cont'd to- 337

Date 1/13/71 Proj.

Cont'd.From-

Title- [illegible]

137

338

IN VIVO CHOLESTEROL SYNTHESIS INHIBITION SCREEN H313

RAT	COMPOUND	REGNO	DOSE mg/kg		nCi/dl		
	BLANK				7		
	14C-STANDARD				20176 x EFFIC=		98
1	CONTROL				983		
2	CONTROL				515	MEAN =	671.8
3	CONTROL				848	STD =	211.0
4	CONTROL				578	SE =	80.9
5	CONTROL				534		
6	CONTROL				354		
79	CONTROL				755		
80	CONTROL				947		
81	CONTROL				814		
82	CONTROL				549		
83	CONTROL				872		
84	CONTROL				714		
7	64-298	28277	1.00		203	MEAN =	151.7
8	64-298	28277	1.00		381	STD =	113.8
9	64-298	28277	1.00		82	SE =	46.4
10	64-298	28277	1.00		78	t =	6.6
11	64-298	28277	1.00		71	P	<.01
12	64-298	28277	1.00		115	%CHG =	-77
13	64-298	28277	.300		311	MEAN =	335.1
14	64-298	28277	.300		284	STD =	81.4
15	64-298	28277	.300		257	SE =	32.2
16	64-298	28277	.300		307	t =	8.3
17	64-298	28277	.300		114	P	<.01
18	64-298	28277	.300		157	%CHG =	-65.0
19	64-298	28277	.100		581	MEAN =	385.7
20	64-298	28277	.100		387	STD =	81.5
21	64-298	28277	.100		248	SE =	33.3
22	64-298	28277	.100		392	t =	4.1
23	64-298	28277	.100		499	P	<.01
24	64-298	28277	.100		425	%CHG =	-42.1
25	64-933	30447	1.00		836	MEAN =	438.1
26	64-933	30447	1.00		275	STD =	253.4
27	64-933	30447	1.00		198	SE =	103.5
28	64-933	30447	1.00		584	t =	2.0
29	64-933	30447	1.00		258	P	N.S.
30	64-933	30447	1.00		447	%CHG =	-33.5
31	64-933	30447	.300		830	MEAN =	557.4
32	64-933	30447	.300		646	STD =	100.5
33	64-933	30447	.300		525	SE =	41.0
34	64-933	30447	.300		598	t =	1.6
35	64-933	30447	.300		388	P	N.S.
36	64-933	30447	.300		818	%CHG =	-17.0

Performed by-

138

Title-

Date 12/24/87 Proj.

Cont'd From 137

INVIVO CHOLESTEROL SYNTHESIS INHIBITION SCREEN H019

RAT	COMPOUND REGNO	DOSE mg/kg	nCi/dl	STATISTICS	
37	64-933	30447	.100	555	MEAN = 547.0
38	64-933	30447	.100	735	STD = 147.2
39	64-933	30447	.100	370	SE = 60.1
40	64-933	30447	.100	378	t = 1.5
41	64-933	30447	.100	581	p N.S.
42	64-933	30447	.100	552	%CHG = -18.6
43	64-935	30441	1.00	182	MEAN = 230.0
44	64-935	30441	1.00	307	STD = 78.2
45	64-935	30441	1.00	198	SE = 31.9
46	64-935	30441	1.00	321	t = 6.4
47	64-935	30441	1.00	124	p <.01
48	64-935	30441	1.00	281	%CHG = -85.8
49	64-935	30441	.300	778	MEAN = 472.2
50	64-935	30441	.300	282	STD = 179.5
51	64-935	30441	.300	520	SE = 73.3
52	64-935	30441	.300	413	t = 2.1
53	64-935	30441	.300	344	p N.S.
54	64-935	30441	.300	438	%CHG = -29.7
55	64-935	30441	.100	411	MEAN = 428.2
56	64-935	30441	.100	320	STD = 119.1
57	64-935	30441	.100	298	SE = 48.6
58	64-935	30441	.100	425	t = 3.1
59	64-935	30441	.100	621	p <.02
60	64-935	30441	.100	495	%CHG = -36.3
61	62-320	30559	.300	90	MEAN = 165.6
62	62-320	30559	.300	107	STD = 107.1
63	62-320	30559	.300	222	SE = 43.7
64	62-320	30559	.300	60	t = 8.6
65	62-320	30559	.300	217	p <.01
66	62-320	30559	.300	327	%CHG = -75.5
67	62-320	30559	.100	262	MEAN = 331.7
68	62-320	30559	.100	434	STD = 185.7
70	62-320	30559	.100	589	SE = 74.1
71	62-320	30559	.100	188	t = 3.5
69	62-320	30559	.100	225	p <.01
72	62-320	30559	.100	804	%CHG = -50.9
73	62-320	30559	.030	421	MEAN = 445.1
74	62-320	30559	.030	472	STD = 94.1
75	62-320	30559	.030	571	SE = 38.4
76	62-320	30559	.030	374	t = 3.1
77	62-320	30559	.030	517	p <.01
78	62-320	30559	.030	815	%CHG = -33.6

Computed 12-09-87

Performed by-

Witness- R Slaughter

Cont'd to-

64562	29851	220-85	>	.1	09-JUN-87	917-065
64569	29852	220-85	=	.16	15-JUN-87	917-081
64602	29743	101-85	>	.3	05-MAY-87	917-050
64602	29743	101-85	>	.3	05-MAY-87	917-050
64604	29744	101-85	>	.3	05-MAY-87	917-051
64604	29744	101-85	>	.3	05-MAY-87	917-051
64604	29745	101-85	=	.48	14-JUL-87	917-086
64508	29756	298-85	>	7.8	15-MAY-87	917-055
64638	29835	570-83		.34	09-DEC-87	917-140
64639	29836	570-83	>	1	09-JUN-87	917-066
64640	29839	367-86	>	1	09-JUN-87	917-068
64641	29840	367-86	>	1	09-JUN-87	917-068
64642	29841	367-86	>	1	09-JUN-87	917-089
64673	29904	280-85	=	2.6	18-SEP-87	917-111
64686	29927	387-85	>	10	18-SEP-87	917-113
64691	29942	366-86		.58	16-DEC-87	917-141
64722	30004	280-85	=	.2	23-OCT-87	917-126
64723	30627	100-85	=	.16	19-FEB-88	917-159
64723	30877	100-85	=	.09	19-FEB-88	917-159

SAHNUM	REGNO	PATENT	R	ED50	EDATE	REF
64723	30766	100-85	=	.22	19-FEB-88	917-159
64723	30009	100-85	=	.36	18-SEP-87	917-107
64744	30059	295-84	>	.1	14-JUL-87	917-090
64745	30765	295-84	=	.016	19-FEB-88	917-154
64745	30060	295-84	=	.016	20-OCT-87	917-127
64747	30067	298-84	=	.11	01-JUL-87	917-087
64748	30068	298-84	=	.04	19-FEB-88	917-155
64792	30146	260-85	=	.74	13-OCT-87	917-123
64816	30199	295-84	=	.1	12-OCT-87	917-119
64844	30280	384-85	=	.07	09-DEC-87	917-135
64844	30769	384-85	=	.08	19-FEB-88	917-167
64896	30378	366-87	>	.3	06-OCT-87	917-119
64897	30379	366-87	>	.3	06-OCT-87	917-120
64906	30393	280-85	=	.045	05-JAN-88	917-150
64906	30772	280-85	=	.1	15-JAN-88	917-155
64933	30441	299-84	>	1	09-DEC-87	917-138
64935	30447	299-84	=	.49	09-DEC-87	917-136
64936	30488	299-84	>	1	09-DEC-87	917-135
64999	30623	298-84	=	.1	19-FEB-88	917-168
65002	30629	101-85	=	.76	05-JAN-88	917-144
65003	30630	101-85	=	.09	19-FEB-88	917-159

SAHNUM	REGNO	PATENT	R	ED50	EDATE	REF
65003	30902	101-85	=	.06	19-FEB-88	917-170
86665	25887	102-82	>	10	06-MAY-87	917-056
87469	26362	101-82	>	10	06-MAY-87	917-056
89825	29587	101-82	>	10	06-MAY-87	917-057
317223	24022		>	16	20-MAR-84	312-183
880349	29591	102-82	>	10	18-AUG-87	917-098
880586	29588	102-82	>	10	18-AUG-87	917-098
880820	29589	102-82	>	10	18-AUG-87	917-098

148 records selected.

SQL>

Case No. 600-7101/CONT/INT.(5)
Patent -

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

WATTANASIN
v.
FUJIKAWA et al.

Interference Nos. 102,648, 102,975
Examiner-in-Chief: M. Sofocleous

SUPPLEMENTAL DECLARATION OF ROBERT G.ENGSTROM PURSUANT TO 37 CFR §1.672

I, Robert G. Engstrom, do hereby declare as follows:

All of the below-indicated activities took place in the United States.

Exhibit Q comprises a true copy of a Biological Activity Data Report dated May 24, 1988 which I sent to the Patent Department concerning the compounds of PD 299/84, together with a computer printout of the Sandoz database dated May 23, 1988. The printout contains IC_{50} and some ED_{50} values for compounds of Patent Disclosure 295/84 and compounds of the subject Patent Disclosure 299/84.

(I note that I became aware of a computer entry error comprising the inadvertent "switching" of the ED_{50} data for compounds 64-933 and 64-935. The corrections on the printout are in my handwriting and would have been made on or about May 23, 1988.)

The undersigned declares further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful

false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

I hereby subscribe my name to the foregoing Declaration this 19 day of February, 1993.

Robert Engstrom

Robert Engstrom

Q

BIOLOGICAL ACTIVITY DATA REPORT (FOR PATENT DEPT.)

INVENTOR: S. Wattanasin DISCL. NO.: 299-84 418

ATTORNEY: M. Kassenoff DATE: May 24, 1988

1. ACTIVITY TO BE DISCLOSED:
Inhibition of cholesterol biosynthesis, antihypercholesteremic, antiatherosclerotic

2. IF ANY COMPOUNDS COVERED BY ABOVE-NOTED DISCLOSURE HAVE MORE THAI ONE ACTIVITY, INDICATE TOTAL NUMBER OF ACTIVITIES AND PREPARE A SEPARATE B.A.D.R. SHEET FOR EACH. TOTAL NO. OF ACTIVITIES: 1

3.a) TEST METHODS USED TO ESTABLISH ACTIVITY:
HMG-CoA reductase inhibition in rat liver microsomes (DT 64)
Cholesterol synthesis inhibition invivo in rats (DT 65)

b) DOSAGE RANGES BASED ON ACTUAL DOSES USED IN TEST PROCEDURE:
0.050 - 1.5 mg/kg

4. COMPOUNDS TESTED WITHIN DISCLOSURE WHICH EXHIBIT WEAK OR GREATER ACTIVITY:
64-935, 64-933

5. DOSAGE SCHEDULE - Broad Ranges:

a) Large / small animals:	.10	to	1.0	mg/kg.
b) Large animals:	20	to	200	mg/day.

6. MOST PREFERED COMPOUND FOR ACTIVITY DESIGNATED:

64-935

7. OTHER PREFERRED OR POTENTIALLY PREFERRED COMPOUNDS FOR DESIGNATEI ACTIVITY:
64-936, 63-366, 64-933, 64-934

8. ED50 FOR THE PREFERRED COMPOUND IN EACH OF THE TEST METHODS INDICATED IN 3a) FOR THE DESIGNATED ACTIVITY:

COMPOUND	IC50 uM DT64	ED50 mg.kg DT65	Potency x Mevinolin*
Compactin	1.01	3.5	0.11
Mevinolin	0.14	0.41	1 (standard)
64-935	0.41	0.49	0.3
64-936	0.53	>1.0	
64-933	2.37	2.40	

* Clinical dose of mevinolin (Lovasatin) = 20-80 mg/day

User: STR -at pr0

<USER02>ENGSTR>IC5 TA>PD295-84

419

299/84

295-84 &
299-84

Label: PRT002 -form

Pathname: <USER02>ENGSTR>IC50DATA>PD295-84
File last modified: 88-05-23. 08:25:36. Mon

Spooled: 88-05-23 08:50:36. Mon [Spooler rev 19.4.6]
Started: 88-05-23 08:50:40. Mon on: PRO by: PRO

IC50 TABLE RAT MICROSOMAL ASSAY (CSI-DT64)

THIS FILE IS A CALCULATED ESTIMATE OF THE IC50 (CONCENTRATION WHICH REDUCES THE CONVERSION OF HMG-CoA TO MEVALONATE BY 50%) USING ALL THE STUDIES ON THE RELEVANT COMPOUNDS UP TO THE SORT DATE.

LAST UPDATE: 02-04-88 SORT BY: DISCLNO

COMPOUND	REGNO	DISCL	IC50 uM	DATE	REF	COMMENTS
SAH-062977	24162	295-84	25.0000	02-07-84	1014-248	
SAH-062978	24163	295-84	0.0180	02-07-84	1014-249	
SAH-063033	24315	295-84	0.0450	04-18-84	1014-257	SAPONIFIED
SAH-063033	24315	295-84	0.5250	02-29-84	1014-257	
SAH-063034	24316	295-84	0.3630	02-22-84	1014-258	
SAH-063035	24317	295-84	0.0400	02-22-84	1014-259	
SAH-063074	24446	295-84	0.4000	05-23-84	1014-277	
SAH-063074	24446	295-84	0.6900	03-26-84	1014-277	
SAH-063075	24448	295-84	0.5300	04-18-84	1014-278	SAPONIFIED
SAH-063075	24448	295-84	0.9040	03-26-84	1014-278	
SAH-063076	24449	295-84	0.5800	06-12-84	1014-279	
SAH-063076	24449	295-84	0.6400	05-23-84	1014-279	
SAH-063076	24449	295-84	0.9000	03-26-84	1014-279	
SAH-063083	24511	295-84	1.9100	03-28-84	1014-281	
SAH-063083	24511	295-84	2.3200	03-28-84	1014-281	
SAH-063084	24512	295-84	3.1600	06-12-84	1014-282	
SAH-063084	24512	295-84	6.3200	03-28-84	1014-282	
SAH-063144	24750	295-84	1.1600	05-10-84	1014-294	SAPONIFIED
SAH-063144	24750	295-84	2.0200	05-10-84	1014-294	
SAH-063145	24755	295-84	>10.0000	05-07-84	1014-295	SAPONIFIED
SAH-063145	24755	295-84	>10.0000	05-10-84	1014-295	
SAH-063146	24756	295-84	>10.0000	05-07-84	1014-296	
SAH-063158	24809	295-84	0.1000	06-04-84	1069-002	SAPONIFIED
SAH-063158	24809	295-84	0.3430	06-04-84	1069-002	
SAH-063159	24810	295-84	0.2250	06-12-84	1069-003	
SAH-063159	24810	295-84	0.2630	06-04-84	1069-003	
SAH-063160	24811	295-84	0.1110	06-04-84	1069-004	SAPONIFIED
SAH-063160	24811	295-84	1.5600	06-04-84	1069-004	
SAH-063161	24821	295-84	0.0020	06-04-84	1069-005	
SAH-063161	24821	295-84	0.0020	06-12-84	1069-005	
SAH-063162	24822	295-84	0.0030	06-04-84	1069-006	
SAH-063162	24822	295-84	0.0035	06-12-84	1069-006	
SAH-063174	24865	295-84	0.0140	06-06-84	1069-013	SAPONIFIED
SAH-063174	24865	295-84	0.0190	06-06-84	1069-013	
SAH-063175	24866	295-84	0.0260	06-06-84	1069-014	
SAH-063229	25075	295-84	>10.0000	08-04-84	1069-036	
SAH-063230	25078	295-84	0.0042	08-01-84	1069-037	
SAH-063231	25079	295-84	0.0058	08-04-84	1069-038	
SAH-063269	25205	295-84	0.0030	09-10-84	1069-053	SAPONIFIED
SAH-063269	25205	295-84	0.0440	09-12-84	1069-053	
SAH-063270	25206	295-84	0.0080	09-05-84	1069-054	SAPONIFIED
SAH-063271	25208	295-84	0.0320	09-10-84	1069-055	
SAH-063271	25208	295-84	0.1450	09-12-84	1069-055	

SAH-064484	F 29413	95-84	0.0320	11-24-86	1149-227
AH-064744	E 30059	95-84	0.0320	05-01-87	1149-293
AH-064745	S 30060	95-84	0.0030	05-01-87	1149-294
SAH-064745	S 30060	95-84	0.0030	07-07-87	1149-297
AH-064815	E 30198	95-84	0.0220	07-07-87	1238-001
AH-064816	S 30199	95-84	0.0450	07-07-87	1238-002
SAH-063162	S 30203	95-84	0.0080	07-07-87	1238-003
SAH-064745	30765	95-84	0.0020	01-12-88	1238-030
SAH-063366	25496	99-84	1.5800	12-13-84	1069-113
AH-063549	26082	99-84	7.3100	06-13-84	1069-197
AH-063548	26080	99-84	3.7750	06-13-84	1069-198
SAH-064933	E 30441	99-84	2.3700	10-08-87	1238-013
AH-064934	S 30442	99-84	2.6100	10-08-87	1238-014
AH-064935	E 30447	99-84	0.4130	10-08-87	1238-015
SAH-064936	S 30448	99-84	0.5300	10-13-87	1238-016

ED50 TABLE RAT INVIVO ACETATE INCORPORATION (CSIV-DT65)

THIS FILE IS A CALCULATED ESTIMATE OF THE ED50 (DOSE WHICH REDUCES THE INCORPORATION OF 14C-ACETATE INTO CHOLESTEROL BY 50%) USING ALL THE STUDIES ON THE RELEVANT COMPOUNDS UP TO THE SORT DATE.

LAST UPDATE: 1-06-88 SORT BY: REGNO

COMPOUND	REGNO	CISCL	ED50 mg/kg	DATE mm-dd-yy	REF bk-pg	COMMENTS
SAH-064745	30060	95-84 =	0.016	10-20-87	917-127	N=9
SAH-064745	30765	95-84 =	0.016	02-19-88	917-154	N=3 BS BATCH
SAH-064745	ALL	95-84 =	0.016	02-19-88	917-154	N=12 2BATCHES
SAH-063162	25500	95-84 =	0.019	09-18-87	917-101	N=10
SAH-063162	ALL	95-84 =	0.040	09-18-87		N=19 3BATCHES
SAH-063162	25085	95-84 =	0.079	10-11-84	812-266	N=8
SAH-064119	27563	95-84 =	0.08	05-16-86	869-228	N=6
SAH-064744	30059	95-84 >	0.10	07-14-87	917-090	N=3 -21% @.10
SAH-064816	30199	95-84 =	0.10	10-12-87	917-119	N=6
SAH-064483	29412	95-84 =	0.13	02-06-87	917-024	N=3
SAH-064063	27424	95-84 =	0.19	04-17-86	869-211	N=3
SAH-064309	28718	95-84 =	0.19	11-03-86	869-283	N=3
SAH-063231	25079	95-84 >	0.25	08-30-84	812-250	
SAH-064393	29163	95-84 =	0.25	02-25-87	917-031	N=6
SAH-063161	24821	95-84 >	0.250	11-29-84	812-293	-12@0.25
SAH-063989	27237	95-84 =	0.28	04-04-86	869-195	N=6
SAH-063425	25687	95-84 >	0.3	03-20-85	869-046	N=3
SAH-064305	28701	95-84 >	0.3	11-03-86	869-280	N=3 -34% @.3
SAH-064480	29404	95-84 >	0.3	02-06-87	917-023	N=3 +3% @.3
SAH-063270	ALL	95-84 =	0.308	02-07-85		N=11 2BATCHES
SAH-063270	25206	95-84 =	0.33	10-11-84	812-267	
SAH-063270	25501	95-84 =	0.362	01-21-85	869-018	
SAH-064307	28705	95-84 =	0.47	02-06-87	917-020	N=6
SAH-063159	24810	95-84 >	0.5	06-19-84	812-219	

422

SAH-063162	24822	E95-84	<	0.5	06-19-84	812-219	N=1 -87@0.5
SAH-063175	24866	E95-84	<	0.5	06-19-84	812-220	
SAH-063230	25078	E95-84	>	0.500	11-29-84	812-294	
SAH-064391	29161	E95-84	=	0.51	10-30-86	917-011	N=3
SAH-063035	24317	E95-84	>	0.6	05-07-84	812-201	
SAH-063145	24755	E95-84	>	0.6	05-18-84	812-208	
SAH-063146	24756	E95-84	>	0.6	05-18-84	812-208	
SAH-063174	24865	E95-84	=	0.706	06-19-84	812-220	
SAH-064481	29406	E95-84	>	1.0	02-06-87	917-024	N=3 -28% @1.0
SAH-064482	29411	E95-84	>	1.0	03-18-87	917-041	N=3 -41% @1.0
SAH-064064	27433	E95-84	=	1.05	07-17-86	869-263	N=6
SAH-064204	27793	E95-84	=	1.21	10-02-86	869-298	N=6
SAH-064141	27630	E95-84	>	1.25	02-24-87	917-029	N=6 -24% @1.25
SAH-064308	28717	E95-84	>	1.5	11-03-86	869-283	N=3 -16% @1.5
SAH-064193	27760	E95-84	>	2.4	07-24-86	869-269	N=3 -24% @2.4
SAH-063076	24449	E95-84	<	2.5	05-14-84	812-204	
SAH-063084	24512	E95-84	>	2.5	05-07-84	812-201	
SAH-064933	30441	E99-84	=	~~0.49~~ 1	12-09-87	917-138	N=3 -3% @1.0
SAH-064935	30447	E99-84	≈	~~1.0~~ .99	12-09-87	917-138	N=3

Paper No. 117

All communications respecting this case should identify it by number and names of parties.

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SEP 16 1994

PAT. & T.M. OFFICE
BOARD OF PATENT APPEALS
AND INTERFERENCES

Interference No. 102,648

Wattanasin

v.

Fujikawa et al

The final hearing in this case is set for November 22, 1994 at 9:00 a.m., in Room A, Crystal Gateway 2, 1225 Jefferson Davis Highway, Arlington, VA 22202.

Counsel who do not expect to attend are requested to promptly notify this Office and such notice must be served on opposing party. 37 CFR 1.646.

Attention of the parties is directed to 35 USC 135(c) regarding the filing of settlement agreements in interferences.

Merrell C. Cashion, Jr.,
Program and Resource Administrator
Board of Patent Appeals &
Interferences
(703) 603-3339

ce

FORM PTO-78B
(Rev. 11-92)

FORM PO-644 (REV. 12-74)

U.S. DEPARTMENT OF COMMERCE PATENT OFFICE

APPEARANCE RECORD

PROCEEDIN[illegible].	PAPER NO.
102,648	118
HEARING DATE	**TIME**
Nov 22, 1994	9:00 am

INSTRUCTIONS - This form, properly filled out, should be placed in the file of the above numbered proceeding at the commencement of the hearing.

HEARING BEFORE (✓)	HEARD BY (NAMES)
☐ TRADEMARK TRIAL AND APPEAL BOARD ☐ BOARD OF PATENT INTERFERENCES	Ian A. Calvert Mary F. Downey X Michael Sofocleous

ADVERSARY PARTIES	COUNSEL
Wattanasin	Diane Furman 31,104
Vs.	
Fujikawa et al	Steven B Kelber 30,073
Vs.	
Vs.	

USCOMM-DC 70447-P75

Paper No. 119

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

SOMPONG WATTANASIN

Junior Party,[1]

v.

YOSHIHIRO FUJIKAWA, MIKIO SUZUKI, HIROSHI IWASAKI, MITSUAKI SAKASHITA and MASAKI KITAHARA

Senior Party.[2]

Patent Interference No. 102,648

Before CALVERT, Vice Chief Administrative Patent Judge, and SOFOCLEOUS and DOWNEY, Administrative Patent Judges.

SOFOCLEOUS, Administrative Patent Judge.

FINAL DECISION

The subject matter of this interference relates to a method of inhibiting cholesterol biosynthesis using novel mevalonolactones. These compounds inhibit the enzyme, ß-hydroxy-ß-methyl-glutaryl-CoA reductase (HMG-CoA), which controls a key step in the biosynthesis of cholesterol, by catalyzing the conversion of the substrate HMG-CoA to mevalonate, an

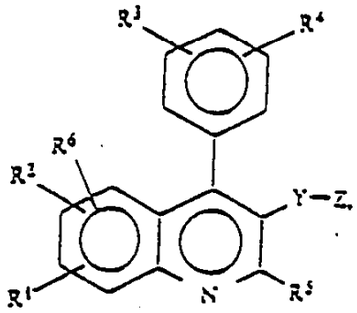
[1] Application 07/498,301 filed March 23, 1990. Accorded the benefit of U.S. Application 07/318,773 filed March 3, 1989, now abandoned. Assignor to Sandoz Pharmaceuticals Corporation.

[2] Application 07/233,752 filed August 19, 1988. Accorded the benefit of Japan Applications 207224 filed August 20, 1987, 193606 filed August 3, 1988 and 15585 filed January 26, 1988. Assignors to Nissan Chemical Industries Ltd.

intermediate of cholesterol. The count of this interference is as follows:

Count 3

A method of inhibiting cholesterol biosynthesis in a patient in need of said treatment comprising administering a cholesterol synthesis inhibiting amount of a compound of the formula:



wherein R^1, R^2, R^3, R^4 and R^6 are independently
hydrogen,
C_{1-6} alkyl,
C_{1-6} cycloalkyl,
C_{1-3} alkoxy,
n-butoxy,
i-butoxy,
sec-butoxy,

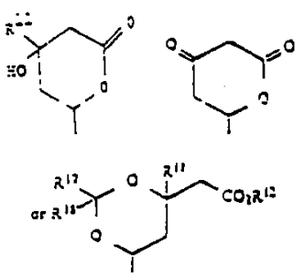
R^7R^8N- (wherein R^7 and R^8 are independently hydrogen or C_{1-3} alkyl),

trifluoromethyl,
trifluoromethoxy,
difluoromethoxy,
fluoro,
chloro,
bromo,
phenyl,
phenoxy,
benzyloxy,
hydroxy,
hydroxymethyl,
$-O(CH_2)_{\alpha}OR^{19}$ (wherein R^{19} is hydrogen or C_{1-3}alkyl and α is 1, 2 or 3),
or when located at the ortho position to each other, R^3 and R^4 together optionally form $-CH=CH-CH=CH-$;

R^5 is hydrogen,
C_{1-6} alkyl,
C_{2-3} alkenyl,
C_{3-6} cycloalkyl,
phenyl substituted by R^9 (wherein R^9 is hydrogen, C_{1-4}alkyl, C_{1-3}alkoxy, fluoro, chloro, bromo or trifluoromethyl),
phenyl-$(CH_2)_m$- (wherein m is 1, 2 or 3), $-(CH_2)_nCH(CH_3)$-phenyl or phenyl-$(CH_2)_nCH(CH_3)$- (wherein n is 0, 1 or 2).

Y is
$-CH_2-$,
$-CH_2CH_2-$,
$-CH=CH-$,
$-CH_2-CH=CH-$, or
$-CH=CH-CH_2-$;

Z is



or $-Q-CH_2WCH_2-CO_2R^{12}$ (where R^{12} is hydrogen or R^{14});

Q is $-CH(OH)-$.
$-C(O)-$, or
$-C(OR^{13})_2-$;

W is $-C(R^{11})(OH)-$ (where R^{11} is hydrogen or C_{1-3} alkyl),
$-C(O)-$, or
$-C(OR^{13})_2-$;

the two R^{13} are independently primary or secondary C_{1-6} alkyl; or two R^{13} together form $-(CH_2)_2-$ or $-(CH_2)_3-$;

R^{14} is physiologically hydrolyzable alkyl or M (wherein M is NH_4, sodium, potassium, 1/2 calcium or a hydrate of lower alkylamine, di-lower alkylamine or tri-lower alkylamine); and

R^{17} and R^{18} are independently hydrogen or C_{1-3} alkyl;

as defined in combination with pharmaceutically acceptable carrier.

Wattanasin's claims 8 and 9 and Fujikawa et al.'s (Fujikawa's) claims 35, 37 and 38 correspond to the count. No question of interference-in-fact or separate patentability of claims under 37 CFR 1.633(b) and (c)(4) has been raised.

This interference was initially declared with three parties on two counts. Count 1 was directed to compounds per se; count 2, to a method of administering the compounds to inhibit cholesterol biosynthesis. The intermediate party, Picard et al., U.S. Patent No. 4,761,419, filed a request for adverse judgment and judgment was entered against it. During the motion period, Fujikawa filed, inter alia, a preliminary motion (Paper No. 15) to add two proposed counts to this interference, which motion was denied by the administrative patent judge (APJ). As a result of the APJ's Decision on Preliminary Motions, method count 3 was substituted for count 2 and Interference No. 102,975 was declared on a count directed to compounds per se. Times for taking testimony were set. Wattanasin presented testimony in order to establish priority of invention within the meaning of 35 U.S.C. 102(g). Fujikawa took cross-examination and presented rebuttal testimony. Both parties filed briefs and appeared, through counsel, at final hearing.

The briefs raise the following issues:

Wattanasin's claims 8 and 9 and Fujikawa et al.'s (Fujikawa's) claims 35, 37 and 38 correspond to the count. No question of interference-in-fact or separate patentability of claims in accordance with 37 CFR 1.633(b) has been raised.

This interference was initially declared with three parties on two counts. Count 1 was directed to compounds per se; count 2, to a method of administering the compounds to inhibit cholesterol biosynthesis. The intermediate party, Picard et al., U.S. Patent No. 4,761,419, filed a request for adverse judgment and judgment was entered against it. During the motion period, Fujikawa filed, inter alia, a preliminary motion (Paper No. 15) to add two proposed counts to this interference, which motion was denied by the administrative patent judge (APJ). As a result of the APJ's Decision on Preliminary Motions, method count 3 was substituted for count 2 and Interference No. 102,975 was declared on a count directed to compounds per se. Times for taking testimony were set. Wattanasin presented testimony in order to establish priority of invention within the meaning of 35 U.S.C. 102(g). Fujikawa took cross-examination and presented rebuttal testimony. Both parties filed briefs and appeared, through counsel, at final hearing.

The briefs raise the following issues:

1. Whether the Fujikawa preliminary motion (Paper No. 15) to add two proposed counts to this interference should have been granted?

2. Whether Wattanasin has established priority of invention prior to August 20, 1987, Fujikawa's effective filing date?

FUJIKAWA'S PRELIMINARY MOTION TO ADD COUNTS

After having reviewed the arguments of the parties, we hold that the party Fujikawa has not sustained its burden to show that the interfering subject matter should have been redefined by adding two proposed counts to this proceeding.

As the moving party, Fujikawa has the burden of proof on the motion. Kubota v. Shibuya, 999 F.2d 517, 27 USPQ2d 1418 (Fed.Cir. 1993). The motion proposed that two counts be added to this interference and that Wattanasin present claims 11 and 12 in his application to correspond to the proposed counts. As the moving party, Fujikawa had the burden to...

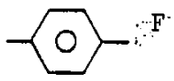
> show the patentability of any proposed claims to the opponent and apply the terms of the claims to the disclosure of the opponent's application. § 1.637(c)(1)(iii).

The APJ denied the motion on the ground the Wattanasin application does not contain a written description with the meaning of 35 U.S.C. 112, first paragraph, for proposed claims 11 and 12. In accordance with 37 CFR 1.655(a), the APJ's decision on a preliminary motion constitutes an interlocutory order which is presumed to have been

correct and the burden of showing error or abuse of discretion is upon the party attacking the order. Gustavsson v. Valenti, 25 USPQ2d 1401 (BPAI 1991) and Suh v. Hoefle, 23 USPQ2d 1321 (BPAI 1991).

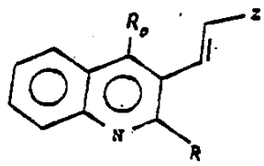
Having reviewed the Wattanasin disclosure, we agree with the APJ that the disclosure does not contain a written description for proposed claims 11 and 12.

Proposed claims 11 and 12 are as follows:

11. The compound of claim 1, wherein R_1 and R_2 are hydrogen, R_o is  , X is -CH=CH-, R is cyclopropyl, Q is  , R_6 is H, R_8 is an alkyl of 1-3 carbon atoms and M is sodium.

12. A method of inhibiting cholesterol biosynthesis in a patient in need of said treatment comprising administering a cholesterol biosynthesis inhibiting amount of the compound of Claim 11 in combination with a pharmaceutically acceptable carrier.

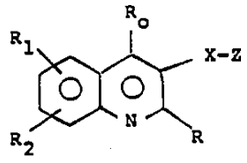
The compounds embraced by proposed claims 11 and 12 are as follows:



wherein R_o is 4-flurophenyl, and
R is cyclopropyl

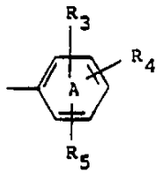
The Wattanasin application has the following pertinent disclosure:

This invention relates to compounds of the formula



(A)

wherein each of R and R_o is, independently C_{1-6}alkyl (primary, secondary or tertiary), C_{3-7}cycloalkyl or ring A



each of R_1, R_2, R_3, R_4 and R_5 is, independently hydrogen, C_{1-4}alkyl, C_{1-4}alkoxy, trifluoromethyl, fluoro, chloro, phenoxy, benzyloxy or hydroxy; with the provisos that not more than one of R_1 and R_2 is trifluoromethyl, not more than one of R_1 and R_2 is phenoxy, not more than one of R_1 and R_2 is benzyloxy, not more than one of R_1 and R_2 is hydroxy, not more than one of R_3-R_5 is the trifluoromethyl, not more than one of R_3-R_5 is phenoxy, not more than one of R_3-R_5 is benzyloxy and not more than one of R_3-R_5 is hydroxy; [page 1, lines 1 to 14]

* * * *

Preferred compounds of this invention are the following.

R_1 and R_2 are preferably hydrogen;

one of R and R_o is preferably C_{-1-6}alkyl, more preferably isopropyl or methyl, and the other is preferably Ring A, more preferably phenyl, 4-fluorophenyl or 3,5-

dimethylphenyl; more preferably R is the alkyl group and R_o is Ring A; [page 4, lines 26 to 34]

It is clear from the foregoing that the application does not describe in ipsis verbis the compounds of proposed claims 11 and 12 where R is cyclopropyl. This, however, is not necessary in order to comply with the description requirement of 35 USC 112, first paragraph, In re Lukach, 442 F.2d 967, 169 USPQ 796 (CCPA 1971); all that is required is that the application reasonably convey to persons skilled in the art that, as of the filing date thereof, the inventor had possession of the subject matter later claimed by him. In re Edwards, 558 F.2d 1349, 196 USPQ 465 (CCPA 1978) and In re Driscoll, 562 F.2d 1245, 195 USPQ 434 (CCPA 1977). The question of whether an application contains a sufficient written description within the meaning of 35 U.S.C. 112, first paragraph, for a compound which is not specifically disclosed but which is among those suggested by general language in the application must be decided on its own facts. In re Driscoll, supra and Prutton v. Fuller, 230 F.2d 459, 109 USPQ 59 (CCPA 1956).

In our view, the Wattanasin application would not reasonably lead one of ordinary skill to the compounds of claims 11 and 12 where R is cyclopropyl, i.e., the application does not reasonably convey to those skilled in the art that Wattanasin invented the compounds. Cf. Flynn v. Eardley, 479 F.2d 1393, 178 USPQ 288 (CCPA 1973); Fields v. Conover, 443 F.2d 1386, 170 USPQ 276

(CCPA 1971); Irikura v. Petersen, 18 USPQ2d 1362 (BPAI 1991); and Heymes v. Takaya, 6 USPQ2d 1448 at 1452 (BPAI 1988).

The Wattanasin application does not disclose any compound where R is C_{3-7} cycloalkyl, much less cyclopropyl. Rather, cyclopropyl is merely one moiety embraced by C_{3-7} cycloalkyl which is among a myriad of possibilities for either R or R_o disclosed in the application on page 1, lines 1 to 5. Further, the application at page 4, lines 26 to 34, lists its preferred compounds. None of the listed preferred compounds includes cyclopropyl or even C_{3-7} cycloalkyl in the R position. Nor does the application have any examples directed to cycloalkyl compounds. Nor are there either any blazemarks or any motivation to guide one skilled in the art to select the cyclopropyl compounds of proposed claims 11 and 12 from Wattanasin's broad generic disclosure. Admittedly, one skilled in the art might fortuitously select a cyclopropyl compound within the scope of claims 11 and 12 out of the myriad of possibilities. This, however, is not sufficient to provide a written description of the small subgenus of claims 11 and 12. The selection of all the substituents of the genus must necessarily happen. Flynn v. Eardley, supra; In re Rushig, 379 F.2d 990, 154 USPQ 118 (CCPA 1967); and Staehelin v. Secher, 24 USPQ2d 1513 (BPAI 1992). As noted by the Court in Rushig, 154 USPQ 122,

> Specific claims to single compounds require reasonably specific supporting disclosure and while

> we agree with the appellants, as the board did, that naming is not essential, something more than the disclosure of a class of 1000, or 100, or even 48, compounds is required. Surely, given time, a chemist could name (especially with the aid of a computer) all of the half million compounds within the scope of the broadest claim, which claim is supported by the broad disclosure. This does not constitute support for each compound individually when separately claimed.

We consider the Court's statement concerning claims to specific compounds is equally applicable to the situation here where proposed claims 11 and 12 are directed to a small subgenus of cyclopropyl compounds within the scope of Wattanasin's broad generic disclosure.

For the foregoing reasons, we hold that the party Fujikawa has not sustained its burden to show that the interfering subject matter should have redefined by adding the two proposed counts to this proceeding.

WATTANASIN'S CASE FOR PRIORITY

Fujikawa is the senior party, having been accorded under the provisions of 35 U.S.C. 119 the benefit of its earliest filed Japan application Serial No. 207224, filed August 20, 1987. For its case for priority of invention, the junior party Wattanasin relies upon actual reduction to practice prior to Fujikawa's effective filing date or upon prior conception coupled with diligence starting just prior to Fujikawa's effective filing date up to actual reduction to practice.

Burden of Proof

Wattanasin, as the junior party, whose application is copending with the senior party's application, has the burden of proving priority of invention by a preponderance of the evidence. Holmwood v. Sugavanam, 948 F.2d 1236, 20 USPQ2d 1712 (Fed.Cir. 1991) and Morgan v. Hirsch, 728 F.2d 1449, 221 USPQ 193 (Fed.Cir. 1984).

Fujikawa's argument that the party Wattanasin must prove its case for priority by clear and convincing evidence is not well taken. This argument is based on the fact that this interference was initially declared with the party Picard, whose patent issued prior to the filing date of Wattanasin's involved application. If the party Picard were involved in this interference, we would have agreed with Fujikawa that Wattanasin, whose application was filed after the issuance of Picard's patent, would have had the burden of proof by clear and convincing evidence with respect to Picard. See Price v. Symsek, 988 F.2d 1187, 26 USPQ2d 1031 (Fed.Cir. 1993). Since Picard is no longer involved in this proceeding, having filed, through counsel, a request for adverse judgment, the burden of proof upon Wattanasin vis-a-vis Fujikawa is the preponderance of the evidence, inasmuch as both Wattanasin's and Fujikawa's applications are copending.

Count Interpretation

The count is directed to a "method of inhibiting cholesterol biosynthesis in a patient in need of said treatment." On

page 54 of its main brief, the party Fujikawa urges that we should construe the count as being directed to a method for "treating human patients," because there is

> no known value in reducing cholesterol, or controlling blood cholesterol levels, in animals other than humans. Main brief at page 32.

In support of its position, the party Fujikawa points to page 35 of the Wattanasin application which specifically identifies humans as the target patients and gives dosage values only for humans.

We note that the term "patient" in the count is neither present in the parties' claims corresponding to the count nor defined in the parties' applications. The count of this interference is a "phantom" count which is not patentable under 35 U.S.C. 112, first paragraph, to either party. A count of an interference is merely the vehicle for determining priority of invention. It is settled interference practice that a count must be given its broadest reasonable interpretation possible, DeGeorge v. Bernier, 768 F.2d 1318, 226 USPQ 758 (Fed.Cir. 1985), and it is an established principle of interference practice that the count must be sufficiently broad as to encompass the broadest corresponding patentable claim of each party. Manual of Patent Examining Procedure, § 2309.02 (Fifth Edition).

Based on our review of the parties' claims corresponding to the count in light of their application disclosures, we necessarily

conclude that the term "patient" as used in the context of the count includes the testing of mammals.

Wattanasin's claim 8 is directed to a method of inhibiting cholesterol biosynthesis comprising administering a compound to a mammal in need of such treatment. The Wattanasin application, page 35, lines 1 to 19, teaches that the compounds of his invention are useful for lowering blood cholesterol level in "animals, e.g., mammals, especially larger primates," with humans being listed as an example of larger primates. Further the application at page 34 contains examples directed to the in vivo testing of male Wistar Royal Hart rats.

Fujikawa's claims 35, 37 and 38 are directed to a method for treating hyperlipidemia, hyperlipoproteinemia, or atherosclerosis which comprises administering an effective amount of the compound. The claims are open-ended in that they do not limit the administration of compound to any particular group; rather, the compound may be administered to either a human, mammal or other animal. The Fujikawa application at page 26, lines 5 to 13, teaches:

> The compounds of the present invention exhibit high inhibitory activities against the cholesterol biosynthesis wherein HMG-CoA reductase acts as a rate limiting enzyme, as shown by the test results given hereinafter, and thus are capable of suppressing or reducing the amount of cholesterol in blood as lipoprotein.

The Fujikawa application contains examples directed to the in vivo testing of male Sprague-Dawley rats.

Since the claims of Wattanasin are directed to the treatment of mammals and the claims of Fujikawa embrace the treatment of any animal, including humans and mammals, and since both applications contain examples directed to the in vivo testing of rats, we necessarily conclude that in the context of this interference, the term "patient" as used in the count embraces the treatment of mammals, and, in particular, rats, the species exemplified by both parties' applications.

The Wattanasin Record

Wattanasin presented a record consisting of the testimony of 16 witnesses together with 51 associated exhibits. The testimony will be referred to by WR followed by its page number; each exhibit, by WX followed by its identifier. The record shows that Sandoz Pharmaceuticals Corporation, the assignee of the involved Wattanasin application, has been involved since 1979 in a research program to discover compounds having HMG-CoA reductase inhibiting activity. In 1979, Dr. Kathawala, a Ph.D., was the section head of a research team responsible for the research. This team was expanded over time to five laboratory units, each headed by a Ph.D. In 1982, Dr. Wattanasin, the named inventor, joined the project, worked under Dr. Kathawala and was later appointed as head of one of the five laboratory units. WR 136.

The First Phase Activity

I

The record shows that during the period from May 31, 1984 to May 17, 1985, Dr. Wattanasin synthesized three compounds (63-366, 63-548 and 63-549) falling within the scope of the count. Employees reporting to Dr. Barcza, a Ph.D chemist and director of the Sandoz Department of Physical Organic Chemistry, performed the spectra, microanalyses and thin layer chromatography (TLC) on the various intermediates and the final compounds. Samples of the final compounds were sent to the Drug Room of Sandoz and their receipt was recorded in the computer database. Dr. Damon, a Ph.D. chemist, who was in charge of the Drug Room, had samples of the compounds forwarded to Dr. Scallen for testing. WR 22 to 24, 27 to 44, 48 to 54, 172 to 185 and 196; WX A-1, A-2, B-1, B-2, C-1 to 3, D-1, D-2, G-1, G-2, H-1 and I-1.

Dr. Scallen, a professor of biochemistry and medical doctor at the School of Medicine, University of New Mexico, received the compounds and had them tested in an established protocol using rat liver microsomes to determine whether they were competitive inhibitors of HMG-CoA reductase, the rate limiting enzyme in cholesterol biosynthesis. On or before December 13, 1984, Dr. Scallen had an <u>in vitro</u> biological assay of compound 63-366 performed in his laboratory under his supervision. The results indicated HMG-CoA reductase activity and Dr. Scallen reported the results to Dr.

Damon of Sandoz. Likewise, on or before June 13, 1985, Dr. Scallen had in vitro biological assays of compounds, 63-548 and 63-549, performed in his laboratory under his supervision. The results indicated HMG-CoA reductase activity and were reported to Dr. Damon of Sandoz. WR 187 to 191; WX E-1 and E-2.

Upon receiving the results, Dr. Damon calculated the IC_{50} for each compound. The IC_{50} value is the concentration of the test substance in the assay system to produce a 50% inhibition of HMG-CoA reductase. The smaller the IC_{50} value, the more active the compound was in the assay. Dr. Damon would send Dr. Wattanasin within three or four days of receiving the test results a report with the assay data (including the IC_{50}) and the structure of the compound. The report (WX E-5), stamp-dated December 20, 1984, indicated that compound 63-366 had an IC_{50} of 1.58 μmoles (μM); the reports (WX E-5), stamp-dated June 28, 1985, indicated that compounds 63-548 and 63-549 each had, respectively, an IC_{50} of 3.775 μM and 7.3100 μM. He compared these values to the IC_{50} value of compactin, a known HMG-CoA inhibitor for administration to patients to inhibit cholesterol biosynthesis. Compactin has an IC_{50} value of 1.011 μM. WR 196 to 201 and 483; WX E-1 and E-5.

Concerning these test results, Dr. Damon testified that based on his knowledge and experience,

> it was my judgment on or prior to December 31, 1984, that there was a high probability that Wattanasin

> compound 63-366 would be active when administered in vivo to a patient to inhibit cholesterol biosynthesis, i.e. for the treatment of hypercholesteremia or atherosclerosis. WR 201.

He testified that he had the same opinion for the other tested compounds.

Dr. Wattanasin testified that no other experimental work was done on his invention after May 17, 1985, because of a manpower shortage in his lab. WR 106 to 110. Ms. Patel was hired in January 1987. In March of 1987, Dr. Wattanasin submitted an Invention Disclosure (A-3), dated March 16, 1987, to the Sandoz Patent and Trademark Department. WR 24 and 25; WX A-3.

II

We hold that during the first phase of activity the Wattanasin record does not establish actual reduction to practice.

It is well settled that a reduction to practice must include every limitation of the count. NewKirk v. Lulejian, 825 F.2d 1581, 3 USPQ2d 1793 (Fed.Cir. 1987); Land v. Regan, 342 F.2d 92, 144 USPQ 661 (CCPA 1965) and Schoenwald v. Waltersdorf, 226 USPQ 446 (Bd.Pat.Int. 1984).

The compounds, 63-366, 63-548 and 63-549, which were made and tested during the first phase, were not administered to a mammal, a necessary step in the performance of the method of the count. Consequently, Wattanasin did not reduce to practice the invention of count 1 during the first phase activity. At best, this work would

establish conception of the invention of the count by at least June 13, 1985.

The Second Phase Activity

I

Pages 31 to 44 of the Wattanasin main brief with references to the testimony and exhibits set forth a detailed explanation of Wattanasin's renewed activity.

Essentially from early March 1987 into September 1987, Ms. Patel synthesized four compounds, 64-933, 64-934/NA, 64-935 and 64-936/NA, within the scope of the count and forwarded the compounds to the Sandoz Drug Room. By July 28, 1987, she synthesized compound 64-933; by July 29, 1987, compound 64-934/NA; by August 20, 1987, compound 64-935; and by August 25, 1987, compound 64-936/NA. During the synthesis, purification and characterization of the compounds, Dr. Wattanasin went to a meeting in New Orleans for over a week and when he returned, he found out that the next scheduled shipment out of the Sandoz drug room to Dr. Scallen would be on October 2, 1987, even though the compounds were made before October 2. He wanted all the compounds shipped together for testing so that he could get a better comparison of their potency in the same study. The compounds were shipped on October 2, 1987 overnight to Dr. Scallen. Dr. Scallen received the compounds, tested them in an established protocol using rat liver microsomes to their biological activity in

vitro and reported the raw results to Dr. Damon on or before October 20, 1987.

Dr. Damon calculated the IC_{50} for each compound and compared each value with compactin which has an IC_{50} of 1.011 μM. Compound 64-933 had an IC_{50} of 2.3700 μM; compound 64-934/NA, an IC_{50} of 2.6100 μM; compound 64-935, an IC_{50} of 0.4130 μM; and compound 64-936/NA, an IC_{50} of 0.5300 μM. WR 183 to 195; WX E-1 to E-5, H-1 and I-1.

Dr. Engstrom of the Sandoz Lipid Metabolism Department commenced the in vivo testing of compound 64-936 on or before October 22, 1987 and the testing of compounds 64-933 and 64-935 on October 29, 1987. The testing was completed on or prior to December 9, 1987. The compounds were administered to male Wistar Royal Hart rats in accordance with the protocol described at WR 204. Mr. Slaughter, Dr. Engstrom's lab assistant, entered the raw data into a computer program which converted the data to nano Curies (nCi) of sterol per 100 ml. of serum at 4 hours after injection of ^{14}C-acetate. Thereafter Dr. Engstrom entered this data into a computer program which calculated the ED_{50} values for the compounds. The ED_{50} value[3] for compound 64-933 is >1; for compound 64-935, 0.49; and for compound 64-936, >1. Dr. Wattanasin testified that the data on WX K-1 indicates that the compounds would have activity as a HMG-CoA

[3] The ED_{50} values for compounds 64-933 and 64-935 were inadvertently switched as explained in Dr. Engstrom's supplemental declaration at WR 207 and 208.

reductase inhibitor when administered to a patient. Compactin has an ED_{50} of 3.5. WR 56, 203 to 212 and 485; WX K-1 and Q.

Contemporaneous with these second phase activities, the Sandoz Patent Committee met on April 29, 1987 and considered the Wattanasin invention disclosure (A-3). According to the testimony of Linda Rothwell and Joanne M. Giesser, the committee deferred a decision for three months on whether to file an application because of the ongoing work. Again at its meeting on July 29, 1987, the committee deferred its decision for another three months. As a result of the October 28, 1987 and November 25, 1987 meetings, the committee's decision was deferred to January, there being no committee meeting during the month of December. At the January 27, 1988 meeting, the committee decided that an application should be filed on the Wattanasin disclosure. The disclosure, which had been assigned to Mr. Weinfeldt, was reassigned to Ms. Giesser, a junior patent attorney in the Sandoz Patent Department. The application was filed on March 3, 1989. WR 213 to 215 and 319 to 323; WX M-1 to M-5 and P-1 to 3.

II

We hold that the Wattanasin record establishes prior conception coupled with due diligence from just prior to August 20, 1987, Fujikawa's effective filing date, up to December 9, 1987, the date of the in vivo testing of compound 64-935.

Prior conception is established by June 13, 1985, when the work performed during the first phase of the interference was completed. Thus the Wattanasin record establishes prior conception.

With respect to diligence, Wattanasin has the burden to establish diligence just prior to August 20, 1987, up to the date of in vivo testing on December 9, 1987. As noted by Wattanasin in his reply brief at page 24, "it does not appear that Fujikawa contest diligence as to this period." We agree. Nowhere in its brief has the party Fujikawa shown where Wattanasin was not reasonably diligent during this period. Accordingly, we hold that the Wattanasin record establishes reasonable diligence during the critical period in question.

III

We hold that the Wattanasin record establishes actual reduction to practice by December 9, 1987, the date compound 64-935 was successfully tested in vivo in rats and found to have an ED_{50} value of 0.49 μM.

Before we discuss the Wattanasin record, we must consider Fujikawa's motion (Paper No. 109) to suppress, which was filed at the same time as Fujikawa's brief. In the motion, Fujikawa requests that we not consider Dr. Engstrom's testimony at WR 204 to 208 because the testimony relies upon a computer-generated summary to obtain the ED_{50} values. We agree with Wattanasin's opposition (Paper No. 113) that

the ED_{50} value for compound 64-935 should not be invalidated because of a purported lack of foundation for the underlying computer programs used to calculate the value from the raw data. As pointed out by Wattanasin, Dr. Holmlund, Fujikawa's rebuttal witness, had "no quarrel with the techniques for determining statistical activity." Likewise, we do not consider that Wattanasin had to have placed in evidence the computer programs used to calculate the value from the experimental data. It is enough to have placed into evidence the experimental data, which showed that the compound had significant activity. Accordingly, the motion to suppress is denied.

As we noted above, a reduction to practice must include every limitation of the count. Newkirk v. Lulejian, supra; Land v. Regan, supra; and Schoenwald v. Waltersdorf, supra. The Wattanasin record shows that by December 9, 1987 compound 64-935 was administered to a rat. The compound exhibited significant activity at levels of 1 and 0.1 milligrams per kilogram and its ED_{50} value was calculated to be 0.49 μM, an activity greater than compactin. Dr. Wattanasin testified that this activity showed that the compound would be active as a HMG-CoA reductase inhibitor when administered to a patient. Further Dr. Holmlund, Fujikawa's rebuttal witness acknowledged that the compound did in fact exhibit significant activity at those levels. See the Fujikawa record at pages 207 to 209 and 243 (FR 207 to 209 and 243).

We do not agree with Fujikawa's position on page 32 of his main brief that the proofs of Wattanasin fail because a human patient was not tested. As we noted above, the count embraces the treatment of mammals. Thus the experiment performed on behalf of Dr. Wattanasin meets the terms of the count.

It is also Fujikawa's position that the testing of compound 64-935 does not demonstrate a practical utility. This position is not well taken. The Fujikawa rebuttal evidence is mainly directed to whether a correlation exists between in vitro activity and in vivo activity, a matter which is not in issue in this interference. To the extent that the evidence is relied upon to show that the Wattanasin record does not demonstrate that the testing establishes a practical utility for compound 64-935, we are not persuaded thereby. Fujikawa relies on Dr. Holmlund's testimony at FR 209 that since the compound was not significantly active at 0.3 milligrams and that since he (Dr. Holmlund) could not have obtained the ED_{50} value on the basis of WX K-1 in the absence of any reasonable dose response curve, he could not make any final conclusion on the compound's activity. In effect, Dr. Holmlund would want a commercially satisfactory performance; however, a commercially satisfactory performance is not necessary for an actual reduction to practice. Creamer v. Kirkwood, 305 F.2d 486, 134 USPQ 330 (CCPA 1962). Practical utility for

compound 64-935 existed when it was found to have significant activity at 1 and 0.1 milligrams.

Nor do we agree with the Fujikawa brief at pages 53 and 54 that the Engstrom declaration should be "severely discounted," because it reflects a ED_{50} value for a compound never tested, i.e., 64-936. The fact that Dr. Engstrom had been provided the sodium salt of 64-936 (64-936NA) and had not assigned any ED_{50} value for that compound does not in any way impugn the test results for compound 64-935.

For the foregoing reasons, we hold that the Wattanasin record establishes actual reduction to practice by December 9, 1987. Accordingly, the Wattanasin record establishes prior conception coupled with due diligence from just prior to August 20, 1987, Fujikawa's effective filing date, up to December 9, 1987, the date of the in vivo testing of compound 64-935.

IV

In view of our foregoing holding, Wattanasin is entitled to judgment vis-a-vis Fujikawa. However, Fujikawa urges that judgment should not be entered in Wattanasin's favor because the evidence shows that Wattanasin suppressed or concealed the invention. In this case, the hiatus in time between the actual reduction to practice on December 9, 1987 up to March 3, 1989, the filing date of Wattanasin's parent application, is approximately fifteen months. In our view,

this hiatus in time is not sufficiently long to raise the inference that Wattanasin suppressed or concealed the invention considering the nature and complexity of the invention here. Cf. Bigham v. Godtfredsen, 222 USPQ 632 (Bd.Pat.Int. 1984) and Halbert v. Schuurs, 220 USPQ 558 (Bd.Pat.Int. 1983).

Since we have held that the hiatus in time is not sufficiently long to raise the inference that Wattanasin suppressed or concealed his invention, we need not evaluate the testimony of Mr. Melvyn Kassenoff, which bears on this question and which the Fujikawa brief requests that we discredit. We consider this matter moot.

JUDGMENT

Judgment with respect to the subject matter of the count in issue is hereby awarded to Sompong Wattanasin, the junior party. Accordingly, on the present record, Wattanasin is entitled to a patent containing claims 8 and 9 and Fujikawa et al. are not entitled to a patent containing claims 35, 37 and 38.

IAN A. CALVERT, Vice Chief)
Administrative Patent Judge)
)
)
MICHAEL SOFOCLEOUS) BOARD OF PATENT
Administrative Patent Judge) APPEALS AND
) INTERFERENCES
)
MARY F. DOWNEY)
Administrative Patent Judge)

Interference No. 102,648

Gerald D. Sharkin
Sandoz Corp.
59 Route 10
E. Hanover, N.J. 07936

Oblon, Fisher, Spivak,
McClelland & Maier
1755 S. Jefferson Davis Hwy.
Crystal Square Five-Ste. 400
Arlington, VA 22202

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

WATTANASIN	:	
	:	INTERFERENCE 102,648
V.	:	EXAMINER-IN-CHIEF:
	:	MICHAEL SOFOCLEOUS
FUJIKAWA ET AL	:	

REQUEST FOR RECONSIDERATION OF FINAL DECISION,
37 CFR §1.658

HONORABLE COMMISSIONER OF PATENTS AND TRADEMARKS
WASHINGTON, DC 20231
BOX INTERFERENCE

SIR:

Pursuant to the provisions of the above-captioned Rule, the party Fujikawa respectfully requests reconsideration of the aspects of the final decision of the Board, dated January 31, 1995, which Fujikawa respectfully submits reflects points misapprehended or overlooked by the Board in rendering its decision. Fujikawa respectfully notes that it will seek court review of this decision, and accordingly, even in the event this Request For Reconsideration does not result in a modification of the decision on final hearing,

a full explanation of the consideration of the points identified herein is respectfully requested, so that the court review sought can be full and complete, without a clear need for remand.

As points misapprehended or overlooked, Fujikawa identifies the following:

> 1. The Board appears to have misapprehended the nature of the disclosure of the involved application of the party Wattanasin in concluding, "it is clear from the foregoing that the application does not describe in *ipsis verbis* the compounds of proposed claims 11 and 12 where R is cyclopropyl." Fujikawa does not seek reconsideration of the court's conclusion that the application lacks "blaze marks or any motivation to guide one skilled in the art to select the cyclopropyl compounds of proposed claims 11 and 12 from Wattanasin's broad generic disclosure". While Fujikawa believes this decision to be in error, there does not appear to be anything misapprehended or overlooked with respect to this aspect of the decision. (This issue applies solely to

Interference 102,648).

2. The Board appears to have overlooked Fujikawa's Motion to Suppress the Supplemental Declaration of Engstrom at WR207-208 and exhibit Q discussed therein, on the grounds that the Engstrom declaration was not timely submitted, was submitted belatedly without an explanation of good cause, or an identification of how the error which is alleged to support the submission occurred.

3. The Board's decision appears to have overlooked the arguments presented by Fujikawa stressing direct evidence of suppression and concealment on the part of Wattanasin. The final decision of the Board deals only with inferred suppression. The Fujikawa Brief is not so confined.

Each of these issues is discussed, in turn, below.

I. CYCLOPROPYL AS AN IDENTITY FOR R DOES APPEAR, *IPSISSIMUS VERBIS*

On page 9 of the Final Decision of the Board in Interference

102,648, after quoting language appearing in the Wattanasin patent application, the decision reflects

> It is clear from the foregoing that the application does not describe *ipsis verbis* the compounds of proposed claims 11 and 12 where R is cyclopropyl.

It is respectfully submitted that the Board has misapprehended the nature of the Wattanasin disclosure. Wattanasin has not contested, and the Board no where indicates, that any of the remaining identities recited in claims 11 and 12 are not described, *ipsissimus verbis* (*ipsis verbis* is a contracted form of the original latin) in the Wattanasin application as filed. Indeed, the remaining identities appear described not only *ipsissimus verbis*, but exemplified as well. Thus, the Board holds that the term "R is cyclopropyl" does not appear *ipsissimus verbis*. In this, the Board may have misapprehended the disclosure of the Wattanasin application, a pertinent portion of which appears on page 8 of the Board's decision. That disclosure includes the statement

> wherein each of R and R_0 is independently C_{1-6} alkyl (primary, secondary or tertiary), C_{3-7} cycloalkyl....

The testimony of Wattanasin confirms that C_3 is cyclopropyl. Thus, the Wattanasin application does in fact include, *ipsissimus verbis*, a description of compounds of the type proposed in claims 11 and 12 wherein "R is cyclopropyl". Fujikawa does acknowledge that there is no exemplification of such compounds. It is not believed, however, that exemplification is necessary.

It is well established that the disclosure of a range identifies at least two points, the beginning and end point of the range. This is true of patent applications, and documents other than patent applications. In re Wertheim, 191 USPQ 90, 90-99 (CCPA 1976) and In re Malageri, 183 USPQ 549, 553, (CCPA 1974). Applying such analysis to the disclosure in Wattanasin of substituent R, it is easy to note that this disclosure specifically identifies, *ipsissimus verbis*, at least 4 compounds, C_1 alkyl (methyl), C_6 alkyl (hexyl), C_3 cycloalkyl (cyclopropyl) and C_7 cycloalkyl (cycloheptyl). While all four of the embodiments do not appear as examples in the Wattanasin application, that is not to say that the language recited in the proposed claims does not appear, *ipsissimus verbis*, in the application as filed.

It is axiomatic that the application is directed to those of skill in the art, and the test is whether or not those of ordinary skill in the art would understand the subject matter to be

described, in this case, *ipsissimus verbis*. In re Edwards, 196 USPQ 465 (CCPA 1978). There is testimony as to what those of ordinary skill in the art would understand the Wattanasin disclosure to describe, *ipsissimus verbis*. See the testimony of Wattanasin himself, FR116, cited at page 22 of Fujikawa's Brief, and FR294, the testimony of Geisser

> Certainly that phrase "C3-7 cycloalkyl" identifies two possible compounds, one cycloalkyl compound with three carbon atoms and one with seven: is that correct?
>
> A. Yes.

The term *ipsissimus verbis* refers to a disclosure appearing in so many words, rather than, e.g., substantially appearing. The terms C3 cycloalkyl and cyclopropyl are legal equivalents, as noted above. This term, as the identity for R, literally appears in the disclosure, and need not be inferred. Thus, this disclosure appears *ipsis verbis*. Reconsideration is respectfully requested.

II. THE ENGSTROM SUPPLEMENTAL DECLARATION

The decision in both interferences, treats, and denies, the Fujikawa motion to suppress the Engstrom Declaration on the grounds that it was not supported as required by the Federal Rules of

Evidence. The decision in both interferences also heavily relies not on the Engstrom Declaration, but rather the Supplemental Engstrom Declaration, see footnote 3, page 20 of the decision in Interference 102,648 and footnote 4 in the decision in Interference 102,975. Fujikawa moved to suppress this document on the grounds that its submission was untimely, that the error relied upon as a grounds for correction was not explained, and that no good cause was shown for submitting it at the time it was submitted. Accordingly, Fujikawa moves to suppress this document, which is critical to the decision in both interferences.

Specifically, the original Engstrom Declaration, which does not contain evidence of a reduction to practice with respect to 64-935 or any other compound (the 0.49 value assigned cannot be supported on the basis on the data provided in the original declaration, see the Homland testimony with respect thereto) was not submitted until after the period for testimony by Wattanasin closed. In response to the Notice by Fujikawa of an intent to argue suppression, abandonment, or concealment, Wattanasin sought, and received, and additional testimony period, <u>confined to the submission of testimony relevant to the issues of abandonment, suppression and concealment</u>.

The Supplemental Engstrom Declaration, which corrects an

earlier Engstrom Declaration, does not pertain to the issues of suppression, abandonment or concealment. It does not reflect on any of these issues at all. Rather, it changes five numbers appearing in the original Engstrom Declaration and Exhibits, relating to activity.

The Motion To Suppress presents the arguments apparently overlooked, and whose treatment on the record Fujikawa now seeks. They are not repeated herein, other than to note that the arguments are independent of the arguments with respect to the original Declaration. The untimely submission of the Declaration, coupled with a total absence of reasoning or excuse of the submission, or an explanation of the error corrected by the submission and when the error that was the basis for the preparation of the Supplemental Declaration was detected, leads to the conclusion that this Declaration must be suppressed. Reconsideration is respectfully requested.

III. THERE IS DIRECT EVIDENCE OF SUPPRESSION

In the decisions in Interference 102,648 and 102,975, the Board disposes of the issue of suppression and concealment, raised by Fujikawa in its Brief, on the grounds that the delay between reduction to practice and filing is simply not long enough to raise

an inference of suppression, see, e.g., page 26 of the Decision in the Interference 102,648. Yet, Fujikawa's arguments with respect to suppression and concealment were not based on inference alone. Rather, Fujikawa specified evidence of deliberate steps taken to a) prevent publication or public access to information regarding the invention, and b) deliberately delayed preparation of the patent application. Moreover, Fujikawa relied on indirect evidence of suppression or concealment, spurring, Sandoz not actually moving toward the preparation of an application until issuance of the '419 patent. These arguments appear beginning on page 71 of Fujikawa's main brief, and are not considered in the Board's Decision. It is concluded that the Board simply overlooked this aspect of the Brief.

Again and again, Sandoz took deliberate action to prevent publication of information with regard to the invention. Thus, Wattanasin testified that he had been told not to publish information regarding his invention even after the date of conception found by the Board herein, and indeed, well after the actual reduction to practice. Further, even after the conception date, the Patent Committee again and again and again decided not to make a decision whether to proceed with the filing or not, thus extending the period in which the application was considered

secret. Even after a decision was made to bring the "secret" forward in the form of an application, Sandoz, through its agent, repeatedly selected work of lesser priority, work docketed in at a later date, and unrelated to the Wattanasin invention, rather than work on the Wattanasin case to bring it forward.

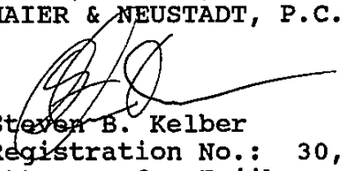
That this is in fact a classic case of suppression is brought home by the fact that the issuance of the '419 patent for Warner-Lambert was the spur that actually caused Sandoz to begin work on a patent application. Inasmuchas, on page 80 of it's brief, Fujikawa specifically noted that this is not a common case, where direct evidence of intention to suppress is difficult to find, but was in fact based on admissions against interest by Wattanasin, and evidence of deliberate attempts to suppress, Fujikawa respectfully submits that, for purposes of a record on appeal if for no other purpose, this argument should be considered. Reconsideration of the Fujikawa arguments with respect to suppression or concealment, and a decision on the record, is respectfully requested.

With respect to this point, it is believed that the date of suppression should be measured from the date of conception, not the date of reduction to practice. In this particular case, Wattanasin must necessarily rely, and the Board has held, that Wattanassin's date "of invention" is a date beginning "early March 1987", page 19

of the decision in Interference 102,648. In any event, the invention date is no later than August 19, 1987, see page 21 of the same decision. This would make the length of delay 18 months, not 16, and consideration of this greater length of delay, which is longer than a delay adequate to raise an inference of suppression in other cases is sought. Accordingly, the Board's Reconsideration of the direct evidence of suppression, and the actual period involved with respect to inferring suppression, is respectfully requested.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.



Steven B. Kelber
Registration No.: 30,073
Attorney for Fujikawa et al

CERTIFICATE OF SERVICE

I hereby certify that true copies of:

1. **REQUEST FOR RECONSIDERATION OF FINAL DECISION, 37 CFR §1.658**

2. **CERTIFICATE OF SERVICE**

were served upon Counsel for Wattanasin as follows:

Diane E. Furman
SANDOZ CORP.
59 Route 10
E. Hanover, New Jersey 07936

via FACSIMILE and FEDERAL EXPRESS, this 28th day of February 1995.

STEVEN B. KELBER

Interference 102,648
Attorney Docket No.: 49-111-0
Wattanasin v. Fujikawa et al
SBK/vdb

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES #121

WATTANASIN

v. Patent Interference No. 102,648

FUJIKAWA et al. Administrative Patent Judge: Sofocleous

FYI

MAR 17 1995

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Commissioner of Patents and Trademarks
Washington, D. C.

WATTANASIN REPLY to

FUJIKAWA REQUEST FOR RECONSIDERATION

In a Final Decision dated January 31, 1995, the Board awarded judgment with respect to the subject matter of count 3, the sole count at issue in the present interference, to Sompong Wattanasin, the junior party. The Board ruled that Wattanasin was entitled to a patent containing claims 8 and 9 of its involved application Serial No. 07/498,301, and Fujikawa et al. (hereinafter "Fujikawa") were not entitled to claims 35, 37 and 38 of their involved application Serial No. 07/233,752.

On February 28, 1995, Fujikawa filed a Request for Reconsideration, indicating that they will be appealing the Board's decision, and seeking reconsideration confined to three issues allegedly "misapprehended" or "overlooked" by the Board.

These three issues comprise the following:

1. Whether the Board "misapprehended" the Wattanasin application by not finding "*ipsis verbis*" 35 USC 112 written description support therein for Fujikawa's proposed claims 11 and 12 corresponding to its proposed added count directed to cyclopropyl-substituted quinoline compounds.

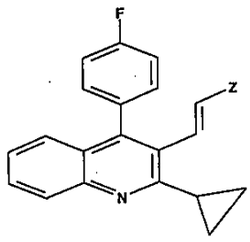
2. Whether the Board "overlooked" Fujikawa's attempt to suppress the Engstrom *Supplemental* Declaration and accompanying Exhibit Q even while the Board denied Fujikawa's motion to suppress the *original* Engstrom Declaration and accompanying Exhibit K-1.

3. Whether the Board "overlooked" Fujikawa's argument that "deliberate" acts of supression were carried out by Wattanasin prior to the filing of the involved Wattanasin application, and even prior to a reduction to practice.

With respect to the above, Wattanasin responds as follows:

1. Literal Support.

As the Board specifically indicated in its Final Decision in companion Interference No. 102,648 (at 7), the proposed Fujikawa claims 11 and 12 are directed to compounds of the following structural formula:



[where Z is a lactone or dihydroxy or keto-hydroxy side chain, as defined in claim 1 of the involved Fujikawa application]

In its analysis, the Board first looked to the Wattanasin application for "*ipsis(sima) verbis*" -- i.e. literal -- support for the Fujikawa claims. Finding neither actual disclosure nor examples, the Board, far from closing its inquiry, continued with a close examination of the Wattanasin disclosure for "blazemarks or motivation" which otherwise would guide one skilled in the art to select the cyclopropyl compounds of the proposed claims from Wattanasin's generic disclosure. The Board concluded that the Wattanasin disclosure was also lacking not only in a literal disclosure of cyclopropyl-substituted compounds, but also in the requisite direction or motivation to prepare such compounds.

Fujikawa, narrowly focusing for purposes of reconsideration on the Board's finding of no literal support for its proposed claims, contends that the Board must have "misapprehended" the Wattanasin disclosure of a C_{3-7}cycloalkyl substituent to arrive at this conclusion.

However, Fujikawa's argument relies on an apparent mischaracterization of the Board's actual holding. That is, while Fujikawa in their Request for Reconsideration represent the Board as holding, in Fujikawa's words, "that the term 'R is cyclopropyl' does not appear *ipsissimus verbis*" [underlining supplied] (Req. Recon. at 4), what the Board actually said -- in *ipsis verbis*, if you will -- is that:

> "It is clear from the foregoing that the application does not describe in *ipsis verbis* the compounds of proposed claims 11 and 12 where R is cyclopropyl...In our view, the Wattanasin application would not reasonably lead one of ordinary skill to the compounds of claims 11 and 12 where R is cyclopropyl, i.e., the application does not reasonably convey to those skilled in the art that Wattanasin invented the compounds [underlining supplied]."

Final Decision in Inteference No. 102,648, at 9.

Thus the Board recognized that there can be a critical difference for section 112 written description purposes, between a disclosure of a particular substituent (assuming arguendo that Wattanasin even made such disclosure), and disclosure of a compound containing that particular substituent among others (e.g., 4-fluorophenyl), which introduces an element of selection, as the Board observed.

In essence, Fujikawa are alleging that the Board has made a mistake of fact in interpreting the literal content of the Wattanasin disclosure.

However, the compounds of the Fujikawa proposed claims are no more disclosed nor exemplified by Wattanasin than compounds bearing a C_7cycloalkyl substituent. In fact, were Wattanasin himself during prosecution to have sought to introduce a claim to a cyclopropyl-substituted compound, there would at least be a question whether the Wattanasin specification provided the requisite written description support for such a claim.

There is no reason why Fujikawa should be accorded any greater benefit from the Wattanasin disclosure for this interference than would be afforded to Wattanasin in ex parte prosecution.

2. Engstrom Supplemental Declaration.

The Board explicitly denied Fujikawa's motion to suppress the Engstrom Declaration and accompanying Exhibit K-1, on which decision had been deferred to final hearing. Fujikawa claims the Board "overlooked" that part of its motion seeking to remove the Engstrom *Supplemental* Declaration, which Wattanasin acknowledges was submitted during the Wattanasin reopened testimony period.

Fujikawa persists in grossly mischaracterizing the Wattanasin *Supplemental* Declaration as being, somehow, a belated attempt to shore up the *original* Engstrom Declaration, and Fujikawa also urges, cryptically, that the Supplemental Declaration entered "critically" into the Board's final decision. (Assuming arguendo this is true, then it must be concluded that the Board already implicitly denied Fujikawa's motion to suppress.)

However, reviewing for a moment the substance of the Engstrom declarations -- it is plainly obvious that the *original* Engstrom Declaration is, within its four corners, fully corroboratory of a reduction to practice of the Wattanasin compounds of the count by in vivo testing in rats. In this declaration, Engstrom describes in detail the methodology by which how the in vivo testing of the Wattanasin compounds was carried out. He refers to appended Exhibit K-1 comprising his notebook pages for the raw computer data obtained by administering a radiolabelled starting material in the cholesterol biosynthesis pathway to rats dosed with test compounds. Exhibit K-1 also contains a computer printout page from the Engstrom notebook listing the ED_{50} values computed from this raw data.[1]

Dr. Engstrom goes on -- redundantly in view of what is already in plain view on the notebook pages of Exhibit K-1 -- to tabulate the ED_{50}'s for the three tested compounds. At this point, a typographical error caused a reversal of the ED_{50} values for 64-933 and 64-935. That this is merely a typographical error is self-evident from the original data in Exhibit K-1, and if that were not enough, from the ED_{50}'s recited elsewhere on the record, beginning

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[1] For example, the raw data on notebook page 137 obtained from rats #25-30 show that a 1 mg/kg dose of compound 64-933 resulted in an average 36.3% reduction in blood cholesterol. On notebook page 138, rats #43-48 registered an average 65.8% reduction in serum cholesterol after being dosed with 1 mg/kg of the most active compound of the Wattanasin series, 64-935. (Note further that the Wattanasin compounds were tested alongside marketed fluvastatin, i.e. compound 62-320).

with page 34 of the involved Wattanasin specification, on which Dr. Wattanasin has given his oath; and continuing into Watanasin Exhibits Y-2 and S-2[2].

In his *Supplemental* Declaration, Engstrom relates that he sent a Biological Activity Data Report dated May 24, 1988 on the Wattanasin compounds (constituting Exhibit Q) to the Sandoz Patent Department, and parenthetically, refers to various handwritten notations and corrections on said Exhibit Q as being made by him at the time the report was prepared. The *Supplemental* Engstrom Declaration and its appended Exhibit Q are wholly consistent with the original Engstrom Declaration as well as the Wattanasin application and other exhibits mentioned above.

This Supplemental Declaration is important to Wattanasin because it contains evidence of activity around May of 1988 toward the filing of a patent application on the Wattanasin invention, which bears on Fujikawa's supression allegations.

Fujikawa complain that there has been no explanation of Wattanasin's typographical errors over which Fujikawa, "late in the day," affect confusion. However, Fujikawa likewise never sought explanation. For whatever reason, Fujikawa chose not to cross-examine Mr. Engstrom, a current employee of Sandoz (the Wattanasin

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[2] Wattanasin Exhibit S-2 was entered into evidence in response to Fujikawa's requests for information and materials at the Kassenoff and Wattanasin depositions, *see* WR 130, 270 and 371-2.

assignee of interest), even when their counsel visited the Sandoz site in New Jersey to cross-examine three other Wattanasin declarants. If Fujikawa had questions about the original or Supplemental Engstrom Declarations, then surely they forwent the opportunity to have their questions answered, and not by counsel for Wattanasin, but by the declarant himself. For this reason alone, Fujikawa should be held to a high degree of persuasion to suppress testimony otherwise important to the Wattanasin, and this burden of persuasion simply has not been met.

3. Suppression.

Fujikawa are also asking the Board to revisit Fujikawa's argument that Wattanasin suppressed his invention.

Fujikawa's current contentions appear to be, on the one hand, that the Board erred in computing the period of time for alleged Wattanasin suppression by not starting from just prior to the Fujikawa critical date; and on the other hand, that the Board overlooked Fujikawa's claims of "deliberate" supression of the Wattanasin invention.

With respect to the first point, if Fujikawa are saying that the relevant time period for analyzing for alleged suppression by Wattanasin begins prior to Wattanasin's reduction practice, then this is surely contrary to fundamental patent law. It is equally inappropriate as Fujikawa's schematic timeline, first produced at final hearing, which went back to Wattanasin's conception document for the start of [sic] "Wattanasin's Period of Suppression of Publications".

35 USC 102(g) does not speak to suppression of a conception, or supression of diligence, or as Fujikawa put it, suppression of "publications". Section 102(g) deals with supression of inventions. The black letter law requiring a reduction to practice before suppression can be found is simply at odds with Fujikawa's contentions. Fujikawa continue to try to "shoehorn" the Wattanasin facts into the configuration of suppression, but the facts just don't fit.

As to Fujikawa's second line of argument, mentioned above, Wattanasin believes that the record amply refutes any allegation of deliberate suppression and/or spurring. The fact that, prior to the meeting of January 27, 1988, the Sandoz Patent Committee voted to defer filing of a patent application on Wattanasin's invention until the in vivo results were in, is not suppression. Moreover, the Committee did act expeditiously to confer an "A" rating for filing as soon as the ED_{50}'s of the Wattanasin compounds were available. Therafter, the record demonstrates that Kassenoff of the Patent Department took early action in February of 1988 to initiate the "spadework" for filing of what ultimately was a 58-page application. Engstrom and Kassenoff have testified about their activities into May of 1988 to enable filing of a patent application, and Giesser testifed working on the draft no later than October 1988 and even prior to September (WR at 450).

Furthermore, there can be no question that the present facts are vastly different from a "spurring" case, where the filing of a patent application is prompted solely by another's entrance into the field, and only after long inactivity by the patent applicant.

Accordingly, the Board is respectfully requested to adhere to its final decision and judgment in this interference.

Respectfully submitted,

Diane Furman

Diane E. Furman
Registration No. 31,104
Attorney for Wattanasin
(201) 503-7332

SANDOZ Corp.
59 Route 10
E. Hanover, NJ 07936

March 14, 1995

Interference No. 102,648
Watt. Reply to
Fuj. Req. Reconsid.

CERTIFICATE OF SERVICE

It is hereby certified that a true copy of the paper entitled:

WATTANASIN REPLY to
FUJIKAWA REQUEST FOR RECONSIDERATION

was served on counsel for the party Fujikawa et al., this 14th day of March 1995, by postage pre-paid first-class mail addressed to the following:

Oblon, Spivak, McClelland, Maier & Neustadt, P.C.
Attn: Steven B. Kelber, Esq.
1755 South Jefferson Davis Highway
Crystal Square 5, Ste. 400
Arlington, VA 22202

Diane Furman

Diane E. Furman

THIS OPINION WAS NOT WRITTEN FOR PUBLICATION

The opinion in support of the decision being entered today (1) was not written for publication in a law journal and (2) is not binding precedent of the Board.

Paper No. 122

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

SOMPONG WATTANASIN,

Junior Party,[1]

v.

YOSHIHIRO FUJIKAWA, MIKIO SUZUKI, HIROSHI IWASAKI, MITSUAKI SAKASHITA and MASAKI KITAHARA,

Senior Party.[2]

Patent Interference No. 102,648

FINAL HEARING: November 22, 1994

Before CALVERT, Vice Chief Administrative Patent Judge, and SOFOCLEOUS and DOWNEY, Administrative Patent Judges.

SOFOCLEOUS, Administrative Patent Judge.

---

[1] Application 07/498,301, filed March 23, 1990. Accorded the benefit of U.S. Application 07/318,773, filed March 3, 1989, now abandoned.

[2] Application 07/233,752, filed August 19, 1988. Accorded the benefit of Japan Applications 207224, filed August 20, 1987; 15585, filed January 26, 1988; and 193606, filed August 3, 1988. Assignors to Nissan Chemical Industries Ltd.

Interference No. 102,648

REQUEST FOR RECONSIDERATION

On February 28, 1995, Fujikawa et al. (hereinafter "Fujikawa") filed a request for reconsideration (Paper No. 120) of our decision of January 31, 1995. Wattanasin has filed a reply (Paper No. 121) thereto.

The request for reconsideration was filed pursuant to 37 C.F.R. § 1.658(b), which requires that a request shall specify with particularity the points believed to have been misapprehended or overlooked in rendering the decision. We have reviewed our decision in light of those arguments and are not persuaded that we overlooked or misapprehended any matters.

The request urges that we overlooked three matters pertaining to this interference. These matters are addressed below.

I

The first matter concerns whether the Wattanasin application contains a written description for proposed claims 11 and 12, which are directed to a limited class of compounds where R is cyclopropyl. In our decision, we agreed with the Administrative Patent Judge (APJ) that the application does not contain a written description for these claims and that the APJ had properly denied Fujikawa's motion to add two proposed counts. At page 9 of our decision, we said, "It is clear from the foregoing that the application does not describe ipsis verbis the

compounds of proposed claims 11 and 12 where R is cyclopropyl." Fujikawa urges that this statement is in error and contends that we overlooked the fact that the application contains a disclosure of cyclopropyl, since the application teaches that each of R and R_o can be C_{3-7} cycloalkyl. Fujikawa states that "Wattanasin has not contested, and the Board no where indicates, that any of the remaining identities recited in claims 11 and 12 are not described . . ." (request, page 4).

We have reviewed our decision and find that we did not overlook the matter complained of. On page 9 of our decision, we stated that "the Wattanasin application would not reasonably lead one of ordinary skill to the compounds of claims 11 and 12 where R is cyclopropyl" (emphasis added). On pages 10 and 11 of our decision, we explained our position and stated, in part, as follows:

> The Wattanasin application does not disclose any compound where R is C_{3-7} cycloalkyl, much less cyclopropyl. Rather, cyclopropyl is merely one moiety embraced by C_{3-7} cycloalkyl which is among a myriad of possibilities for either R or R_o disclosed in the application on page 1, lines 1 to 5. Further, the application at page 4, lines 26 to 34, lists its preferred compounds. None of the listed preferred compounds includes cyclopropyl or even C_{3-7} cycloalkyl in the R position. (Page 10 of our decision.)

Thus we did not overlook the matter since we specifically acknowledged that the Wattanasin application describes cyclopropyl as being a possible moiety for the compounds described therein.

Proposed claims 11 and 12 describe only four compounds out of the thousands of compounds embraced by the generic description of the Wattanasin application. See page 8 of our decision which sets forth Wattanasin's disclosure appearing on page 1, lines 1 to 14 of his application. To obtain any one of these four compounds, one skilled in the art must fortuitously pick and choose from among the nine different variables, i.e., R, R^{o}, R^{1}, R^{2}, R^{3}, R^{4}, R^{4}, X and Z, the specific moieties including 4-flurophenyl as R_{o} and cyclopropyl as R. As we noted in our decision, the application provides no blazemarks or any motivation to guide one skilled in the art to these specific moieties in order to obtain any one of these four compounds. In support of our position, we cited, inter alia, In re Rushig, 379 F.2d 990, 154 USPQ 118 (CCPA 1967), wherein the Court stated, id. at 994, 154 USPQ at 122:

> Specific claims to single compounds require reasonably specific supporting disclosure and while we agree with the appellants, as the board did, that naming is not essential, something more than the disclosure of a class of 1000, or 100, or even 48, compounds is required. Surely, given time, a chemist could name (especially with the aid of a computer) all of the half million compounds within the scope of the broadest claim, which claim is supported by the broad disclosure. This does not constitute support for each compound individually when separately claimed. [Emphasis original.]

As we noted in our decision, this principle is equally applicable to the situation here where the proposed claims are directed to four specific compounds. Thus we did not overlook this matter.

II

The second matter concerns Fujikawa's motion to suppress. The motion requested that we deny consideration of certain portions of Engstrom's declaration and his supplemental declaration insofar as the declarations rely upon a computer-generated summary to obtain the ED_{50} values. On page 22 and 23 of our decision, we denied the motion to suppress and addressed the substance of the motion insofar as it urged that we deny consideration to the testimony concerning the computer-generated summary. We did not explicitly discuss the motion with regard to an error pointed out by Wattanasin, an error which we acknowledged in footnote 3 on page 20 of our decision, with respect to the switching the ED_{50} values for compounds 64-933 and 64-935.

Fujikawa now urges that we overlooked the fact that the motion to suppress also urged that the supplemental declaration was not timely submitted, was submitted belatedly without an explanation of good cause or an identification of how the error concerning switching the ED_{50} values for compounds 64-933 and 64-935 had occurred. However, in denying the motion, we implicitly agreed with Wattanasin's opposition that the error which we noted in footnote 3 should be corrected. The correction did not in any way alter the substance of Engstrom's testimony and Fujikawa's objection did not in any way show that the correction should not have been made or show any undue prejudice inuring to him by our permitting Wattanasin to

correct the error. Cf. Gunn v. Bosch, 181 USPQ 758, 759 (Bd.Pat.Int. 1973). Thus we did not overlook the foregoing matter.

III

The third matter concerns the issue of suppression or concealment. Fujikawa asserts that we overlooked his arguments stressing direct and indirect evidence of suppression and concealment on the part of Wattanasin and that Wattanasin's assignee took deliberate action to prevent publication of information with regard to the invention. Contrary to any assertions in the request, we did not overlook any of Fujikawa's arguments concerning suppression.

As we noted on pages 18 and 19 of our decision, Wattanasin could not rely upon any experimental work completed by June 13, 1985 as an actual reduction to practice because of the failure of the experimental work to meet all the limitations of the count. However, we found that during Wattanasin's second phase of activity actual reduction to practice had occurred by December 9, 1987 (the date of the in vivo testing of compound 64-935). The hiatus in time from the date for actual reduction to practice to Wattanasin's filing date is approximately fifteen months. On pages 25 and 26 of our decision, we found that this hiatus is insufficient to raise the inference of suppression.

At page 9 of the request, Fujikawa states that Sandoz, Wattanasin's assignee, "took deliberate action to prevent publication of information with regard to the invention" (emphasis added), that

Wattanasin "had even been told not to publish information regarding his invention even after the date of conception found by the Board herein, and indeed, well after the actual reduction to practice . . . " (emphasis added), and that the "Patent Committee again and again and again decided not to make a decision whether to proceed with the filing or not. . . ." At page 10 of the request, Fujikawa urges that we should have measured the hiatus from Wattanasin's date of conception and not from the date of actual reduction to practice. These positions are not well taken. It is well settled that without an actual reduction to practice, there is no invention which can be abandoned, suppressed or concealed. Correge v. Murphy, 705 F.2d 1326, 217 USPQ 753 (Fed.Cir. 1983) and Peeler v. Miller, 535 F.2d 647, 190 USPQ 117 (CCPA 1976).

Further at page 10 of the request, Fujikawa urges that this is a classic case of suppression because Wattanasin was spurred into filing his application by the issuance of the Picard patent. As we noted on page 12 of our decision, Picard is not involved in this interference, having filed, through counsel, a request for an adverse judgment. This interference is between Wattanasin and Fujikawa and any action taken with respect to the Picard patent is not relevant to the question of priority between Wattanasin and Fujikawa.

For the foregoing reasons, the request for reconsideration is granted to the extent that we have reviewed our decision and is denied insofar as it seeks any modification thereof.

IAN A. CALVERT, Vice Chief
Administrative Patent Judge

MICHAEL SOFOCLEOUS
Administrative Patent Judge

MARY F. DOWNEY
Administrative Patent Judge

BOARD OF PATENT APPEALS AND INTERFERENCES

svt

Interference No. 102,648

Gerald D. Sharkin
Sandoz Corp.
59 Route 10
E. Hanover, NJ 07936

Oblon, Fisher, Spivak,
McClelland & Maier
1755 S. Jefferson Davis Hwy.
Crystal Square Five-Ste. 400
Arlington, VA 22202

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

SOMPONG WATTANASIN	:	
	:	**INTERFERENCE 102,648**
V.	:	**ADMINISTRATIVE LAW JUDGE**
	:	**MICHAEL SOFOCLEOUS**
YOSHIHIRO FUJIKAWA ET AL	:	

FUJIKAWA ET AL, NOTICE OF APPEAL, 37 CFR §1.301

HONORABLE COMMISSIONER OF PATENTS AND TRADEMARKS
WASHINGTON, DC 20231
BOX INTERFERENCE

SIR:

Pursuant to the provisions of the above-captioned Rule, 37 CFR §1.302 and 37 CFR §1.304, Fujikawa et al hereby serves notice that it appeals the Decision on Final Hearing in the above-captioned Interference, and Decision on Reconsideration, to the U.S. Court of Appeals for the Federal Circuit. Pursuant to the provisions of Rule 301(b), a copy of this Notice of Appeal, together with the requisite fee, has been filed in the Court this day.

It is noted that the Decision on Request for Reconsideration being dated April 6, 1995, this filing on June 2, 1995 is timely.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.

Steven B. Kelber
Registration No.: 30,073
Attorney for Fujikawa et al

Crystal Square Five
Fourth Floor
1755 Jefferson Davis Highway
Arlington, Virginia 22202
(703) 413-3000
(703) 413-2220 (Facsimile)

CERTIFICATE OF SERVICE

I hereby certify that true copies of:

1. **FUJIKAWA ET AL, NOTICE OF APPEAL, 37 CFR §1.301**

2. **CERTIFICATE OF SERVICE**

were served as follows:

Counsel for Wattanasin:

Diane E. Furman
SANDOZ CORP.
59 Route 10
E. Hanover, New Jersey 07936

via FIRST-CLASS MAIL, postage prepaid,

U.S. Court of Appeals for the Federal Circuit

Clerk
U.S. Court of Appeals for the Federal Circuit
717 Madison Place, NW
Washington, DC 20439

via HAND DELIVERY TO THE CLERK'S OFFICE WITH $100.00 FEE

this SECOND day of JUNE, 1995.

STEVEN B. KELBER

Interference No. 102,648

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

SOMPONG WATTANASIN	:	
	:	**INTERFERENCE 102,648**
V.	:	**ADMINISTRATIVE LAW JUDGE**
	:	**MICHAEL SOFOCLEOUS**
YOSHIHIRO FUJIKAWA ET AL	:	

FUJIKAWA ET AL, NOTICE OF APPEAL, 37 CFR §1.301

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Respectfully submitted,

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Steven B. Kelber
Registration No.: 30,073
Attorney for Fujikawa et al

Crystal Square Five
Fourth Floor
1755 Jefferson Davis Highway
Arlington, Virginia 22202
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(703) 413-2220 (Facsimile)

CERTIFICATE OF SERVICE

I hereby certify that true copies of:

1. **FUJIKAWA ET AL, NOTICE OF APPEAL, 37 CFR §1.301**
2. **CERTIFICATE OF SERVICE**

were served as follows:

Counsel for Wattanasin:

Diane E. Furman
SANDOZ CORP.
59 Route 10
E. Hanover, New Jersey 07936

via FIRST-CLASS MAIL, postage prepaid,

U.S. Court of Appeals for the Federal Circuit

Clerk
U.S. Court of Appeals for the Federal Circuit
717 Madison Place, NW
Washington, DC 20439

via HAND DELIVERY TO THE CLERK'S OFFICE WITH $100.00 FEE

this SECOND day of JUNE, 1995.

STEVEN B. KELBER

Interference No. 102,648

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

SOMPONG WATTANASIN	:	
	:	INTERFERENCE 102,648
V.	:	ADMINISTRATIVE LAW JUDGE
	:	MICHAEL SOFOCLEOUS
YOSHIHIRO FUJIKAWA ET AL	:	

FUJIKAWA ET AL, NOTICE OF APPEAL, 37 CFR §1.301

HONORABLE COMMISSIONER OF PATENTS AND TRADEMARKS
WASHINGTON, DC 20231
BOX INTERFERENCE

SIR:

Pursuant to the provisions of the above-captioned Rule, 37 CFR §1.302 and 37 CFR §1.304, Fujikawa et al hereby serves notice that it appeals the Decision on Final Hearing in the above-captioned Interference, and Decision on Reconsideration, to the U.S. Court of Appeals for the Federal Circuit. Pursuant to the provisions of Rule 301(b), a copy of this Notice of Appeal, together with the requisite fee, has been filed in the Court this day.

It is noted that the Decision on Request for Reconsideration being dated April 6, 1995, this filing on June 2, 1995 is timely.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.

Steven B. Kelber
Registration No.: 30,073
Attorney for Fujikawa et al

Crystal Square Five
Fourth Floor
1755 Jefferson Davis Highway
Arlington, Virginia 22202
(703) 413-3000
(703) 413-2220 (Facsimile)

CERTIFICATE OF SERVICE

I hereby certify that true copies of:

1. **FUJIKAWA ET AL, NOTICE OF APPEAL, 37 CFR §1.301**
2. **CERTIFICATE OF SERVICE**

were served as follows:

Counsel for Wattanasin:

Diane E. Furman
SANDOZ CORP.
59 Route 10
E. Hanover, New Jersey 07936

via FIRST-CLASS MAIL, postage prepaid,

U.S. Court of Appeals for the Federal Circuit

Clerk
U.S. Court of Appeals for the Federal Circuit
717 Madison Place, NW
Washington, DC 20439

via HAND DELIVERY TO THE CLERK'S OFFICE WITH $100.00 FEE

this SECOND day of JUNE, 1995.

STEVEN B. KELBER

Interference No. 102,648

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

SOMPONG WATTANASIN	:	
	:	INTERFERENCE 102,648
V.	:	ADMINISTRATIVE LAW JUDGE
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FUJIKAWA ET AL, NOTICE OF APPEAL, 37 CFR §1.301

HONORABLE COMMISSIONER OF PATENTS AND TRADEMARKS
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this SECOND day of JUNE, 1995.

STEVEN B. KELBER

Interference No. 102,648

UNITED STATES COURT OF APPEALS #124

FOR THE FEDERAL CIRCUIT

YOSHIHIRO FUJIKAWA, MIKIO SUZUKI, HIROSHI IWASAKI, MITSUAKI SAKASHITA, and MASAKI KITAHARA, Appellant, v. SOMPONG WATTANASIN, Appellee. Interference No. 102,648	Appeal No. 95-

NOTICE FORWARDING CERTIFIED LIST

A notice of appeal to the U.S. Court of Appeals for the Federal Circuit was timely filed on June 2, 1995, in the Patent and Trademark Office in connection with the above-identified interference. Pursuant to 35 U.S.C. § 143 and Federal Circuit Rule 17(b)(1), a certified list is this day being forwarded to the Federal Circuit.

A copy of the list is this day being forwarded to counsel for appellant and appellee in envelopes addressed as follows:

Norman F. Oblon et al.
Oblon, Fisher, Spivak,
McClelland & Maier
1755 S. Jefferson Davis Highway
Crystal Square 5, Suite 400
Arlington, VA 22202

Gerald D. Sharkin
Sandoz Corporation
59 Route 10
E. Hanover, NJ 07936

If copies of the notice of appeal and the docketing fee of $100.00 have not been already filed with the Federal Circuit, counsel is reminded that three copies of the notice and the docketing fee should be promptly filed with the Federal Circuit. The mailing address of the Federal Circuit is:

U.S. Court of Appeals for
the Federal Circuit
717 Madison Place, N.W.
Washington, D.C. 20439

Counsel for appellant may contact counsel for appellee to arrange for designating the record.

Respectfully submitted,

BRUCE A. LEHMAN
Assistant Secretary of Commerce
and Commissioner of Patents
and Trademarks

Date: July 3, 1995

By: Laura Lee Feldman
Laura Lee Feldman
Paralegal Specialist
P.O. Box 15667
Arlington, Virginia 22215
703-305-9035

Form PTO 55 (12-80)

U. S DEPARTMENT OF COMMERCE
United States Patent and Trademark Office

June 30, 1995
(Date)

THIS IS TO CERTIFY that the annexed is a true copy from the records of this office

of the "Contents" page of the file wrapper of the interference proceeding identified below, said "Contents" page being a list of the papers comprising the record before the United States Court of Appeals for the Federal Circuit in the matter of

Sompong Wattanasin

v.

Yoshihiro Fujikawa, Mikio Suzuki, Hiroshi Iwasaki, Mitsuaki Sakashita and Masaki Kitahara

Interference No. 102,648 Declared March 11, 1992

By authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

Certifying Officer.

Wattanasin v. ~~Picard et al~~ patentee v. Fujikawa et al

102648

11 MAR 1992 **DECLARATION, MOTIONS DUE**

11 MAR 1992 – PS & MOS DUE 11 JUN 1992

Mar. 17, 92 – Designation of lead Counsel – Fujikawa et al

Mar. 18, 92 – Power to Inspect & make Copies – Fujikawa et al

Mar. 26, 92 – Suppl. Designation of lead counsel (C.60(b)) – Fujikawa et al

Mar. 25, 92 – (R.602) – Notification of Interest (C 9/13-24-92) – Wattanasin

Mar. 24, 92 – Designation of lead atty. (C of M 3/23/92) – Wattanasin

Apr. 7, 92 – Power to inspect and Make Copies – Wattanasin

Apr. 8, 92 – Designation of Lead Attorney (C 9/14-6-92) – Picard et al

Apr. 8, 92 – Request – (R.662(a)) For Entry of Adverse Judgment as to Cnts 1 & 2 of Picard et al. Picard et al.

Apr. 10, 92 – Judgment adverse to Picard et al.

Jun. 11, 92 – Certificate of Service of Papers filed – Fujikawa et al.

Jun. 11, 92 – Notice of Filing (Sealed) P.S. – Fujikawa et al.

Jun. 11, 92 – Motion For Benefit (R.633(E)) – Fujikawa et al

Jun. 11, 92 – Motion to Add Counts (R.633(c)) – Fujikawa et al

Jun. 11, 92 – Motion For Benefit (R.633(E)) – Fujikawa et al.

Jun. 11, 92 – Statement of Related applications – Fujikawa et al.

Jun. 15, 92 – Notice of Filing (Sealed) P.S. – Wattanasin

Jun. 15, 92 – Prelim. Motion (R.633(c)(1)) – Wattanasin

Jun. 15, 92 – Prelim Motion (R.635) (w/attach.) – Wattanasin

Jun. 15, 92 – Contingent Preliminary Motion (R.633(e)) – Wattanasin

Jun. 15, 92 – Cont'g. Prelim. Mo. For Benefit (R.633(E)) – Wattanasin

Jun. 19, 92 – Power to inspect and Make Copies – Wattanasin

July 1, 92 – Oppos. to Contingent Prelim. Mo. (R.633(E)) & P/Mo. (R.635) – Fujikawa et al

July 1, 92 – Oppos. to the Contingent Prelim. Mo. For Benefit (R.633(E)) – Fujikawa et al.

July 1, 92 – Motion For Benefit (R.633(j)) – Fujikawa et al.

July 1, 92 – Opposition to Prelim. Motion to Substitute a Count – Fujikawa et al.

July 1, 1992 – Oppos. to mo. to add count and to add claims – Wattanasin

July 7, 92 – Power to Inspect – Wattanasin

July 16, 92 – Motion For Extension of time – Fujikawa et al.

* U.S. GOVERNMENT PRINTING OFFICE 1985-468-832

Wattanasin v. Fujikawa et al

102 648

[SHEET 2]

3	1	Ext. of Time Granted (Reply due 7-21-92) Fujikawa et al (Wattanasin)	5/4
3	2	Jul. 21, 92 - Reply to the oppos. to mo. to add Cts. 3 & 4 -	
3	3	Jul. 21 92 - Joint stip. to designate Inv 1 as corresponding to Ct. 1 etc. Wattanasin (Cofm 7/21/92)	
3	4	Jul. 27, 92 - Reply to oppos. to mo. to subst. Ct. - Wattanasin (Cofm 7/21/92)	
3	5	Jul. 27, 92 Motion to Correct typographical Error etc. - (R. 635 + 638) (Cofm 7/21/92)	
3	6	Jul. 27, 92 - Reply to oppos. to motions - Wattanasin (Cofm 7/21/92)	
3	7	Jul. 27, 92 - Reply to oppos. to mo. for benefit - (R. 633) (Cofm 7/21/92)	
3	8	Jul. 27, 92 - second Cont. mo. for benefit - Wattanasin (R. 633) (Cofm 7/21/92)	
3	9	Jul. 27, 92 - Cont. Opposition to mo. for benefit - Wattanasin Service 7.30.92 due 8/17/92	
4	0	Aug 1, 92 - EIC proposes to set up new des. Fujikawa et al.	
4	1	Aug. 3, 92 - Reply to belated oppos. to mo. for benefit - Fujikawa et al	
4	2	Aug. 3, 92 - oppos. to mo. to correct typo error etc. - Fujikawa et al	
4	3	Aug. 11, 92 - Refiling of supplemental declaration - Fujikawa et al 8/31	
4	4	Aug. 10, 92 - Response to Reply to oppos. to Mo. to add counts & Clmst. to appl. - Wattanasin	
4	5	Aug 21, 92 - Counts 1 + 2 are stricken + Ct 3 is added Fujikawa et al	
4	6	Aug. 18, 92 - Power to Inspect + make copies - (R. 635 + 645)	
4	7	Aug. 17, 92 - Request for ext. of time - Wattanasin	
4	8	Aug. 21, 92 - Extension of time granted to 8/27/92	9/
4	9	Aug. 21, 92 - Comment on mo. for ext. of time - Fujikawa et al	
8	0	Aug. 21, 92 - Request for Reconsideration Fujikawa et al	
5	1	Aug 17, 92 - Notice of Service - Fujikawa et al (Cofm 8/27/92)	
5	2	Aug. 31, 92 - Acknowledgement of Notification - Wattanasin	
5	3	Aug. 31, 92 Notification of Service of P. Stmt - Wattanasin (Cofm 8/27/92)	
5	4	Aug. 31, 92 - Response to Request for Reconsideration - Wattanasin (Cofm 8/27/92)	
5	5	Aug. 31, 92 - Response to Comment of mo. for ext. of time - Wattanasin (Cofm 8/27/92)	
5	6	Aug. 31, 92 - Notice of filing Dec. of Stephen Pieken Stmt. - Wattanasin (Cofm 8/27/92)	
5	7	Sep. 3, 92 - Modification of Request for Reconsid. etc. - Fujikawa et al	
5	8	Sep. 21, 92 - Reconsideration granted to foregoing extent	
5	9	Sept. 22, 92 - Jr. parties reply Brief due 6/15/93	6/
6	0	Sept. 30, 92 - Request For preservation of issues + Evidence - Fujikawa et al	6/29

FORM PTO-257(A)
(REV. 3-78)

U. S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE

102648

[SHEET 3]

6 1 Oct. 30, 92 Prof. of Invention - Wattanasin
6 2 Nov. 19, 92 Motion to Consolidate Record - Wattanasin
6 3 Nov. 19, 92 Motion for Ext. of Time - Wattanasin (GRANTED 11/16/92)
6 4 Nov. 19, 92 Notice of Intent to Rely - Wattanasin
6 5 Nov. 19, 92 TESTIMONY FOR Wattanasin, 12 vols., (Rm. 10C06) (c.d.m 11/16/92)
6 6 Nov. 19, 92 EXHIBITS FOR Wattanasin, 2 vols., (Rm. 10C06) (c.d.m 11/16/92)
6 7 Dec. 10, 92 - Request for Extension of time - Fujikawa et al.
6 8 Dec. 7, 92 Request for Cross-Exam - Fujikawa
6 9 Dec. 15, 92 - Notice of Intent to Argue Abandonment, Suppression or Concealment - Fujikawa et al.
7 0 Dec. 14, 92 Notice of Deposition - Wattanasin, (c.d.m 12/11/92)
7 1 DEC. 24, 192 - EXT. OF TIME APPROVED - TESTY due 2/25/193 7/11
7 2 Jan. 8, 93 Mot. for Additional Testy - Wattanasin
7 3 Jan. 13, 93 - Opposition to Motion For leave to present additional Testy - Fujikawa et al
7 4 Feb. 1, 93 Notice of Intent to Rely - Fujikawa et al.
7 5 Feb. 1, 93 Official Records & Printed Publications TESTIMONY FOR Fujikawa (c.d.m 1/28/93)
7 6 Feb. 1, 93 Reply to Opp. to Mot. for Leave - Wattanasin
7 7 Feb. 5, 92 - Times remaining as set in Paper No 59
7 8 Feb. 18, 93 - Motion For Extension of time (R.645) (R635) - Fujikawa et al.
7 9 Feb. 19, 93 - Extension of time granted to 3/25/93 3/8
8 0 Feb. 25, 93 - Request For Cross-Examination - Fujikawa
8 1 Mar. 1, 93 Notice of Deposition - Fujikawa et al.
8 2 Feb. 24, 93 TESTIMONY FOR Wattanasin, (c.d.m 2/22/93)
8 3 Mar. 19, 93 - Joint Request For Extension of time - Wattanasin & Fujikawa, et al.
8 4 Mar. 19, 93 - Extension of time granted to 8/09/93 - R.B. due
8 5 Mar. 29, 93 - Notice of Deposition - Fujikawa et al. 8/18
8 6 Apr. 6, 93 Notice of Deposition - Wattanasin
8 7 Apr. 22, 93 TESTIMONY FOR Fujikawa, 3 vols. Room 10C06 (c.d.m 4/22/93)
8 8 Apr. 26, 93 TESTIMONY FOR Fujikawa, 1 vol. Room 10C06
8 9 May 10, 93 TESTIMONY FOR Wattanasin, 1 vol. Room 10C06
9 0 May 17, 93 Motion to Consolidate Record - Fujikawa et al.

FORM PTO-257(A)
REV. 3-78)

U. S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE

102648

[SHEET 4]

1. May 17,93 RECORD FOR Fujikawa et. al., 5 vols., 3 copies Room 10C06
2. May 17,93 EXHIBITS FOR Fujikawa et. al. Room 10C06
3. May 19,93 RECORD FOR Wattanasin, 5 vols., 3 copies Room 10C06 (C of M 5/17/93)
4. May 19,93 EXHIBITS FOR Wattanasin Room 10C06
5. May 26,93 - Motion for Sanctions - (Wattach) - Fujikawa
6. June 1,93 - Receipt acknowledged paper no. 90 + 95
7. May 28,93 Communication - Wattanasin
8. Jun. 4,93 - Request for extension of time - Wattanasin
9. June 8,93 - Extension of time granted to 9/6/93 RB, Lee (C of M 6/14/93) Wattanasin 9/20
10. Jun. 17,93 - Opposition to motion for sanctions - Fujikawa et al
11. Jun. 21,93 - Reply to oppos. to motions for Sanctions
12. June 23,93 - Times remain as set in Paper No. 99
13. July 19,93 Motion for Extension of Time - Wattanasin (C of M 7/15/93)
14. July 22,93 - Extension of time approved to 7/16/93
15. July 19,93 BRIEF FOR Wattanasin, 1 orig., 3 copies, (C of M 7/16/93) Rm. 10C06
16. July 19,93 Proposed Findings of Fact & Conclusions of Law - Wattanasin Rm. 10C06
17. Aug. 16,93 BRIEF FOR Fujikawa et. al., 1 orig., 3 copies Rm. 10C06
18. Aug. 16,93 Oppo. to Proposed Findings of Fact - Fujikawa Rm. 10C06
19. Aug. 16,93 Motion to Suppress Evidence - Fujikawa Rm. 10C06
20. Sept. 7,93 Errata Sheet for Brief - Fujikawa Rm. 10C06
21. Sept 7,93 Errata Sheet for findings of fact - Fujikawa Rm. 10C06
22. Sept. 13,93 REPLY BRIEF FOR Wattanasin, 1 orig., 3 copies (C of M 9/17/93)
23. Sept. 13,93 Oppo to MS. to Suppress - Wattanasin
24. Sept. 13,93 Reply to Oppo. to Proposed Findings of Fact - Wattanasin
25. Sept. 22,93 Reply to Oppo. to M.S. to suppress - Fujikawa
26. Sept. 22,93 Extra copies of M.S. to suppress + findings of fact - Wattanasin
27. Sep 16,94 Final hearing set for 11-22-94
28. Nov 22,94 - Appearance Record
29. Jan. 31,95 - Final hearing, judgment awarded to Wattanasin
30. 2-8-95 - Request For Reconsideration of Final Decision - Fujikawa et al. (R. 658)

FORM PTO-257(A) (REV. 3-78)

U. S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE

102648

[SHEET 5]

12 1 Mar. 17, 95 - Reply to Request for Reconsideration - Watanabe
12 2 April 6, 95 - Reconsideration - Denied
12 3 June 2, 1995 Appeal to Fed. Cir.

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FORM PTO-257(A)
(REV. 3-75)

U. S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE

PAPER NO. 125

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PAT. & T.M. OFFICE
BOARD OF PATENT APPEALS
AND INTERFERENCES

Interference No. 102,648

Wattanasin

v.

Fujikawa et al

Receipt is acknowledged of the Notice of Appeal to the U.S. Court of Appeals for the Federal Circuit filed by Fujikawa et al on June 2, 1995.

Olivia M. Duvall

Olivia M. Duvall, Sup'v Legal
Instruments Examiner
Board of Patent Appeals &
Interferences
(703) 603-3298

MISCELLANEOUS PAGE(S)

FROM THE U.S. PATENT OFFICE

OFFICIAL FILE WRAPPER

United States Court of Appeals for the Federal Circuit

95-1418

YOSHIHIRO FUJIKAWA, MIKIO SUZUKI,
HIROSHI IWASAKI, MITSUAKI SAKASHITA
and MASAKI KITAHARA,
Appellants,

v.

SOMPONG WATTANASIN,
Appellee.

- - - - - - - - - - - -

95-1425

YOSHIHIRO FUJIKAWA, MIKIO SUZUKI,
HIROSHI IWASAKI, MITSUAKI SAKASHITA
and MASAKI KITAHARA,
Appellants,

v.

SOMPONG WATTANASIN,
Appellee.

JUDGMENT

Appeal from decisions of the Board of Patent Appeals and Interference Nos. 102,648 and 102,975 dated January 31, 1995, and upon reconsideration on April 6, 1995.

This CAUSE having been heard and considered, it is

ORDERED and ADJUDGED: **AFFIRMED**

ENTERED BY ORDER OF THE COURT

DATED: AUGUST 28, 1996

Francis X. Gindhart
Francis X. Gindhart, Clerk

ISSUED AS A MANDATE: SEP [illegible] 1996

A True Copy.
Attest: 9/18/96
Linda R. Rudie
Deputy Clerk

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

95-1418

YOSHIHIRO FUJIKAWA, MIKIO SUZUKI,
HIROSHI IWASAKI, MITSUAKI SAKASHITA
and MASAKI KITAHARA,
Appellants,

v.

SOMPONG WATTANASIN,
Appellee.

- - - - - - - - - - - - -

95-1425

YOSHIHIRO FUJIKAWA, MIKIO SUZUKI,
HIROSHI IWASAKI, MITSUAKI SAKASHITA
and MASAKI KITAHARA,
Appellants,

v.

SOMPONG WATTANASIN,
Appellee.

Steven B. Kelber, Oblon, Spivak, McClelland, Maier & Neustadt, P.C., of Arlington, Virginia, argued for appellants.

Diane E. Furman, Sandoz Corporation, of East Hanover, New Jersey, argued for appellee.

Appealed from: U.S. Patent and Trademark Office
Board of Patent Appeals and Interferences

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

95-1418

YOSHIHIRO FUJIKAWA, MIKIO SUZUKI,
HIROSHI IWASAKI, MITSUAKI SAKASHITA
and MASAKI KITAHARA

Appellants,

v.

SOMPONG WATTANASIN

Appellee.

- - - - - - - - - - - - -

95-1425

YOSHIHIRO FUJIKAWA, MIKIO SUZUKI,
HIROSHI IWASAKI, MITSUAKI SAKASHITA
and MASAKI KITAHARA

Appellants,

v.

SOMPONG WATTANASIN

Appellee.

DECIDED: August 28, 1996

Before MAYER, CLEVENGER, and RADER, Circuit Judges.
CLEVENGER, Circuit Judge.

Yoshihiro Fujikawa et al (Fujikawa) appeal from two decisions of the Board of Patent Appeals and Interferences of the United States Patent & Trademark Office (Board) granting priority of invention in two related interferences to Sompong Wattanasin, and denying Fujikawa's motion to add an additional sub-genus count to the interferences. We affirm.

I

These interferences pertain to a compound and method for inhibiting cholesterol biosynthesis in humans and other animals. The compound count recites a genus of novel mevalonolactones. The method count recites a method of inhibiting the biosynthesis of cholesterol by administering to a "patient in need of said treatment" an appropriate dosage of a compound falling within the scope of the compound count.

The real parties in interest are Sandoz Pharmaceuticals Corporation (Sandoz), assignee of Wattanasin, and Nissan Chemical Industries, Ltd. (Nissan), assignee of Fujikawa.

The inventive activity of Fujikawa, the senior party, occurred overseas. Fujikawa can thus rely only on his effective filing date, August 20, 1987, to establish priority. 35 U.S.C. § 102(g) (1994). Whether Wattanasin is entitled to priority as against Fujikawa therefore turns on two discrete questions. First, whether Wattanasin has shown conception coupled with diligence from just prior to Fujikawa's effective filing date until reduction to practice. Id. Second, whether Wattanasin suppressed or concealed the invention between reduction to practice and filing. Id. With respect to the first question, Fujikawa does not directly challenge the Board's holdings on Wattanasin's conception or diligence, but rather contends that the Board incorrectly fixed the date of Wattanasin's reduction to practice. As for the second question, Fujikawa contends that the Board erred in concluding that Wattanasin had not suppressed or concealed the invention. Fujikawa

seeks reversal, and thus to establish priority in its favor, on either ground.

II

The Board divided Wattanasin's inventive activity into two phases. The first phase commenced in 1979 when Sandoz began searching for drugs which would inhibit the biosynthesis of cholesterol. Inventor Wattanasin was assigned to this project in 1982, and during 1984-1985 he synthesized three compounds falling within the scope of the compound count. When tested in vitro, each of these compounds exhibited some cholesterol-inhibiting activity, although not all the chemicals were equally effective. Still, according to one Sandoz researcher, Dr. Damon, these test results indicated that, to a high probability, the three compounds "would be active when administered in vivo to a patient to inhibit cholesterol biosynthesis, i.e. for the treatment of hypercholesteremia or atherosclerosis." Notwithstanding these seemingly positive results, Sandoz shelved Wattanasin's project for almost two years, apparently because the level of in vitro activity in two of the three compounds was disappointingly low.

By January 1987, however, interest in Wattanasin's invention had revived, and the second phase of activity began. Over the next several months, four more compounds falling within the scope of the compound count were synthesized. In October, these compounds were tested for in vitro activity, and each of the four compounds yielded positive results. Again, however, there were significant differences in the level of in vitro activity of the four

compounds. Two of the compounds in particular, numbered 64-935 and 64-936, exhibited in vitro activity significantly higher than that of the other two compounds, numbered 64-933 and 64-934.

Soon after, in December 1987, the three most active compounds in vitro were subjected to additional in vivo testing. For Sandoz, one primary purpose of these tests was to determine the in vivo potency of the three compounds relative to that of Compactin, a prior art compound of known cholesterol-inhibiting potency. From the results of the in vivo tests, reproduced in the margin,[1] Sandoz calculated an ED_{50}[2] for each of the compounds and compared it to the ED_{50} of Compactin. Only one of the compounds, compound 64-935, manifested a better ED_{50} than Compactin: an ED_{50} of 0.49 as compared to Compactin's ED_{50} of 3.5. All of the tests performed by Sandoz were conducted in accordance with established protocols.

1

Compound	dosage	% change
64-933	1.0	-36.3%
	0.3	-17.0%
	0.1	-18.6%
64-935	1.0	-65.8%
	0.3	-29.7%
	0.1	-36.3%
64-936	1.0	-9.0%
	0.3	-39.2%
	0.1	-22.5%

[2] The ED_{50} of a compound represents the effective concentration, measured in milligrams of compound per kilogram of laboratory specimen, which inhibits cholesterol biosynthesis by 50%.

During this period, Sandoz also began to consider whether, and when, a patent application should be filed for Wattanasin's invention. Several times during the second phase of activity, the Sandoz patent committee considered the question of Wattanasin's invention but decided that it was too early in the invention's development to file a patent application. Each time, however, the patent committee merely deferred decision on the matter and specified that it would be taken up again at subsequent meetings. Finally, in January 1988, with the in vivo testing completed, the Committee assigned Wattanasin's invention an "A" rating which meant that the invention was ripe for filing and that a patent application should be prepared. The case was assigned to a Ms. Geisser, a young patent attorney in the Sandoz patent department with little experience in the pharmaceutical field.

Over the next several months the Sandoz patent department collected additional data from the inventor which was needed to prepare the patent application. This data gathering took until approximately the end of May 1988. At that point, work on the case seems to have ceased for several months until Ms. Geisser began preparing a draft sometime in the latter half of 1988. The parties dispute when this preparation began. Fujikawa contends that it occurred as late as October, and that Ms. Geisser was spurred to begin preparing the draft application by the discovery that a patent to the same subject matter had been issued to a third party, Picard. Fujikawa, however, has no evidence to support that contention. In contrast, Sandoz contends that Ms. Geisser began

the draft as early as August, and that she was already working on the draft when she first heard of Picard's patent. The evidence of record, and in particular the testimony of Ms. Geisser, supports that version of events. In any event, the draft was completed in November and, after several turn-arounds with the inventor, ultimately filed in March of 1989.

Both Wattanasin and Fujikawa requested an interference with Picard. The requests were granted and a three-party interference between Picard, Fujikawa, and Wattanasin was set up. Early in the proceedings, however, Picard filed a request for an adverse judgment presumably because he could not antedate Fujikawa's priority date. What remained was a two-party interference between Fujikawa and Wattanasin. Ultimately, for reasons not significant to this appeal, the interference was divided into two interferences: one relating to the method count and one relating to the compound count. The Board decided each of these interferences adverse to Fujikawa.

With respect to the compound count, the Board made two alternative findings regarding reduction to practice. First, it found that the in vitro results in October 1987 showed sufficient practical utility for the compound so as to constitute a reduction to practice as of the date of those tests.[3] In the alternative, the Board held, the in vivo tests which showed significant activity

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[3] As explained more fully below, reduction to practice requires a showing of practical utility, which may be satisfied by an "adequate showing of any pharmacological activity." Nelson v. Bowler, 626 F.2d 853, 856, 206 USPQ 881, 883 (CCPA 1980).

in the 64-935 compound at doses of 1.0 and 0.1 mg were sufficient to show practical utility. Consequently, Wattanasin had reduced the compound to practice, at the latest, as of December 1987. Since Fujikawa did not challenge Wattanasin's diligence for the period between Fujikawa's effective filing date of August 20, 1987 and Wattanasin's reduction to practice in either October or December 1987, the Board held that Wattanasin was de facto the first inventor of the compound count. Finally, the Board found that the seventeen month period (counting from the in vitro testing) or fifteen month period (counting from the in vivo testing) between Wattanasin's reduction to practice and filing was not sufficient to raise an inference of suppression or concealment given the complexity of the invention, and therefore awarded priority of the compound count to Wattanasin. In reaching this conclusion, the Board rejected Fujikawa's argument that Wattanasin was spurred to file by Picard because it held that spurring by Picard, a third party, had no legal effect in a priority dispute between Fujikawa and Wattanasin.

With respect to the method count, the Board determined that Wattanasin reduced to practice in December 1987 on the date that in vivo testing of the 64-935 compound was concluded. In reaching that conclusion, the Board first noted that a reduction to practice must include every limitation of the count. Consequently, Wattanasin's early in vitro testing could not constitute a reduction to practice of the method count, since that count recites administering the compound to a "patient." The in vivo testing,

however, met the limitations of the count since the word "patient" was sufficiently broad to include the laboratory rats to whom the compounds were administered. The in vivo testing also proved that 64-935 had practical utility because the compound displayed significant cholesterol inhibiting activity at doses of 1.0 and 0.1 mg. Given this date of reduction to practice, the Board again held that Wattanasin was the de facto first inventor of the count and that the delay in filing of fifteen months was not sufficient to trigger an inference of suppression or concealment. The Board therefore awarded priority of the method count to Wattanasin.

Before this court, Fujikawa seeks review of these adverse priority determinations. In addition, during the motions period of the interference, Fujikawa moved to have an additional sub-genus count added to the interference. The Board denied that motion on the ground that the Wattanasin disclosure did not contain a sufficient written description to support the proposed count. Fujikawa appeals that decision, as well. We have jurisdiction to hear this appeal under 28 U.S.C. § 1295(a)(4)(A) (1994).

III

We first address Fujikawa's argument that Wattanasin's in vitro and in vivo tests failed to establish a practical utility for either the compound or method count. The Board held that the in vitro tests established a practical utility for the compound and that the in vivo tests established a practical utility for both the compound and method counts. For the reasons set out below, we affirm these findings of the Board.

For over 200 years, the concept of utility has occupied a central role in our patent system. See Brenner v. Manson, 383 U.S. 519, 529, 148 USPQ 689, 693 (1966). Indeed, "[t]he basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." Id. at 534, 148 USPQ at 695. Consequently, it is well established that a patent may not be granted to an invention unless substantial or practical utility for the invention has been discovered and disclosed. See Cross v. Iizuka, 753 F.2d 1040, 1044, 224 USPQ 739, 742 (Fed. Cir. 1985). Similarly, actual reduction to practice, which constitutes in law the final phase of invention, cannot be established absent a showing of practical utility. See Blicke v. Treves, 241 F.2d 718, 720-21, 112 USPQ 472, 474-75 (CCPA 1957).

In the pharmaceutical arts, our court has long held that practical utility may be shown by adequate evidence of any pharmacological activity. See, e.g., Nelson v. Bowler, 626 F.2d 853, 856, 206 USPQ 881, 883 (CCPA 1980); In re Krimmel, 292 F.2d 948, 952-53, 130 USPQ 215, 219 (CCPA 1961). For example, in Campbell v. Wettstein, 476 F.2d 642, 646-47, 177 USPQ 376, 379 (C.C.P.A. 1973) we stated that "[m]oreover, the interference counts contain no limitation relating to intended use or to discovered properties of the claimed compounds. Accordingly, under well-established precedent, evidence establishing substantial utility for any purpose is sufficient to show reduction to practice." The rule in Campbell was applied in Rey-Bellet v. Engelhardt, 493 F.2d

1380, 1383, 181 USPQ 453, 454 (C.C.P.A. 1974) ("Since the count contains no limitation related to any utility, evidence which would establish a substantial utility for any purpose is sufficient to show its reduction to practice.").[4] Such activity constitutes a practical utility because "[i]t is inherently faster and easier to combat illnesses and alleviate symptoms when the medical profession is armed with an arsenal of chemicals having known pharmacological activities. Since it is crucial to provide researchers with an incentive to disclose pharmacological activities in as many compounds as possible, we conclude that adequate proof of any such activity constitutes a showing of practical utility." Nelson, 626 F.2d at 856, 206 USPQ at 883; see also Krimmel, 292 F.2d at 952-53, 130 USPQ at 219.

It may be difficult to predict, however, whether a novel compound will exhibit pharmacological activity, even when the behavior of analogous compounds is known to those skilled in the art. Consequently, testing is often required to establish practical utility. See, e.g., Blicke, 241 F.2d at 720, 112 USPQ at 475. But the test results need not absolutely prove that the

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[4] Strictly speaking, this articulation of the standard (i.e. evidence of any pharmacological activity) applies only when the count does not recite a particular utility. See Rey-Bellet v. Engelhardt, 493 F.2d 1380, 1383, 181 USPQ 453, 454 (CCPA 1974). In contrast, when the count recites a particular utility, practical utility requires an adequate showing of the recited utility. In this case, the compound count does not recite a particular utility, and practical utility is thus satisfied by evidence of any pharmacological activity. The method count, however, does recite a particular utility (i.e., cholesterol inhibition in patients in need of such treatment), and practical utility for that count therefore requires an adequate showing of that recited utility.

compound is pharmacologically active. All that is required is that the tests be "reasonably indicative of the desired [pharmacological] response." Nelson, 626 F.2d at 856, 206 USPQ at 884. (emphasis added). In other words, there must be a sufficient correlation between the tests and an asserted pharmacological activity so as to convince those skilled in the art, to a reasonable probability, that the novel compound will exhibit the asserted pharmacological behavior. See Cross, 753 F.2d at 1050, 224 USPQ at 747.

The ultimate determination of reduction to practice is a question of law which we review de novo. See Holmwood v. Sugavanam, 948 F.2d 1236, 1238, 20 USPQ2d 1712, 1714 (Fed. Cir. 1991). In contrast, we review the Board's factual findings supporting its legal conclusions about reduction to practice for clear error. Id. Whether a practical utility has been established for a novel compound is a question of fact. See Cross, 753 F.2d at 1044 n.7, 224 USPQ at 742 n.7. We therefore review the Board's findings with respect to practical utility for clear error.

A

This court has, on many occasions, considered the type and quantity of testing necessary to establish a practical utility for a novel compound. Although each case of practical utility must be considered on its own facts, see, e.g., Blicke, 241 F.2d at 720, 112 USPQ at 475, examination of our precedent illustrates the degree of proof which we have deemed sufficient to establish practical utility in the past.

The facts in this case are substantially similar to those in Cross v. Iizuka, 753 F.2d 1040, 224 USPQ 739 (Fed. Cir. 1985). There, we expressly held that, in appropriate circumstances, evidence of in vitro testing could adequately establish a practical utility.[5] As we there explained:

> We perceive no insurmountable difficulty, under appropriate circumstances, in finding that the first link in the screening chain, in vitro testing, may establish a practical utility for the compound in question. . . . [U]nder the circumstances of the instant case, where [an application] discloses an in vitro utility, . . . and where the disclosed in vitro utility is supplemented by the similar in vitro and in vivo pharmacological activity of structurally similar compounds, . . . we agree with the Board that this in vitro utility is sufficient to [establish utility].

Id. at 1051, 224 USPQ at 748. Thus, Cross holds that positive in vitro results, in combination with a known correlation between such in vitro results and in vivo activity, may be sufficient to establish practical utility.

Fujikawa does not argue that the law as stated in Cross is incorrect. Instead, Fujikawa contends that Wattanasin has failed to establish an adequate correlation between in vitro and in vivo results in the field of cholesterol-inhibiting compounds to permit Wattanasin to rely on affirmative in vitro results to establish a practical utility for the compound.

The Board determined that Wattanasin had reduced the compound count to practice in October 1987 when several compounds falling within the scope of the genus count exhibited activity in vitro.

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[5] While Cross involved a constructive reduction to practice, the same general principles are applicable to an actual reduction to practice. See id. at 1046 n.14, 224 USPQ at 744 n.14.

In reaching that conclusion, the Board relied on testimony from those skilled in the art that the in vitro results convinced them that the claimed compounds would exhibit the desired pharmacological activity when administered in vivo. This included testimony that "in vivo activity is typically highly correlatable to a compound's in vitro activity" in this field. The facts in this case are thus analogous to the ones in Cross where the court relied on positive in vitro test results in combination with a known correlation between such in vitro tests and in vivo activity to support a finding of practical utility.

To counter the Board's decision, Fujikawa points to the testimony of its own expert, Dr. Holmlund, who testified that:

> there is a reasonable element of doubt that some elements may be encountered which are active in the in vitro assay, but yet inactive in the in vivo assay.

According to Fujikawa, this testimony establishes that the in vitro tests were insufficient to prove practical utility.

We note first that to the extent the record presents a conflict in the testimony, the Board was well within its discretion as fact finder to credit the testimony of Wattanasin's witnesses over that of Fujikawa's. More fundamentally, however, we do not consider Dr. Holmlund's testimony as a whole to contradict the Board's finding. Of course, it is possible that some compounds active in vitro may not be active in vivo. But, as our predecessor court in Nelson explained, a "rigorous correlation" need not be shown in order to establish practical utility; "reasonable correlation" suffices. Here, even Dr. Holmlund implied in the

question and answer immediately following the above quoted portion of his testimony, that such a "reasonable correlation" exists:

> Q. Would you accept, subject to exceptions that might occur, that the failure to find [in vivo] activity would be considered an exception, that there would be a reasonable expectancy [that in vitro activity implies that the compound will be active in vivo]?
> A. I think I would probably accept that.

Fujikawa also cites two articles[6] which it claims show that there is no reliable relationship between in vitro results and in vivo results in cholesterol inhibiting compounds similar to the ones at issue in this case. We disagree. Although the Sliskovic article, for example, teaches that in vitro testing is sometimes not a good indicator of how potent a compound will be in vivo, it does imply that compounds which are active in vitro will normally exhibit some in vivo activity. See Sliskovic, at 370. Similarly, the Kathawala article expressly states: "For most substances, although not for all, the relative potency determined in in vitro microsomal assay against HMG-CoA reductase parallels the in vivo activity in rats for the inhibition of ^{14}C-acetate into sterols." Kathawala at 136-37. On these facts, we hold that the Board did not err in finding that Wattanasin's in vitro tests established a practical utility for the genus recited in the compound count.

B

Turning to the method count, the Board found that Wattanasin

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[6] The two articles are D. R. Sliskovic et al, Inhibitors of Cholesterol Biosynthesis, 34 J. Med. Chemistry 367 (1991) (Sliskovic); and F. G. Kathawala, HMG-CoA Reductase Inhibitors: An Exciting Development in the Treatment of Hyperlipoproteinemia, 11 Medicinal Research Reviews 121 (1991) (Kathawala).

reduced the method to practice in December 1987 when successful in vivo testing of the compound was completed. This finding, too, was based on testimony that the in vivo data for one of the compounds tested, 64-935, showed significant cholesterol inhibiting activity in the laboratory rats tested.

Fujikawa challenges the Board's holding by referring to an anomaly in the test data of the 64-935 compound which it contends undercuts the reliability of the in vivo tests. In particular, Fujikawa points to the fact that the compound's potency was less at a dosage of 0.3 mg than it was at a dosage of 0.1 mg. On the basis of this aberration, Fujikawa's expert, Dr. Holmlund, testified that this test data was unreliable and could not support a finding that the compound was pharmacologically active.

It is clear from the Board's opinion, however, that to the extent Dr. Holmlund was testifying that this aberration would lead one of ordinary skill to completely reject these test results, the Board did not accept his testimony. This decision of the Board was not clear error. Admittedly, the decreased potency at 0.3 mg is curious. The question remains, however, as to how much this glitch in the data would undercut the persuasiveness of the test results as a whole in the mind of one of ordinary skill. Each party presented evidence on this point and the Board resolved this disputed question of fact by finding that the test results as a whole were sufficient to establish pharmacological activity in the minds of those skilled in the art. In doing so, the Board properly exercised its duty as fact finder, and we therefore affirm its

finding on this point.[7]

As noted above, Fujikawa does not challenge the Board's conclusions that Wattanasin conceived prior to Fujikawa's effective date or that Wattanasin pursued the invention with diligence from just prior to Fujikawa's date until his reductions to practice in October and December 1987. Consequently, we affirm the Board's finding that Wattanasin has shown conception coupled with diligence from just prior to Fujikawa's effective date of August 20, 1987 up to the date he reduced the invention to practice in October 1987, for the compound, or December 1987, for the method.

IV

Having determined that Wattanasin was the de facto first inventor, the remaining question before the Board was whether Wattanasin had suppressed or concealed the invention between the

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[7] Before the Board, Fujikawa additionally argued that in vivo testing cannot establish reduction to practice of the method count because it does not fulfill every limitation of the count. In particular, Fujikawa argued that only human beings can be considered "patients in need of" cholesterol biosynthesis inhibition, as required by the count. As noted above, the Board rejected this argument and held that the term "patient" in the count is broad enough to encompass mammals, such as the laboratory rats tested in vivo.

In its brief to this court, Fujikawa renews this argument. In the process, however, Fujikawa seems to add an additional ground which it did not argue before the Board below. We are not absolutely certain, but it appears that Fujikawa is now contending that in vivo testing cannot constitute a reduction to practice because the rats tested were, from all that would appear, healthy animals, rather than animals in need of cholesterol biosynthesis inhibition. To the extent that Fujikawa's argument before this court is directed to this novel ground not raised below, we consider the argument waived and decline to address it. To the extent that Fujikawa is still arguing that the count requires administration of the compound to a human, we disagree, and affirm the Board's decision on this point.

time he reduced to practice and the time he filed his patent application. Suppression or concealment of the invention by Wattanasin would entitle Fujikawa to priority. 35 U.S.C. § 102(g).

Suppression or concealment is a question of law which we review de novo. Brokaw v. Vogel, 429 F.2d 476, 480, 166 USPQ 428, 431 (CCPA 1970). Our case law distinguishes between two types of suppression and concealment: cases in which the inventor deliberately suppresses or conceals his invention, and cases in which a legal inference of suppression or concealment is drawn based on "too long" a delay in filing a patent application. Paulik v. Rizkalla, 760 F.2d 1270, 1273, 226 USPQ 224, 226 (Fed. Cir. 1985) (in banc).

Fujikawa first argues that there is evidence of intentional suppression or concealment in this case. Intentional suppression refers to situations in which an inventor "designedly, and with the view of applying it indefinitely and exclusively for his own profit, withholds his invention from the public." Id. (quoting Kendall v. Winsor, 62 U.S. (21 How.) 322, 328 (1858)). Admittedly, Sandoz was not overly efficient in preparing a patent application, given the time which elapsed between its reduction to practice in late 1987 and its ultimate filing in March 1989. Intentional suppression, however, requires more than the passage of time. It requires evidence that the inventor intentionally delayed filing in order to prolong the period during which the invention is maintained in secret. Cf. Peeler v. Miller, 535 F.2d 647, 653-54, 190 USPQ 117, 122 (CCPA 1976) (implying that intentional

suppression requires showing of specific intent). Fujikawa presented no evidence that Wattanasin delayed filing for this purpose. On the contrary, all indications are that throughout the period between reduction to practice and filing, Sandoz moved slowly (one might even say fitfully), but inexorably, toward disclosure. We therefore hold that Wattanasin did not intentionally suppress or conceal the invention in this case.

Absent intentional suppression, the only question is whether the 17 month period between the reduction to practice of the compound, or the 15 month period between reduction to practice of the method, and Wattanasin's filing justify an inference of suppression or concealment. See id. The Board held that these facts do not support such an inference. As the Board explained: "In our view, this hiatus in time is not sufficiently long to raise the inference that Wattanasin suppressed or concealed the invention considering the nature and complexity of the invention here."

Fujikawa attacks this finding of the Board on two grounds. First, it contends that the Board should not have held that a 15 or 17 month delay is per se insufficient to raise an inference of suppression or concealment without examining the circumstances surrounding the delay and whether, in view of those circumstances, Wattanasin's delay was reasonable. Second, Fujikawa argues that the Board failed to consider evidence that Wattanasin was spurred to file by the issuance of a patent to a third party, Picard, directed to the same genus of compounds invented by Wattanasin. Evidence that a first inventor was spurred to disclose by the

activities of a second inventor has always been an important factor in priority determinations because it creates an inference that, but for the efforts of the second inventor, "the public would never have gained knowledge of [the invention]." Brokaw, 429 F.2d at 480, 166 USPQ at 431. Here, however, the Board expressly declined to consider the evidence of spurring because it held that spurring by a third party who is not a party to the interference is irrelevant to a determination of priority as between Wattanasin and Fujikawa. We first address Fujikawa's arguments concerning spurring.

A

We are not certain that the Board is correct that third party spurring is irrelevant in determining priority. After all, "[w]hat is involved here is a policy question as to which of the two rival inventors has the greater right to a patent." Brokaw, 429 F.2d at 480, 166 USPQ at 430. Resolution of this question could well be affected by the fact that one of the inventors chose to maintain his invention in secrecy until disclosure by another spurred him to file, even when the spurrer was a third party not involved in the interference. We need not resolve that question here, however, because we hold that no reasonable fact finder could have found spurring on the facts of this case. The only evidence in the record on the question of spurring is the testimony of Ms. Geisser who expressly testified that she had already begun work on the Wattanasin draft application before she learned of Picard's patent, in other words, that she had not been spurred by Picard.

Consequently, we leave the question of the relevance of third party spurring for another case.

B

Fujikawa's other argument also requires us to examine the evidence of record in this case. As Fujikawa correctly notes, this court has not set strict time limits regarding the minimum and maximum periods necessary to establish an inference of suppression or concealment. See Correge v. Murphy, 705 F.2d 1326, 1330, 217 USPQ 753, 756 (Fed. Cir. 1983). Rather, we have recognized that "it is not the time elapsed that is the controlling factor but the total conduct of the first inventor." Young v. Dworkin, 489 F.2d 1277, 1285, 180 USPQ 388, 395 (CCPA 1974) (Rich, J., concurring). Thus, the circumstances surrounding the first inventor's delay and the reasonableness of that delay are important factors which must be considered in deciding questions of suppression or concealment. See, e.g., id. at 1281-82, 180 USPQ at 392-93. Fujikawa again correctly notes that the Board's opinion gives short shrift to the question of whether this delay on the facts of this case was reasonable. In seeking reversal of the Board's decision, Fujikawa asks us to assess the factual record for ourselves to determine whether Wattanasin engaged in sufficient disclosure-related activity to justify his 17-month delay in filing. The facts of record, however, do not support Fujikawa's position.

In our view, the circumstances in this case place it squarely within the class of cases in which an inference of suppression or concealment is not warranted. We acknowledge, of course, that each

case of suppression or concealment must be decided on its own facts. Still, the rich and varied case law which this court has developed over many years provides some guidance as to the type of behavior which warrants an inference of suppression or concealment. See Paulik, 760 F.2d at 1280, 226 USPQ at 231-32 (Rich, J., concurring). In this case Wattanasin delayed approximately 17 months between reduction to practice and filing. During much of that period, however, Wattanasin and Sandoz engaged in significant steps towards perfecting the invention and preparing an application. For example, we do not believe any lack of diligence can be ascribed to Wattanasin for the period between October and December 1987 when in vivo testing of the invention was taking place. See Young, 489 F.2d at 1281, 180 USPQ at 392. Similarly, at its first opportunity following the in vivo testing, the Sandoz patent committee approved Wattanasin's invention for filing. This takes us up to the end of January 1988.

Over the next several months, until May 1988, the Sandoz patent department engaged in the necessary collection of data from the inventor and others in order to prepare Wattanasin's patent application. We are satisfied from the record that this disclosure-related activity was sufficient to avoid any inference of suppression or concealment during this period.[8] Cf. Correge,

[8] Our conclusion in this regard is based, in small part, on the testimony of Mr. Melvyn Kassenoff, a lawyer in Sandoz's patent department. Before the Board, Fujikawa challenged large parts of this testimony as inadmissible. In this opinion we therefore rely only on those portions of the testimony which even Fujikawa concedes are admissible, i.e., testimony relating to Mr. (continued...)

705 F.2d at 1330-31, 217 USPQ at 756 (five significant acts of disclosure-related activity over the course of seven months sufficient to rebut any inference of suppression). Also, as noted above, the record indicates that by August 1988, Ms. Geisser was already at work preparing the application, and that work continued on various drafts until Wattanasin's filing date in March 1989. Thus, the only real period of unexplained delay in this case is the approximately three month period between May and August of 1988.

Given a total delay of 17 months, an unexplained delay of three months, the complexity of the subject matter at issue, and our sense from the record as a whole that throughout the delay Sandoz was moving, albeit slowly, towards filing an application, we conclude that this case does not warrant an inference of suppression or concealment. Consequently, we affirm the Board on this point.

C

Finally, Fujikawa contends that assuming in vitro tests are sufficient to establish reduction to practice, Wattanasin reduced the compound count to practice in 1984 when he completed in vitro testing of his first three compounds falling within the scope of the count. If so, Fujikawa argues, the delay between reduction to practice and filing was greater than four years, and an inference

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[8](...continued)
Kassenoff's legal services rendered in connection with the prosecution of Wattanasin's application.

of suppression or concealment is justified.[9]

We reject this argument in view of Paulik v. Rizkalla, 760 F.2d 1270, 226 USPQ 224 (Fed. Cir. 1985) (in banc). In Paulik, we held that a suppression or concealment could be negated by renewed activity prior to an opposing party's effective date. There, inventor Paulik reduced his invention to practice and submitted an invention disclosure to his employer's patent department. For four years the patent department did nothing with the disclosure. Then, just two months before Rizkalla's effective date, the patent department allegedly picked up Paulik's disclosure and worked diligently to prepare a patent application which it ultimately filed. See id. at 1271-72, 226 USPQ at 224-25. We held that although Paulik could not rely on his original date of reduction to practice to establish priority, he could rely on the date of renewed activity in his priority contest with Rizkalla. In large measure, this decision was driven by the court's concern that denying an inventor the benefit of his renewed activity, might "discourage inventors and their supporters from working on projects that had been 'too long' set aside, because of the impossibility of relying, in a priority contest, on either their original work or their renewed work." Id. at 1275-76, 226 USPQ at 227-28.

Paulik's reasoning, if not its holding, applies squarely to this case. A simple hypothetical illustrates why this is so. Imagine a situation similar to the one facing Sandoz in early 1987.

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[9] This argument, of course, relates only to the compound count, since, as explained above, the method count was not reduced to practice until the in vivo testing in December 1987.

A decisionmaker with limited funds must decide whether additional research funds should be committed to a project which has been neglected for over two years. In making this decision, the decisionmaker would certainly take into account the likelihood that the additional research might yield valuable patent rights. Furthermore, in evaluating the probability of securing those patent rights, an important consideration would be the earliest priority date to which the research would be entitled, especially in situations where the decisionmaker knows that he and his competitors are "racing" toward a common goal. Thus, the right to rely on renewed activity for purposes of priority would encourage the decisionmaker to fund the additional research. Conversely, denying an inventor the benefit of renewed activity would discourage the decisionmaker from funding the additional research.

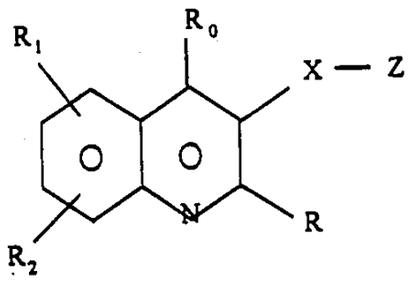
Here, Wattanasin returned to his abandoned project well before Fujikawa's effective date and worked diligently towards reducing the invention to practice a second time. For the reasons explained above, we hold that, on these facts, Wattanasin's earlier reduction to practice in 1984 does not bar him from relying on his earliest date of renewed activity for purposes of priority.

V

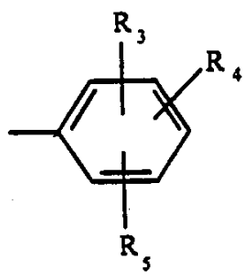
Fujikawa also appeals the Board's decision denying Fujikawa's motion to add a sub-genus count to the interference. The Board denied the motion because it found that Wattanasin's disclosure did not sufficiently describe Fujikawa's proposed count. Whether a disclosure contains a sufficient written description to support a

proposed count, is a question of fact which we review for clear error. Ralston Purina Co. v. Far-Mar-Co, Inc., 772 F.2d 1570, 1575, 227 USPQ 177, 179 (Fed. Cir. 1985). We affirm the Board's denial of Fujikawa's motion because we do not believe it was clearly erroneous.

Wattanasin's application disclosed compounds of the following structure:



wherein each of R and R_0 is, independently, C_{1-6} alkyl (primary, secondary, or tertiary), C_{3-7} cycloalkyl, or the following ring,



and each of R_1, R_2, R_3, R_4, and R_5 is, independently, hydrogen, C_{1-4}alkyl, C_{1-4}alkoxy, trifluoromethyl, fluoro, chloro, phenoxy, benzyloxy, or hydroxy.

In addition to this genus of compounds, Wattanasin disclosed as his preferred embodiments that: R_1 and R_2 are most preferably hydrogen, R_0 is most preferably phenyl, 4-fluorophenyl, or 3,5-dimethylphenyl; and R is most preferably methyl[10] or isopropyl.[11]

Essentially, Fujikawa's proposed sub-genus is directed to compounds of the above structure in which R is cyclopropyl[12] and R_0 is 4-fluorophenyl. In other respects, the parties do not dispute that the particular constituents recited in Fujikawa's proposed count are adequately disclosed in Wattanasin's application. Thus, for example, both Wattanasin's most preferred embodiment and Fujikawa's proposed count describe R_1 and R_2 as hydrogen.

In denying Fujikawa's motion, the Board first noted that the proposed sub-genus was not disclosed ipsis verbis by Wattanasin. Specifically, the Board noted that Wattanasin preferred methyl and isopropyl for R, rather than cyclopropyl as in the proposed count. In addition, Wattanasin listed three preferred choices for R_0 only one of which was 4-fluorophenyl and gave no indication in his application as to whether he would prefer any one of the choices over the other two.

As the Board recognized, however, ipsis verbis disclosure is not necessary to satisfy the written description requirement of section 112. Instead, the disclosure need only reasonably convey to persons skilled in the art that the inventor had possession of

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[10] Methyl is another name for C_1 alkyl.

[11] isopropyl is another name for C_3 alkyl.

[12] cyclopropyl is another name for C_3 cycloalkyl.

the subject matter in question. In re Edwards, 568 F.2d 1349, 1351-52, 196 USPQ 465, 467 (CCPA 1978). In other words, the question is whether Wattanasin's "application provides adequate direction which reasonably [would lead] persons skilled in the art" to the sub-genus of the proposed count. Id. at 1352, 196 USPQ at 467.

Many years ago our predecessor court graphically articulated this standard by analogizing a genus and its constituent species to a forest and its trees. As the court explained:

> It is an old custom in the woods to mark trails by making blaze marks on the trees. It is no help in finding a trail . . . to be confronted simply by a large number of unmarked trees. Appellants are pointing to trees. We are looking for blaze marks which single out particular trees. We see none.

In re Ruschig, 379 F.2d 990, 994-95, 154 USPQ 118, 122 (CCPA 1967).

In finding that Wattanasin's disclosure failed to sufficiently describe the proposed sub-genus, the Board again recognized that the compounds of the proposed count were not Wattanasin's preferred, and that his application contained no blazemarks as to what compounds, other than those disclosed as preferred, might be of special interest. In the absence of such blazemarks, simply describing a large genus of compounds is not sufficient to satisfy the written description requirement as to particular species or sub-genuses. See, e.g., id. at 994, 154 USPQ at 122 ("Specific claims to single compounds require reasonably specific supporting disclosure and while . . . naming [each species] is not essential, something more than the disclosure of a class of 1000, or 100, or even 48 compounds is required.").

Before this court, Fujikawa challenges the Board's denial of its motion on two grounds. First, Fujikawa persists in arguing that its proposed count is disclosed ipsis verbis in Wattanasin's application. The basis for this contention seems to be that Wattanasin lists cyclopropyl as one possible moiety for R in his disclosure of the genus. Clearly, however, just because a moiety is listed as one possible choice for one position does not mean there is ipsis verbis support for every species or sub-genus that chooses that moiety. Were this the case, a "laundry list" disclosure of every possible moiety for every possible position would constitute a written description of every species in the genus. This cannot be because such a disclosure would not "reasonably lead" those skilled in the art to any particular species. We therefore reject Fujikawa's argument on this point.

Second, Fujikawa claims that the Board erred in finding that Wattanasin's disclosure contained insufficient blazemarks to direct one of ordinary skill to the compounds of its proposed count. Specifically, Fujikawa points out that with respect to practically every position on the compound, the proposed count recites at least one of Wattanasin's preferred choices. Even with respect to position R, Fujikawa further explains, one of ordinary skill would have been moved by Wattanasin's disclosure to substitute cyclopropyl for isopropyl because the two substituents are isosteric.

While Fujikawa's arguments are not without merit, we cannot say, on this record, that the Board's decision was clearly

erroneous. As the Board pointed out, Fujikawa's proposed sub-genus diverges from Wattanasin's preferred elements at least with respect to position R. Although, in hindsight, the substitution of cyclopropyl for isopropyl might seem simple and foreseeable, Wattanasin's disclosure provides no indication that position R would be a better candidate for substitution than any other. Thus, faced with Wattanasin's disclosure, it was not clear error to hold that one of ordinary skill would not be led to Fujikawa's sub-genus in particular.

Were we to extend Ruschig's metaphor to this case, we would say that it is easy to bypass a tree in the forest, even one that lies close to the trail, unless the point at which one must leave the trail to find the tree is well marked. Wattanasin's preferred embodiments do blaze a trail through the forest; one that runs close by Fujikawa's proposed tree. His application, however, does not direct one to the proposed tree in particular, and does not teach the point at which one should leave the trail to find it. We therefore affirm the Board's denial of Fujikawa's motion.

VI

For the reasons we set forth above, the decision of the Board is, in all respects,

AFFIRMED.

A True Copy.

Attest: 9/18/96

Linda R. Pardue
Deputy Clerk

Paper No. 119

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

SOMPONG WATTANASIN

Junior Party,[1]

v.

YOSHIHIRO FUJIKAWA, MIKIO SUZUKI, HIROSHI IWASAKI, MITSUAKI SAKASHITA and MASAKI KITAHARA

Senior Party.[2]

Patent Interference No. 102,648

Before CALVERT, Vice Chief Administrative Patent Judge, and SOFOCLEOUS and DOWNEY, Administrative Patent Judges.

SOFOCLEOUS, Administrative Patent Judge.

FINAL DECISION

The subject matter of this interference relates to a method of inhibiting cholesterol biosynthesis using novel mevalonolactones. These compounds inhibit the enzyme, ß-hydroxy-ß-methyl-glutaryl-CoA reductase (HMG-CoA), which controls a key step in the biosynthesis of cholesterol, by catalyzing the conversion of the substrate HMG-CoA to mevalonate, an

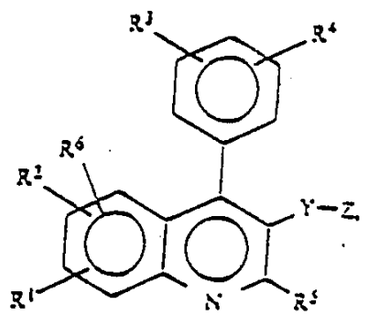
[1] Application 07/498,301 filed March 23, 1990. Accorded the benefit of U.S. Application 07/318,773 filed March 3, 1989, now abandoned. Assignor to Sandoz Pharmaceuticals Corporation.

[2] Application 07/233,752 filed August 19, 1988. Accorded the benefit of Japan Applications 207224 filed August 20, 1987, 193606 filed August 3, 1988 and 15585 filed January 26, 1988. Assignors to Nissan Chemical Industries Ltd.

intermediate of cholesterol. The count of this interference is as follows:

Count 3

A method of inhibiting cholesterol biosynthesis in a patient in need of said treatment comprising administering a cholesterol synthesis inhibiting amount of a compound of the formula:



wherein R^1, R^2, R^3, R^4 and R^6 are independently

hydrogen,

C_{1-6} alkyl,

C_{1-6} cycloalkyl,

C_{1-3} alkoxy,

n-butoxy,

i-butoxy,

sec-butoxy,

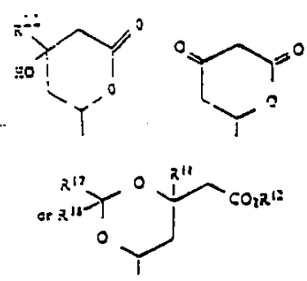
R^7R^8N- (wherein R^7 and R^8 are independently hydrogen or C_{1-3} alkyl),

trifluoromethyl,
trifluoromethoxy,
difluoromethoxy,
fluoro,
chloro,
bromo,
phenyl,
phenoxy,
benzyloxy,
hydroxy,
hydroxymethyl,
$-O(CH_2)_\alpha OR^{19}$ (wherein R^{19} is hydrogen or C_{1-3}alkyl and α is 1, 2 or 3),
or when located at the ortho position to each other, R^3 and R^4 together optionally form $-CH=CH-CH=CH-$;

R^5 is hydrogen,
C_{1-6} alkyl,
C_{2-3} alkenyl,
C_{3-6} cycloalkyl,
phenyl substituted by R^9 (wherein R^9 is hydrogen, C_{1-4}alkyl, C_{1-3}alkoxy, fluoro, chloro, bromo or trifluoromethyl),
phenyl-$(CH_2)_m$- (wherein m is 1, 2 or 3), $-(CH_2)_nCH(CH_3)$-phenyl or phenyl-$(CH_2)_nCH(CH_3)$- (wherein n is 0, 1 or 2).

Y is
$-CH_2-$,
$-CH_2CH_2-$,
$-CH=CH-$,
$-CH_2-CH=CH-$, or
$-CH=CH-CH_2-$;

Z is



or $-Q-CH_2WCH_2-CO_2R^{12}$ (where R^{12} is hydrogen or R^{14});

Q is $-CH(OH)-$.
$-C(O)-$, or
$-C(OR^{13})_2-$;

W is $-C(R^{11})(OH)-$ (where R^{11} is hydrogen or C_{1-3} alkyl),
$-C(O)-$, or
$-C(OR^{13})_2-$;

the two R^{13} are independently primary or secondary C_{1-6} alkyl; or two R^{13} together form $-(CH_2)_2-$ or $-(CH_2)_3-$;

R^{14} is physiologically hydrolyzable alkyl or M (wherein M is NH_4, sodium, potassium, 1/2 calcium or a hydrate of lower alkylamine, di-lower alkylamine or tri-lower alkylamine); and

R^{17} and R^{18} are independently hydrogen or C_{1-3} alkyl;

as defined in combination with pharmaceutically acceptable carrier.

Wattanasin's claims 8 and 9 and Fujikawa et al.'s (Fujikawa's) claims 35, 37 and 38 correspond to the count. No question of interference-in-fact or separate patentability of claims under 37 CFR 1.633(b) and (c)(4) has been raised.

This interference was initially declared with three parties on two counts. Count 1 was directed to compounds per se; count 2, to a method of administering the compounds to inhibit cholesterol biosynthesis. The intermediate party, Picard et al., U.S. Patent No. 4,761,419, filed a request for adverse judgment and judgment was entered against it. During the motion period, Fujikawa filed, inter alia, a preliminary motion (Paper No. 15) to add two proposed counts to this interference, which motion was denied by the administrative patent judge (APJ). As a result of the APJ's Decision on Preliminary Motions, method count 3 was substituted for count 2 and Interference No. 102,975 was declared on a count directed to compounds per se. Times for taking testimony were set. Wattanasin presented testimony in order to establish priority of invention within the meaning of 35 U.S.C. 102(g). Fujikawa took cross-examination and presented rebuttal testimony. Both parties filed briefs and appeared, through counsel, at final hearing.

The briefs raise the following issues:

Wattanasin's claims 8 and 9 and Fujikawa et al.'s (Fujikawa's) claims 35, 37 and 38 correspond to the count. No question of interference-in-fact or separate patentability of claims in accordance with 37 CFR 1.633(b) has been raised.

This interference was initially declared with three parties on two counts. Count 1 was directed to compounds per se; count 2, to a method of administering the compounds to inhibit cholesterol biosynthesis. The intermediate party, Picard et al., U.S. Patent No. 4,761,419, filed a request for adverse judgment and judgment was entered against it. During the motion period, Fujikawa filed, inter alia, a preliminary motion (Paper No. 15) to add two proposed counts to this interference, which motion was denied by the administrative patent judge (APJ). As a result of the APJ's Decision on Preliminary Motions, method count 3 was substituted for count 2 and Interference No. 102,975 was declared on a count directed to compounds per se. Times for taking testimony were set. Wattanasin presented testimony in order to establish priority of invention within the meaning of 35 U.S.C. 102(g). Fujikawa took cross-examination and presented rebuttal testimony. Both parties filed briefs and appeared, through counsel, at final hearing.

The briefs raise the following issues:

1. Whether the Fujikawa preliminary motion (Paper No. 15) to add two proposed counts to this interference should have been granted?

2. Whether Wattanasin has established priority of invention prior to August 20, 1987, Fujikawa's effective filing date?

FUJIKAWA'S PRELIMINARY MOTION TO ADD COUNTS

After having reviewed the arguments of the parties, we hold that the party Fujikawa has not sustained its burden to show that the interfering subject matter should have been redefined by adding two proposed counts to this proceeding.

As the moving party, Fujikawa has the burden of proof on the motion. Kubota v. Shibuya, 999 F.2d 517, 27 USPQ2d 1418 (Fed.Cir. 1993). The motion proposed that two counts be added to this interference and that Wattanasin present claims 11 and 12 in his application to correspond to the proposed counts. As the moving party, Fujikawa had the burden to...

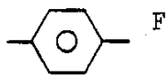
> show the patentability of any proposed claims to the opponent and apply the terms of the claims to the disclosure of the opponent's application. § 1.637(c)(1)(iii).

The APJ denied the motion on the ground the Wattanasin application does not contain a written description with the meaning of 35 U.S.C. 112, first paragraph, for proposed claims 11 and 12. In accordance with 37 CFR 1.655(a), the APJ's decision on a preliminary motion constitutes an interlocutory order which is presumed to have been

correct and the burden of showing error or abuse of discretion is upon the party attacking the order. Gustavsson v. Valenti, 25 USPQ2d 1401 (BPAI 1991) and Suh v. Hoefle, 23 USPQ2d 1321 (BPAI 1991).

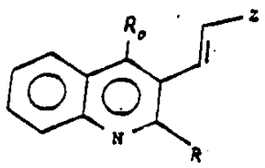
Having reviewed the Wattanasin disclosure, we agree with the APJ that the disclosure does not contain a written description for proposed claims 11 and 12.

Proposed claims 11 and 12 are as follows:

11. The compound of claim 1, wherein R_1 and R_2 are hydrogen, R_o is  , X is -CH=CH-, R is cyclopropyl, Q is  , R_6 is H, R_8 is an alkyl of 1-3 carbon atoms and M is sodium.

12. A method of inhibiting cholesterol biosynthesis in a patient in need of said treatment comprising administering a cholesterol biosynthesis inhibiting amount of the compound of Claim 11 in combination with a pharmaceutically acceptable carrier.

The compounds embraced by proposed claims 11 and 12 are as follows:

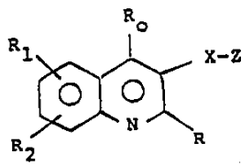


wherein R_o is 4-flurophenyl, and
R is cyclopropyl

Interference No. 102,648

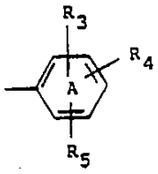
The Wattanasin application has the following pertinent disclosure:

This invention relates to compounds of the formula



(A)

wherein each of R and R_o is, independently C_{1-6}alkyl (primary, secondary or tertiary), C_{3-7}cycloalkyl or ring A



each of R_1, R_2, R_3, R_4 and R_5 is, independently hydrogen, C_{1-4}alkyl, C_{1-4}alkoxy, trifluoromethyl, fluoro, chloro, phenoxy, benzyloxy or hydroxy; with the provisos that not more than one of R_1 and R_2 is trifluoromethyl, not more than one of R_1 and R_2 is phenoxy, not more than one of R_1 and R_2 is benzyloxy, not more than one of R_1 and R_2 is hydroxy, not more than one of R_3-R_5 is the trifluoromethyl, not more than one of R_3-R_5 is phenoxy, not more than one of R_3-R_5 is benzyloxy and not more than one of R_3-R_5 is hydroxy; [page 1, lines 1 to 14]

* * * *

Preferred compounds of this invention are the following.

R_1 and R_2 are preferably hydrogen;

one of R and R_o is preferably C-$_{1-6}$alkyl, more preferably isopropyl or methyl, and the other is preferably Ring A, more preferably phenyl, 4-fluorophenyl or 3,5-

dimethylphenyl; more preferably R is the alkyl group and R_o is Ring A; [page 4, lines 26 to 34]

It is clear from the foregoing that the application does not describe in ipsis verbis the compounds of proposed claims 11 and 12 where R is cyclopropyl. This, however, is not necessary in order to comply with the description requirement of 35 USC 112, first paragraph, In re Lukach, 442 F.2d 967, 169 USPQ 796 (CCPA 1971); all that is required is that the application reasonably convey to persons skilled in the art that, as of the filing date thereof, the inventor had possession of the subject matter later claimed by him. In re Edwards, 558 F.2d 1349, 196 USPQ 465 (CCPA 1978) and In re Driscoll, 562 F.2d 1245, 195 USPQ 434 (CCPA 1977). The question of whether an application contains a sufficient written description within the meaning of 35 U.S.C. 112, first paragraph, for a compound which is not specifically disclosed but which is among those suggested by general language in the application must be decided on its own facts. In re Driscoll, supra and Prutton v. Fuller, 230 F.2d 459, 109 USPQ 59 (CCPA 1956).

In our view, the Wattanasin application would not reasonably lead one of ordinary skill to the compounds of claims 11 and 12 where R is cyclopropyl, i.e., the application does not reasonably convey to those skilled in the art that Wattanasin invented the compounds. Cf. Flynn v. Eardley, 479 F.2d 1393, 178 USPQ 288 (CCPA 1973); Fields v. Conover, 443 F.2d 1386, 170 USPQ 276

(CCPA 1971); Irikura v. Petersen, 18 USPQ2d 1362 (BPAI 1991); and Heymes v. Takaya, 6 USPQ2d 1448 at 1452 (BPAI 1988).

The Wattanasin application does not disclose any compound where R is C_{3-7} cycloalkyl, much less cyclopropyl. Rather, cyclopropyl is merely one moiety embraced by C_{3-7} cycloalkyl which is among a myriad of possibilities for either R or R_o disclosed in the application on page 1, lines 1 to 5. Further, the application at page 4, lines 26 to 34, lists its preferred compounds. None of the listed preferred compounds includes cyclopropyl or even C_{3-7} cycloalkyl in the R position. Nor does the application have any examples directed to cycloalkyl compounds. Nor are there either any blazemarks or any motivation to guide one skilled in the art to select the cyclopropyl compounds of proposed claims 11 and 12 from Wattanasin's broad generic disclosure. Admittedly, one skilled in the art might fortuitously select a cyclopropyl compound within the scope of claims 11 and 12 out of the myriad of possibilities. This, however, is not sufficient to provide a written description of the small subgenus of claims 11 and 12. The selection of all the substituents of the genus must necessarily happen. Flynn v. Eardley, supra; In re Rushig, 379 F.2d 990, 154 USPQ 118 (CCPA 1967); and Staehelin v. Secher, 24 USPQ2d 1513 (BPAI 1992). As noted by the Court in Rushig, 154 USPQ 122,

> Specific claims to single compounds require reasonably specific supporting disclosure and while

> we agree with the appellants, as the board did, that naming is not essential, something more than the disclosure of a class of 1000, or 100, or even 48, compounds is required. Surely, given time, a chemist could name (especially with the aid of a computer) all of the half million compounds within the scope of the broadest claim, which claim is supported by the broad disclosure. This does not constitute support for each compound individually when separately claimed.

We consider the Court's statement concerning claims to specific compounds is equally applicable to the situation here where proposed claims 11 and 12 are directed to a small subgenus of cyclopropyl compounds within the scope of Wattanasin's broad generic disclosure.

For the foregoing reasons, we hold that the party Fujikawa has not sustained its burden to show that the interfering subject matter should have redefined by adding the two proposed counts to this proceeding.

WATTANASIN'S CASE FOR PRIORITY

Fujikawa is the senior party, having been accorded under the provisions of 35 U.S.C. 119 the benefit of its earliest filed Japan application Serial No. 207224, filed August 20, 1987. For its case for priority of invention, the junior party Wattanasin relies upon actual reduction to practice prior to Fujikawa's effective filing date or upon prior conception coupled with diligence starting just prior to Fujikawa's effective filing date up to actual reduction to practice.

Burden of Proof

Wattanasin, as the junior party, whose application is copending with the senior party's application, has the burden of proving priority of invention by a preponderance of the evidence. Holmwood v. Sugavanam, 948 F.2d 1236, 20 USPQ2d 1712 (Fed.Cir. 1991) and Morgan v. Hirsch, 728 F.2d 1449, 221 USPQ 193 (Fed.Cir. 1984).

Fujikawa's argument that the party Wattanasin must prove its case for priority by clear and convincing evidence is not well taken. This argument is based on the fact that this interference was initially declared with the party Picard, whose patent issued prior to the filing date of Wattanasin's involved application. If the party Picard were involved in this interference, we would have agreed with Fujikawa that Wattanasin, whose application was filed after the issuance of Picard's patent, would have had the burden of proof by clear and convincing evidence with respect to Picard. See Price v. Symsek, 988 F.2d 1187, 26 USPQ2d 1031 (Fed.Cir. 1993). Since Picard is no longer involved in this proceeding, having filed, through counsel, a request for adverse judgment, the burden of proof upon Wattanasin vis-a-vis Fujikawa is the preponderance of the evidence, inasmuch as both Wattanasin's and Fujikawa's applications are copending.

Count Interpretation

The count is directed to a "method of inhibiting cholesterol biosynthesis in a patient in need of said treatment." On

page 54 of its main brief, the party Fujikawa urges that we should construe the count as being directed to a method for "treating human patients," because there is

> no known value in reducing cholesterol, or controlling blood cholesterol levels, in animals other than humans. Main brief at page 32.

In support of its position, the party Fujikawa points to page 35 of the Wattanasin application which specifically identifies humans as the target patients and gives dosage values only for humans.

We note that the term "patient" in the count is neither present in the parties' claims corresponding to the count nor defined in the parties' applications. The count of this interference is a "phantom" count which is not patentable under 35 U.S.C. 112, first paragraph, to either party. A count of an interference is merely the vehicle for determining priority of invention. It is settled interference practice that a count must be given its broadest reasonable interpretation possible, DeGeorge v. Bernier, 768 F.2d 1318, 226 USPQ 758 (Fed.Cir. 1985), and it is an established principle of interference practice that the count must be sufficiently broad as to encompass the broadest corresponding patentable claim of each party. Manual of Patent Examining Procedure, § 2309.02 (Fifth Edition).

Based on our review of the parties' claims corresponding to the count in light of their application disclosures, we necessarily

conclude that the term "patient" as used in the context of the count includes the testing of mammals.

Wattanasin's claim 8 is directed to a method of inhibiting cholesterol biosynthesis comprising administering a compound to a mammal in need of such treatment. The Wattanasin application, page 35, lines 1 to 19, teaches that the compounds of his invention are useful for lowering blood cholesterol level in "animals, e.g., mammals, especially larger primates," with humans being listed as an example of larger primates. Further the application at page 34 contains examples directed to the in vivo testing of male Wistar Royal Hart rats.

Fujikawa's claims 35, 37 and 38 are directed to a method for treating hyperlipidemia, hyperlipoproteinemia, or atherosclerosis which comprises administering an effective amount of the compound. The claims are open-ended in that they do not limit the administration of compound to any particular group; rather, the compound may be administered to either a human, mammal or other animal. The Fujikawa application at page 26, lines 5 to 13, teaches:

> The compounds of the present invention exhibit high inhibitory activities against the cholesterol biosynthesis wherein HMG-CoA reductase acts as a rate limiting enzyme, as shown by the test results given hereinafter, and thus are capable of suppressing or reducing the amount of cholesterol in blood as lipoprotein.

The Fujikawa application contains examples directed to the in vivo testing of male Sprague-Dawley rats.

Since the claims of Wattanasin are directed to the treatment of mammals and the claims of Fujikawa embrace the treatment of any animal, including humans and mammals, and since both applications contain examples directed to the in vivo testing of rats, we necessarily conclude that in the context of this interference, the term "patient" as used in the count embraces the treatment of mammals, and, in particular, rats, the species exemplified by both parties' applications.

The Wattanasin Record

Wattanasin presented a record consisting of the testimony of 16 witnesses together with 51 associated exhibits. The testimony will be referred to by WR followed by its page number; each exhibit, by WX followed by its identifier. The record shows that Sandoz Pharmaceuticals Corporation, the assignee of the involved Wattanasin application, has been involved since 1979 in a research program to discover compounds having HMG-CoA reductase inhibiting activity. In 1979, Dr. Kathawala, a Ph.D., was the section head of a research team responsible for the research. This team was expanded over time to five laboratory units, each headed by a Ph.D. In 1982, Dr. Wattanasin, the named inventor, joined the project, worked under Dr. Kathawala and was later appointed as head of one of the five laboratory units. WR 136.

The First Phase Activity

I

The record shows that during the period from May 31, 1984 to May 17, 1985, Dr. Wattanasin synthesized three compounds (63-366, 63-548 and 63-549) falling within the scope of the count. Employees reporting to Dr. Barcza, a Ph.D chemist and director of the Sandoz Department of Physical Organic Chemistry, performed the spectra, microanalyses and thin layer chromatography (TLC) on the various intermediates and the final compounds. Samples of the final compounds were sent to the Drug Room of Sandoz and their receipt was recorded in the computer database. Dr. Damon, a Ph.D. chemist, who was in charge of the Drug Room, had samples of the compounds forwarded to Dr. Scallen for testing. WR 22 to 24, 27 to 44, 48 to 54, 172 to 185 and 196; WX A-1, A-2, B-1, B-2, C-1 to 3, D-1, D-2, G-1, G-2, H-1 and I-1.

Dr. Scallen, a professor of biochemistry and medical doctor at the School of Medicine, University of New Mexico, received the compounds and had them tested in an established protocol using rat liver microsomes to determine whether they were competitive inhibitors of HMG-CoA reductase, the rate limiting enzyme in cholesterol biosynthesis. On or before December 13, 1984, Dr. Scallen had an <u>in vitro</u> biological assay of compound 63-366 performed in his laboratory under his supervision. The results indicated HMG-CoA reductase activity and Dr. Scallen reported the results to Dr.

Damon of Sandoz. Likewise, on or before June 13, 1985, Dr. Scallen had in vitro biological assays of compounds, 63-548 and 63-549, performed in his laboratory under his supervision. The results indicated HMG-CoA reductase activity and were reported to Dr. Damon of Sandoz. WR 187 to 191; WX E-1 and E-2.

Upon receiving the results, Dr. Damon calculated the IC_{50} for each compound. The IC_{50} value is the concentration of the test substance in the assay system to produce a 50% inhibition of HMG-CoA reductase. The smaller the IC_{50} value, the more active the compound was in the assay. Dr. Damon would send Dr. Wattanasin within three or four days of receiving the test results a report with the assay data (including the IC_{50}) and the structure of the compound. The report (WX E-5), stamp-dated December 20, 1984, indicated that compound 63-366 had an IC_{50} of 1.58 μmoles (μM); the reports (WX E-5), stamp-dated June 28, 1985, indicated that compounds 63-548 and 63-549 each had, respectively, an IC_{50} of 3.775 μM and 7.3100 μM. He compared these values to the IC_{50} value of compactin, a known HMG-CoA inhibitor for administration to patients to inhibit cholesterol biosynthesis. Compactin has an IC_{50} value of 1.011 μM. WR 196 to 201 and 483; WX E-1 and E-5.

Concerning these test results, Dr. Damon testified that based on his knowledge and experience,

> it was my judgment on or prior to December 31, 1984, that there was a high probability that Wattanasin

> compound 63-366 would be active when administered in vivo to a patient to inhibit cholesterol biosynthesis, i.e. for the treatment of hypercholesteremia or atherosclerosis. WR 201.

He testified that he had the same opinion for the other tested compounds.

Dr. Wattanasin testified that no other experimental work was done on his invention after May 17, 1985, because of a manpower shortage in his lab. WR 106 to 110. Ms. Patel was hired in January 1987. In March of 1987, Dr. Wattanasin submitted an Invention Disclosure (A-3), dated March 16, 1987, to the Sandoz Patent and Trademark Department. WR 24 and 25; WX A-3.

II

We hold that during the first phase of activity the Wattanasin record does not establish actual reduction to practice.

It is well settled that a reduction to practice must include every limitation of the count. NewKirk v. Lulejian, 825 F.2d 1581, 3 USPQ2d 1793 (Fed.Cir. 1987); Land v. Regan, 342 F.2d 92, 144 USPQ 661 (CCPA 1965) and Schoenwald v. Waltersdorf, 226 USPQ 446 (Bd.Pat.Int. 1984).

The compounds, 63-366, 63-548 and 63-549, which were made and tested during the first phase, were not administered to a mammal, a necessary step in the performance of the method of the count. Consequently, Wattanasin did not reduce to practice the invention of count 1 during the first phase activity. At best, this work would

establish conception of the invention of the count by at least June 13, 1985.

The Second Phase Activity

I

Pages 31 to 44 of the Wattanasin main brief with references to the testimony and exhibits set forth a detailed explanation of Wattanasin's renewed activity.

Essentially from early March 1987 into September 1987, Ms. Patel synthesized four compounds, 64-933, 64-934/NA, 64-935 and 64-936/NA, within the scope of the count and forwarded the compounds to the Sandoz Drug Room. By July 28, 1987, she synthesized compound 64-933; by July 29, 1987, compound 64-934/NA; by August 20, 1987, compound 64-935; and by August 25, 1987, compound 64-936/NA. During the synthesis, purification and characterization of the compounds, Dr. Wattanasin went to a meeting in New Orleans for over a week and when he returned, he found out that the next scheduled shipment out of the Sandoz drug room to Dr. Scallen would be on October 2, 1987, even though the compounds were made before October 2. He wanted all the compounds shipped together for testing so that he could get a better comparison of their potency in the same study. The compounds were shipped on October 2, 1987 overnight to Dr. Scallen. Dr. Scallen received the compounds, tested them in an established protocol using rat liver microsomes to their biological activity in

vitro and reported the raw results to Dr. Damon on or before October 20, 1987.

Dr. Damon calculated the IC_{50} for each compound and compared each value with compactin which has an IC_{50} of 1.011 μM. Compound 64-933 had an IC_{50} of 2.3700 μM; compound 64-934/NA, an IC_{50} of 2.6100 μM; compound 64-935, an IC_{50} of 0.4130 μM; and compound 64-936/NA, an IC_{50} of 0.5300 μM. WR 183 to 195; WX E-1 to E-5, H-1 and I-1.

Dr. Engstrom of the Sandoz Lipid Metabolism Department commenced the in vivo testing of compound 64-936 on or before October 22, 1987 and the testing of compounds 64-933 and 64-935 on October 29, 1987. The testing was completed on or prior to December 9, 1987. The compounds were administered to male Wistar Royal Hart rats in accordance with the protocol described at WR 204. Mr. Slaughter, Dr. Engstrom's lab assistant, entered the raw data into a computer program which converted the data to nano Curies (nCi) of sterol per 100 ml. of serum at 4 hours after injection of ^{14}C-acetate. Thereafter Dr. Engstrom entered this data into a computer program which calculated the ED_{50} values for the compounds. The ED_{50} value[3] for compound 64-933 is >1; for compound 64-935, 0.49; and for compound 64-936, >1. Dr. Wattanasin testified that the data on WX K-1 indicates that the compounds would have activity as a HMG-CoA

[3] The ED_{50} values for compounds 64-933 and 64-935 were inadvertently switched as explained in Dr. Engstrom's supplemental declaration at WR 207 and 208.

reductase inhibitor when administered to a patient. Compactin has an ED_{50} of 3.5. WR 56, 203 to 212 and 485; WX K-1 and Q.

Contemporaneous with these second phase activities, the Sandoz Patent Committee met on April 29, 1987 and considered the Wattanasin invention disclosure (A-3). According to the testimony of Linda Rothwell and Joanne M. Giesser, the committee deferred a decision for three months on whether to file an application because of the ongoing work. Again at its meeting on July 29, 1987, the committee deferred its decision for another three months. As a result of the October 28, 1987 and November 25, 1987 meetings, the committee's decision was deferred to January, there being no committee meeting during the month of December. At the January 27, 1988 meeting, the committee decided that an application should be filed on the Wattanasin disclosure. The disclosure, which had been assigned to Mr. Weinfeldt, was reassigned to Ms. Giesser, a junior patent attorney in the Sandoz Patent Department. The application was filed on March 3, 1989. WR 213 to 215 and 319 to 323; WX M-1 to M-5 and P-1 to 3.

II

We hold that the Wattanasin record establishes prior conception coupled with due diligence from just prior to August 20, 1987, Fujikawa's effective filing date, up to December 9, 1987, the date of the in vivo testing of compound 64-935.

Prior conception is established by June 13, 1985, when the work performed during the first phase of the interference was completed. Thus the Wattanasin record establishes prior conception.

With respect to diligence, Wattanasin has the burden to establish diligence just prior to August 20, 1987, up to the date of in vivo testing on December 9, 1987. As noted by Wattanasin in his reply brief at page 24, "it does not appear that Fujikawa contest diligence as to this period." We agree. Nowhere in its brief has the party Fujikawa shown where Wattanasin was not reasonably diligent during this period. Accordingly, we hold that the Wattanasin record establishes reasonable diligence during the critical period in question.

III

We hold that the Wattanasin record establishes actual reduction to practice by December 9, 1987, the date compound 64-935 was successfully tested in vivo in rats and found to have an ED_{50} value of 0.49 μM.

Before we discuss the Wattanasin record, we must consider Fujikawa's motion (Paper No. 109) to suppress, which was filed at the same time as Fujikawa's brief. In the motion, Fujikawa requests that we not consider Dr. Engstrom's testimony at WR 204 to 208 because the testimony relies upon a computer-generated summary to obtain the ED_{50} values. We agree with Wattanasin's opposition (Paper No. 113) that

the ED_{50} value for compound 64-935 should not be invalidated because of a purported lack of foundation for the underlying computer programs used to calculate the value from the raw data. As pointed out by Wattanasin, Dr. Holmlund, Fujikawa's rebuttal witness, had "no quarrel with the techniques for determining statistical activity." Likewise, we do not consider that Wattanasin had to have placed in evidence the computer programs used to calculate the value from the experimental data. It is enough to have placed into evidence the experimental data, which showed that the compound had significant activity. Accordingly, the motion to suppress is denied.

As we noted above, a reduction to practice must include every limitation of the count. Newkirk v. Lulejian, supra; Land v. Regan, supra; and Schoenwald v. Waltersdorf, supra. The Wattanasin record shows that by December 9, 1987 compound 64-935 was administered to a rat. The compound exhibited significant activity at levels of 1 and 0.1 milligrams per kilogram and its ED_{50} value was calculated to be 0.49 μM, an activity greater than compactin. Dr. Wattanasin testified that this activity showed that the compound would be active as a HMG-CoA reductase inhibitor when administered to a patient. Further Dr. Holmlund, Fujikawa's rebuttal witness acknowledged that the compound did in fact exhibit significant activity at those levels. See the Fujikawa record at pages 207 to 209 and 243 (FR 207 to 209 and 243).

We do not agree with Fujikawa's position on page 32 of his main brief that the proofs of Wattanasin fail because a human patient was not tested. As we noted above, the count embraces the treatment of mammals. Thus the experiment performed on behalf of Dr. Wattanasin meets the terms of the count.

It is also Fujikawa's position that the testing of compound 64-935 does not demonstrate a practical utility. This position is not well taken. The Fujikawa rebuttal evidence is mainly directed to whether a correlation exists between in vitro activity and in vivo activity, a matter which is not in issue in this interference. To the extent that the evidence is relied upon to show that the Wattanasin record does not demonstrate that the testing establishes a practical utility for compound 64-935, we are not persuaded thereby. Fujikawa relies on Dr. Holmlund's testimony at FR 209 that since the compound was not significantly active at 0.3 milligrams and that since he (Dr. Holmlund) could not have obtained the ED_{50} value on the basis of WX K-1 in the absence of any reasonable dose response curve, he could not make any final conclusion on the compound's activity. In effect, Dr. Holmlund would want a commercially satisfactory performance; however, a commercially satisfactory performance is not necessary for an actual reduction to practice. Creamer v. Kirkwood, 305 F.2d 486, 134 USPQ 330 (CCPA 1962). Practical utility for

compound 64-935 existed when it was found to have significant activity at 1 and 0.1 milligrams.

Nor do we agree with the Fujikawa brief at pages 53 and 54 that the Engstrom declaration should be "severely discounted," because it reflects a ED_{50} value for a compound never tested, i.e., 64-936. The fact that Dr. Engstrom had been provided the sodium salt of 64-936 (64-936NA) and had not assigned any ED_{50} value for that compound does not in any way impugn the test results for compound 64-935.

For the foregoing reasons, we hold that the Wattanasin record establishes actual reduction to practice by December 9, 1987. Accordingly, the Wattanasin record establishes prior conception coupled with due diligence from just prior to August 20, 1987, Fujikawa's effective filing date, up to December 9, 1987, the date of the in vivo testing of compound 64-935.

IV

In view of our foregoing holding, Wattanasin is entitled to judgment vis-a-vis Fujikawa. However, Fujikawa urges that judgment should not be entered in Wattanasin's favor because the evidence shows that Wattanasin suppressed or concealed the invention. In this case, the hiatus in time between the actual reduction to practice on December 9, 1987 up to March 3, 1989, the filing date of Wattanasin's parent application, is approximately fifteen months. In our view,

this hiatus in time is not sufficiently long to raise the inference that Wattanasin suppressed or concealed the invention considering the nature and complexity of the invention here. Cf. Bigham v. Godtfredsen, 222 USPQ 632 (Bd.Pat.Int. 1984) and Halbert v, Schuurs, 220 USPQ 558 (Bd.Pat.Int. 1983).

Since we have held that the hiatus in time is not sufficiently long to raise the inference that Wattanasin suppressed or concealed his invention, we need not evaluate the testimony of Mr. Melvyn Kassenoff, which bears on this question and which the Fujikawa brief requests that we discredit. We consider this matter moot.

JUDGMENT

Judgment with respect to the subject matter of the count in issue is hereby awarded to Sompong Wattanasin, the junior party. Accordingly, on the present record, Wattanasin is entitled to a patent containing claims 8 and 9 and Fujikawa et al. are not entitled to a patent containing claims 35, 37 and 38.

IAN A. CALVERT, Vice Chief
Administrative Patent Judge

MICHAEL SOFOCLEOUS
Administrative Patent Judge

MARY F. DOWNEY
Administrative Patent Judge

BOARD OF PATENT
APPEALS AND
INTERFERENCES

Interference No. 102,648

Gerald D. Sharkin
Sandoz Corp.
59 Route 10
E. Hanover, N.J. 07936

Oblon, Fisher, Spivak,
McClelland & Maier
1755 S. Jefferson Davis Hwy.
Crystal Square Five-Ste. 400
Arlington, VA 22202

CERTIFICATE OF SERVICE

I hereby certify that true copies of:

1. the foregoing 2-page letter
2. Exhibits S-1, S-2, S-3 and S-4
3. Certificate of Service

were served upon Counsel for Wattanasin as follows:

Diane E. Furman
SANDOZ CORPORATION
59 Route 10
E. Hanover, New Jersey 07936

via first-class mail, postage prepaid, this 5th day of December, 1994.

Steven B. Kelber

OBLON, SPIVAK, McCLELLAND, MAIER & NEUSTADT, P.C.
ATTORNEYS AT LAW
FOURTH FLOOR
1755 JEFFERSON DAVIS HIGHWAY
ARLINGTON, VIRGINIA 22202 U.S.A.

TELEPHONE
(703) 413-3000
FACSIMILE
(703) 413-2220
TELEX
248855 OPAT UR

PATENT, TRADEMARK AND COPYRIGHT LAW
AND RELATED FEDERAL AND ITC LITIGATION

WEST COAST OFFICE
224 AIRPORT PARKWAY, SUITE 300
SAN JOSE, CALIFORNIA 95110
TELEPHONE
(408) 436-2070
FACSIMILE
(408) 436-2075

*BAR MEMBERSHIP OTHER THAN VIRGINIA
*REGISTERED PATENT AGENT

NORMAN F. OBLON
MARVIN J. SPIVAK
C. IRVIN McCLELLAND
GREGORY J. MAIER
ARTHUR I. NEUSTADT
ROBERT C. MILLER
RICHARD D. KELLY
JAMES D. HAMILTON
ECKHARD H. KUESTERS
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DAVID J. KERA
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WILLIAM E. BEAUMONT
STEVEN B. KELBER*
STUART D. DWORK
ROBERT F. GNUSE
JEAN-PAUL LAVALLEYE, PH.D.
JEFFREY H. KAUFMAN
BRIAN D. ANDERSON
ROBERTA S. BREN
WILLIAM B. WALKER*
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KAREN L. SHANNON, PH.D.*
DAVID H. VANCE, PH.D.*
PAUL E. RAUCH, PH.D.*

December 5, 1994

Administrative Patent Judge Sofocleous
United States Patent and Trademark Office
Board of Patent Appeals and Interferences
Crystal Gateway 2
10th Floor
Arlington, Virginia 22202

RE: Interference No. 102,648 and 102,975
Exhibits S-1, S-2, S-3 and S-4
Our Ref.: 49-111-0

Dear Judge Sofocleous:

Pursuant to our telephone discussion of this morning, enclosed please find copies of Exhibits S-1, S-2, S-3 and S-4, identified on pages 9 and 10 of volume 1 of the Wattanasin consolidated record for the above-captioned interferences. These Exhibits were obtained and copied from the deposition transcript of Joanne Geisser. The Geisser deposition was based on Fujikawa's request for cross-examination in response to the filing of the Geisser declaration which appears as Exhibit F-20. Please don't hesitate to let me know if there are further exhibits not immediately available to you, and we will try to provide the same.

The presentation of this material has been discussed with counsel for Wattanasin, Diane Furman. I should point out, as I discussed with Ms. Furman, that these Exhibits were not introduced by Fujikawa, nor did Fujikawa call any of the depositions in which these Exhibits were introduced. The sole deposition for which Fujikawa was responsible, the deposition of Chester Holmlund, includes only one new exhibit, Exhibit F-10, Holmlund's c.v.

Nonetheless, we would be glad to provide whatever additional exhibits are required.

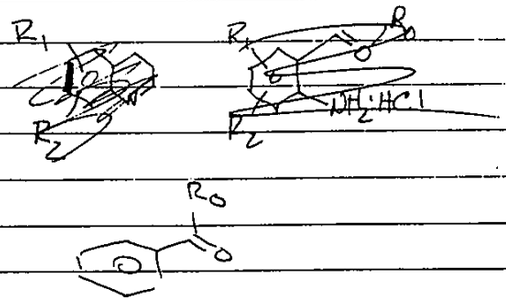
Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.

Steven B. Kelber
Registration No.: 30,073
Attorney of Record

SBK:ew
Enclosure:
Copies of Exhibits S-1, S-2, S-3, S-4

Add before pg 4



A_1 ~~reflux~~ - condensation

X_1 = any alkyl group

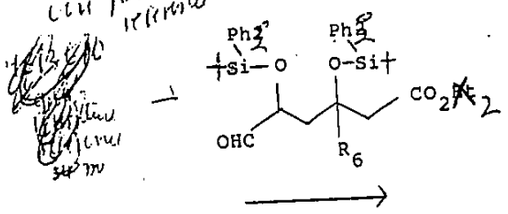
X_2 = $R_{1,3}$ of indene

X_3 = any alkyl

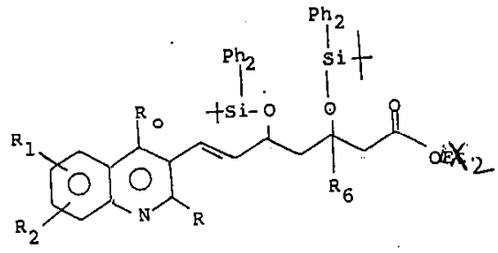
X'_3 = ~~dppp~~ ethyl or methyl

R_6 as defined

List of all var before table p11
incorp Rx scheme into example



B-3



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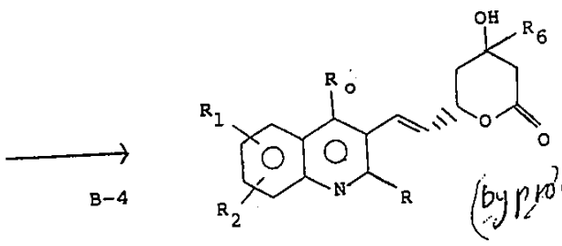
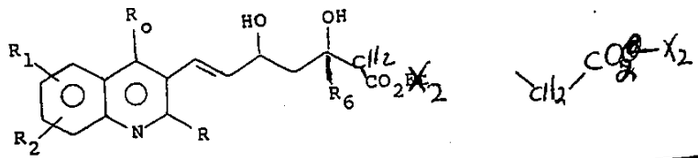


B-4

(II)

and

(by product formed only sometimes)



(I)

Need 1) Statement that when any compound of Formula A contains an hydroxy group as R_1-R_5, said hydroxy group is protected by a diphenyl t-butylsilyl group in the compounds of formula XII - XI and XIV - XVI which group is cleaved at the end of the synthesis by Reaction B-4.

2) Hydrogenation reaction to get compounds wherein X is O.

(3) Process for obtaining compounds wherein X is 4-CH=CH- (cis). Add phosphonium wittig chloride to Reaction B-2

(4) Process for Q = $-\overset{O}{\overset{\|}{C}}-$ compound

(5) Process for lactamization, hydrolysis of lactone formation of esters, salts, free acid, etc.

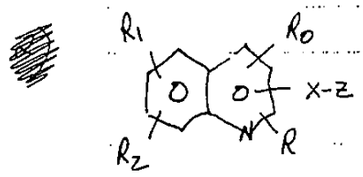
7064

Z-compound
3- method

Insert

but are not limited to the following

1) 1) Those Compounds which are included in the formula of the Proposed Count 1 including those (referring to the formula of Proposed Count 1.)



i) Compound 63-366, where R_1 = H; R_2 = H; R_D = 3,5-dimethylphenyl; R = isopropyl; X = -CH=CH-; Z = (a); Q = -C(OH)-; and R_g = ethyl

ii) Compound 63-548, where R_1 = H; R_2 = H; R_D = 3,5-dimethylphenyl; R = CH_3, X = -CH=CH-; Z = (a); Q = -C(OH)-; and R_7 = ethyl.

iii) Compound 63-549, where R_1 = H; R_2 = H; R_D = 3,5-dimethylphenyl; R = CH_3, X = -CH=CH-; and Z = (b).

iv) Compound 64-933, where R_1 = H; R_2 = H; R_D = phenyl; R = isopropyl; X = -CH=CH-; Z = (a); Q = -C(OH)- and R_g = ethyl

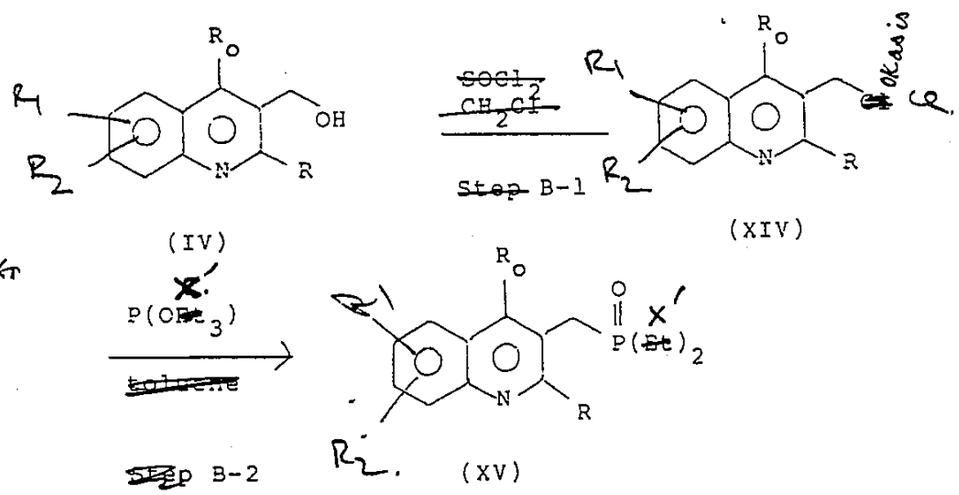
v) Compound 64-934, where R_1 = H; R_2 = H; R_D = phenyl; R = isopropyl; X = -CH=CH; Z = (a); Q = -C(OH)-; R_7 = M; M = Na^+

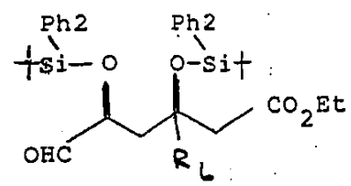
vi) Compound 64-935, where R_1 = H; R_2 = H; R_D = 4-fluorophenyl, R = isopropyl; Z = (a); Q = -C(OH)-; R_g = ethyl

Starting material III is known and can be obtained by methods described by Morrison and Mulholland, 1958, J. Chem. Soc. p. 2702, which is hereby incorporated by reference. Next, V is reduced with lithium aluminum hydride, (LAH) to give VI. This reaction has also been described by Fehnel, 1968. J. Heterocyclic Chem 4:565, which is also hereby incorporated by reference. In Step A-3, VI is oxidized to VII. Step A-4 is a Wittig reaction producing VIII. Compound VIII is then reduced using diisobutylaluminum hydride (DIBAL) to IX. In Step A-6, IX is oxidized to X. The aldehyde X is then reacted with ethyl acetoacetate in Step A-7 to give XI. Compound XI is reduced to give XII. Next, in Step A-9, XII is hydrolyzed to the salt form XIII.

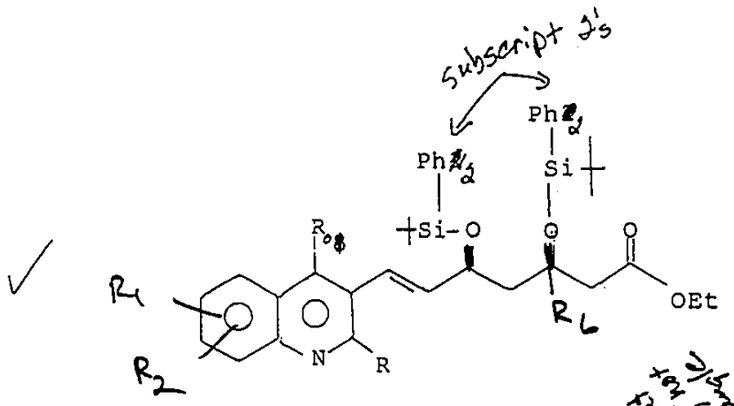
Compounds of both Formula I and II may be made according to Reaction Scheme B. Starting material for Reaction Scheme B is Compound VI from Reaction Scheme A.

REACTION SCHEME B





B-3



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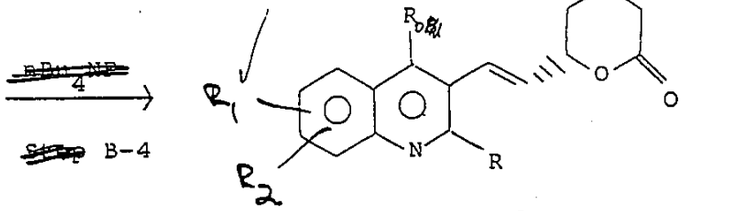
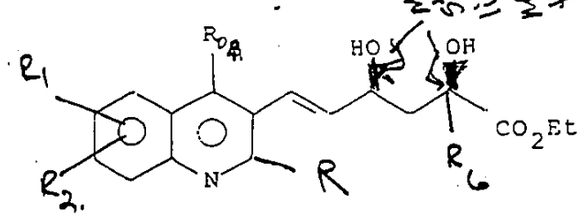


B-4

and

(II)



(I)

3A

11-26-84
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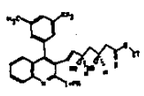
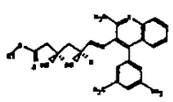
LD
SAH-063366
25496 D OR E OR C
1079-111-19
KATH 299-84
CSI



2

05-17-85
MW 433.552
LD 13329.0
SAH-063548
26080 C OR D OR E
1127-011-34
KATH 299-84
CSI. CSTC. CSTV



2

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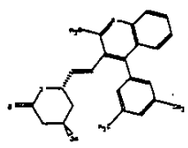
KATH 299-84
CSI



09-21-87
MW 433.552
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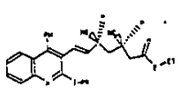
1206-176-43
WATT 299-84
CSI CSIC CSIV



13

09-21-87
MW 427.48
LD
SAH-064934 NA
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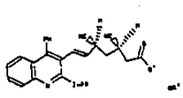
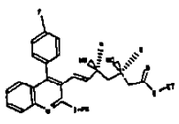
1206-179-30
WATT 299-84
CSI CSIC CSIV



3C

09-21-87
MW 451.543
LD
SAH-064935
30447 D OR E OR C
1206-190-41
WATT 299-84
CSI CSIC CSIV



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1206-201-30
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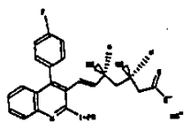

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Ex 4

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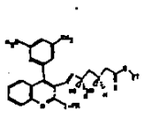

Ex 3A

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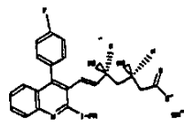

05-17-85
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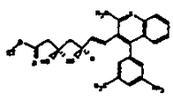
LD 13329.0
SAH-063548
26080 C OR D OR E
1127-011-34
KATH 299-84
CSI. CSTC. CSTV



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KATH 299-84
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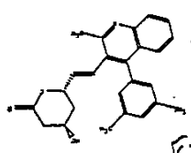

Ex 2

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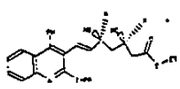

Ex 1

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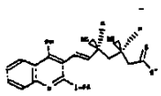

Ex 3B

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WATT 299-84
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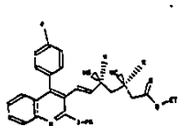

Ex 3C

DISCLOSURE

Back mail 5/4/89

LIST FOR PUBLICATION CLEARANCES

1) Running number of publication: 4751 (Will be attributed by ST)

2) Names of all the authors:

S. WATTANASIN/F. G. KATHAWALA/R. PATEL/T. SCALLEN/
R. G. ENGSTROM/D. B. WEINSTEIN

3) Full title of the publication:

QUINOLINES AS HMG-CoA REDUCTASE INHIBITORS

4) Date of the receipt of the publication:

APRIL 4, 1989

5) Type of publication (lecture/article, poster/abstract or full publication) and proposed date of publication (if known):

POSTER - 5TH SCI-RSC MEDICINAL CHEMISTRY SYMPOSIUM CHURCHILL COLLEGE, CAMBRIDGE, SEPTEMBER 10-13, 1989

6) Bereiche: HANOVER,

7) SB Patent Department: MRS. J. M. GIESSER Joanne M. Giesser

8) Subject matter ("Stichwort"), e.g. "Zaditen", "20-511", "Allylamines", "HPLC-apparatus" etc. and/or Case-No. if possible:

The compounds are covered in Case 600-7101

63-366	63-549	64-934	64-936
63-548	64-933	64-935	

9) Date of return of the publication to source:

10) PA comments to source:

☐ No Objection

☐ Objection

Scientific Publication Release Request

SANDOZ

Name of Requestor	Date
Dr. S. Wattanasin	3/30/89

I. STATEMENT OF REQUEST

I request release of the attached ☐ *manuscript,* ☐ *abstract,* ☐ *lecture* ☐ *other* Poster

By (names of all authors)

S. Wattanasin, F. G. Kathawala, R. Patel, T. Scallen
R. G. Engstrom, D. B. Weinstein

Entitled

Quinolines as HMG-CoA Reductase Inhibitors

For Disclosure in (periodical, symposium, meeting, correspondence, etc.) on (date, if known).

5th SCI-RSC Medicinal Chemistry Symposium
Churchill College, Cambridge September 10-13, 1989

Listed below in numerical order are SANDOZ compounds:

63-366, 63-548, 63-549, 64-933, 64-934, 64-935, 64-936

PATENT AND TRADEMARK DEPT.
APR 4 - 1989
JMG

II. CIRCULATION ORDER, RECOMMENDATIONS, AND ACTION

CO-AUTHOR APPROVAL (Initials)

1. Supervisor Dr. F. G. Kathawala FGK	☒ Approve	☐ Withhold	Date 4/3/89
2. Department Director Dr. F. G. Kathawala FGK	☒ Approve	☐ Withhold	Date 4/3/89
3. Patent Department Joanne M. Giesser	☒ Approve	☐ Withhold	Date 4/19/89
4. V.P. Clinical or Preclinical Research	☐ Approve	☐ Withhold	Date

COMMENTS:

The material in this abstract is covered under Case No. 600-7101-U.S., Quinoline Analogs of Mevalonolactone and Derivatives Thereof, which was filed with the Patent Office on March 3, 1989.
SIMILAR WORK HAS APPEARED AFTER THE START OF OUR WORK & COMPLETION IN A PATENT FILED BY WARNER LAMBERT Co.

5. President *SANDOZ RESEARCH INSTITUTE*	☐ Released	☐ Withheld	Date

86704/84

QUINOLINES AS HMG-CoA REDUCTASE INHIBITORS.

S. Wattanasin[1], F.G. Kathawala[1], R. Patel[1], T. Scallen[2], R.G. Engstrom[1], and D.B. Weinstein[1]

[1]Sandoz Research Institute, E. Hanover, New Jersey 07936

[2]Department of Biochemistry, School of Medicine, University of New Mexico, Albuquerque, New Mexico 87131

Inhibition of HMG-CoA reductase, the rate limiting enzyme in cholesterol biosynthesis, has proved to be an effective method of lowering serum low density lipoprotein(LDL-C) levels in both animals and man. Efforts at Sandoz Research Institute in the design and synthesis of new HMG-CoA reductase inhibitors have led to the discoverry of a number of classes of compounds which inhibit the enzyme HMG-CoA reductase. We present here the synthesis of quinolines as potent inhibitors of this enzyme *in vitro* and cholesterol biosynthesis *in vivo*.

April 19, 1989

Dr. S. Wattanasin/
Dr. F. Kathawala

Joanne M. Giesser

Abstract entitled:
"Quinolines as HMG-CoA Reductase Inhibitors"

The above abstract to be presented at the 5th SCI-RSC Medicinal Chemistry Symposium Churchill College, Cambridge, September 10-13 is approved by the Patent Department. However, the full text will still have to be reviewed and cleared by this department before presentation.

Joanne M. Giesser

JMG:lmc
Enc.

SANDOZ

Patent and Trademark Department
59 Route 10
E. Hanover, New Jersey 07936

Telex 240867
Telefax (201) 503-8807

May 4, 1989

SANDOZ LTD.
Patents and Trademarks Division
CH-4002
Basle, Switzerland

Re: Clearance for Abstract Entitled
"QUINOLINES AS HMG-CoA REDUCTASE
INHIBITORS"
Ref: 3700/RA

Dear Sirs:

Enclosed please find the Publication Clearance regarding the above-identified abstract.

We look forward to receiving the corresponding number in due course.

Very truly yours,

Linda C. Rothwell

Linda C. Rothwell

LCR
Enc. Publication Clearance

Basle Mail 6/15/89

LIST FOR PUBLICATION CLEARANCES

1) Running number of publication: 4878 (Will be attributed by ST)

2) Names of all the authors:

S. WATTANASIN/F.G. KATHAWALA/R. PATEL/T. SCALLEN/
R.G. ENGSTROM/D.B. WEINSTEIN

3) Full title of the publication:

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4) Date of the receipt of the publication:

MAY 23, 1989

5) Type of publication (lecture/article, poster/abstract or full publication) and proposed date of publication (if known):

Poster for 5th SCI-RSC Medicinal Chemistry Symposium
Churchill College, Cambridge
September 10-13, 1989

6) Bereiche: HANOVER

7) SB Patent Department: MRS. GIESSER Joanne M. Giesser

8) Subject matter ("Stichwort"), e.g. "Zaditen", "20-511", "Allylamines", "HPLC-apparatus" etc. and/or Case-No. if possible:
The compounds are covered in case 600-7101
63-366 64-933 64-936
63-548 64-934
63-549 64-935

9) Date of return of the publication to source:

10) PA comments to source:

☒ No Objection

☐ Objection

Scientific Publication Release Request

SANDOZ

Name of Requestor: Dr. S. Wattanasin

Date: 5/12/89 ~~3/30/89~~

I. STATEMENT OF REQUEST

I request release of the attached ☐ *manuscript,* ☐ *abstract,* ☐ *lecture* ☐ *other* Poster

By (names of all authors) S. Wattanasin, F. G. Kathawala, R. Patel, T. Scallen, R. G. Engstrom, D. B. Weinstein

Entitled: Quinolines as HMG-CoA Reductase Inhibitors

For Disclosure in (periodical, symposium, meeting, correspondence, etc.) on (date, if known).
5th SCI-RSC Medicinal Chemistry Symposium
Churchill College, Cambridge September 10-13, 1989

Listed below in numerical order are SANDOZ compounds:

63-366	64-933	64-936
63-548	64-934	
63-549	64-935	

PATENT AND TRADEMARK DEPT.
MAY 23 1989
JMG

II. CIRCULATION ORDER, RECOMMENDATIONS, AND ACTION

CO-AUTHOR APPROVAL (Initials)

1. Supervisor Dr. F. G. Kathawala FGKathawala	☒ Approve	☐ Withhold	Date 5/19/89
2. Department Director Dr. F. G. Kathawala FGKathawala	☒ Approve	☐ Withhold	Date 5/19/89
3. Patent Department	☐ Approve	☐ Withhold	Date
4. V.P. Clinical or Preclinical Research	☐ Approve	☐ Withhold	Date

COMMENTS:

The material in this abstract is covered under Case No. 600-7101-U.S., Quinoline Analogs of Mevalonolactone and Derivatives Thereof, which was filed with the Patent Office on March 3, 1989.
The abstract of this poster had been approved.

5. President *SANDOZ RESEARCH INSTITUTE*	☐ Released	☐ Withheld	Date

QUINOLINES AS HMG-CoA REDUCTASE INHIBITORS.

S. Wattanasin[1], F.G. Kathawala[1], R. Patel[1], T. Scallen[2], R.G. Engstrom[1], and D.B. Weinstein[1]

[1]Sandoz Research Institute, E. Hanover, New Jersey 07936

[2]Department of Biochemistry, School of Medicine, University of New Mexico, Albuquerque, New Mexico 87131

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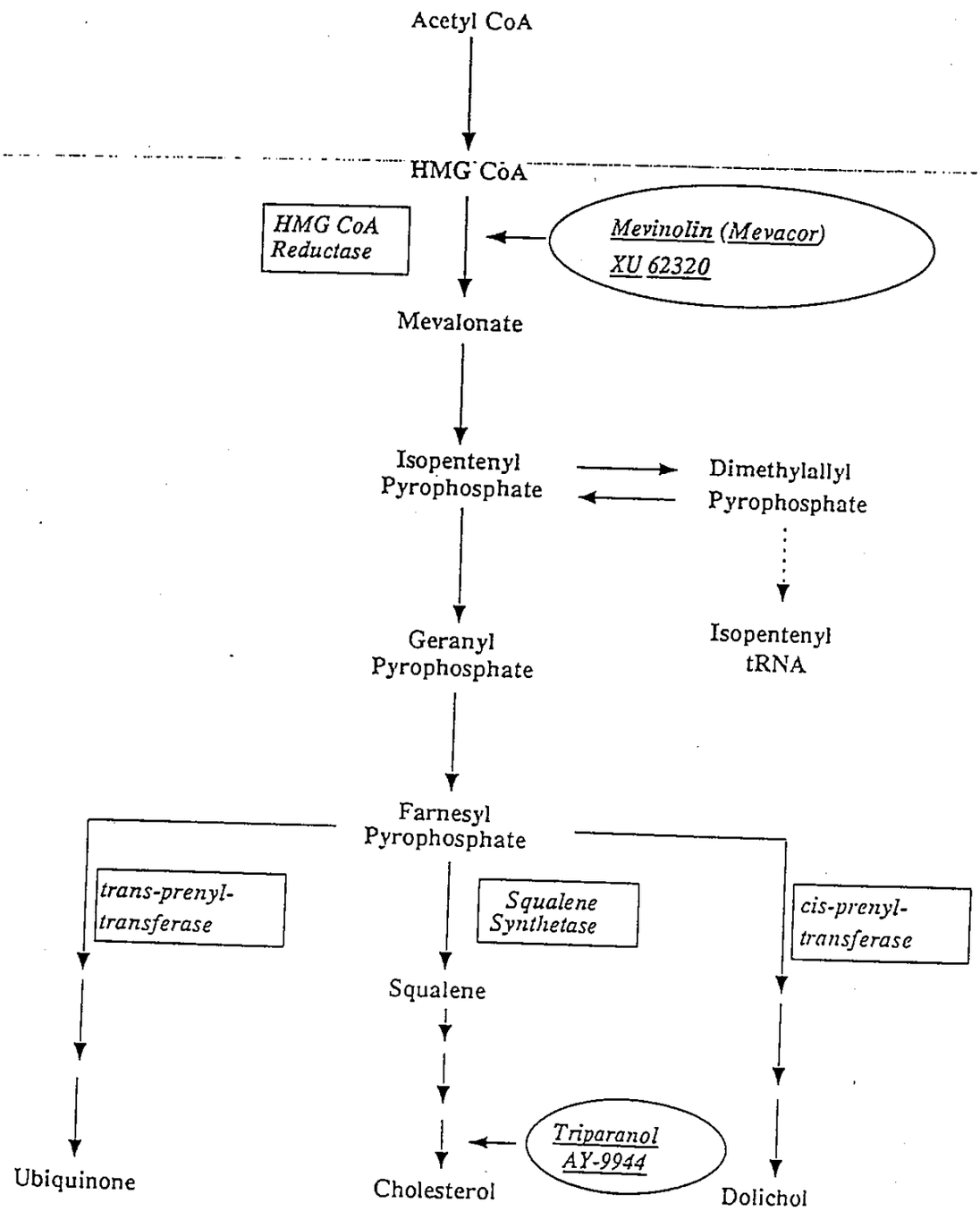
INTRODUCTION

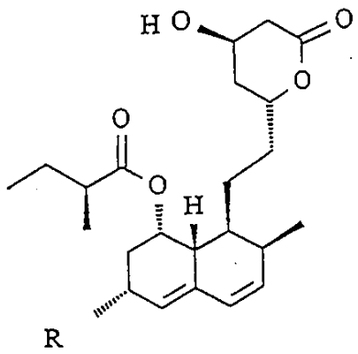
Inhibition of 3-hydroxy-3-methylglutaryl-coenzymeA, the rate-limiting enzyme in cholesterol biosynthesis, has proved to be an effective method of lowering serum low density lipoprotein (LDL-C) levels in both animals and man. Epidemiological evidence implicating elevated LDL-C as a major risk factor for the development of coronary heart disease, have stimulated intensive efforts directed towards the development of agents affecting serum LDL-C levels.

Recent reports have described XU 62-320, an indole analog of compactin and mevinolin, as one of the most potent HMG-CoA reductase inhibitors both in vitro and in vivo studies.

Discovery of XU 62-320 has prompted a search of a variety of new structural prototypes as potential inhibitors of HMG-CoA reductase. Described in this paper are the results of our initial study with a series of quinoline derivatives as HMG-CoA reductase inhibitors.

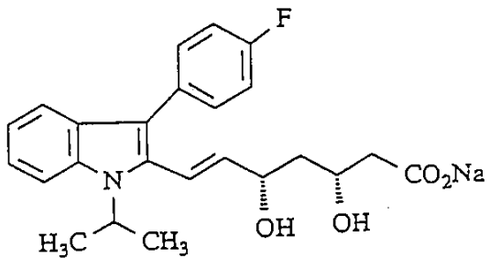

Acetyl CoA
HMG CoA
HMG CoA Reductase
Mevinolin (Mevacor)
XU 62320
Mevalonate
Isopentenyl Pyrophosphate
Dimethylallyl Pyrophosphate
Isopentenyl tRNA
Geranyl Pyrophosphate
Farnesyl Pyrophosphate
trans-prenyl-transferase
Squalene Synthetase
cis-prenyl-transferase
Squalene
Triparanol
AY-9944
Ubiquinone
Cholesterol
Dolichol

HMG-CoA REDUCTASE INHIBITORS



R = H; COMPACTIN

R = Me ; MEVINOLIN (LOVASTATIN)

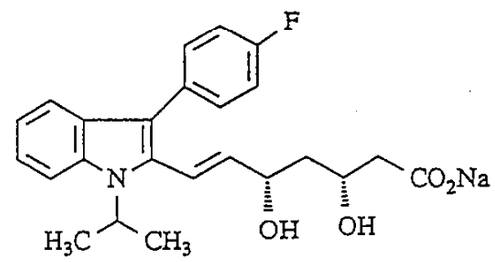


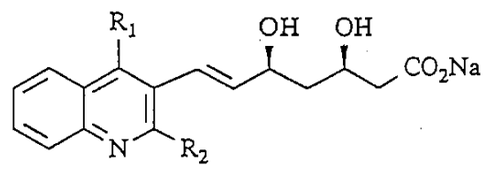
XU 62-320

q2
slide1

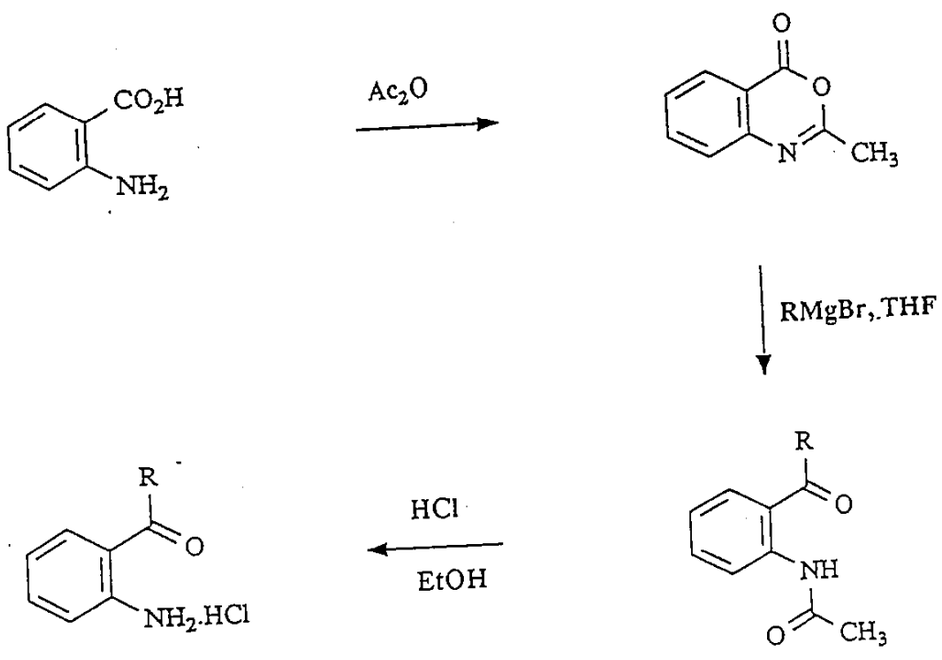
GENERATION OF NEW LEADS

INDOLE XU 62-320



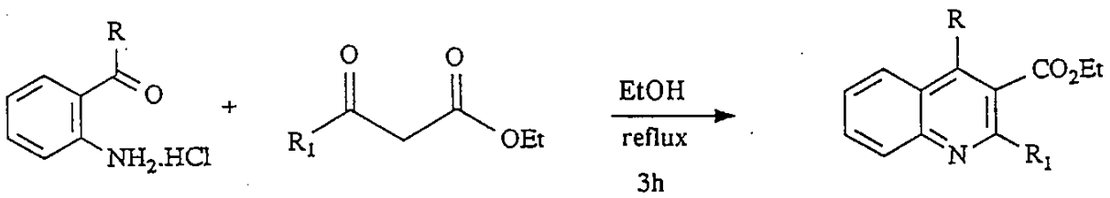


SYNTHESIS OF ortho-AMINO KETONES



R = 3,5-Dimethylphenyl
= isoPropyl
= 4-Fluorophenyl

SYNTHESIS OF 2,3,4-SUBSTITUTED QUINOLINES

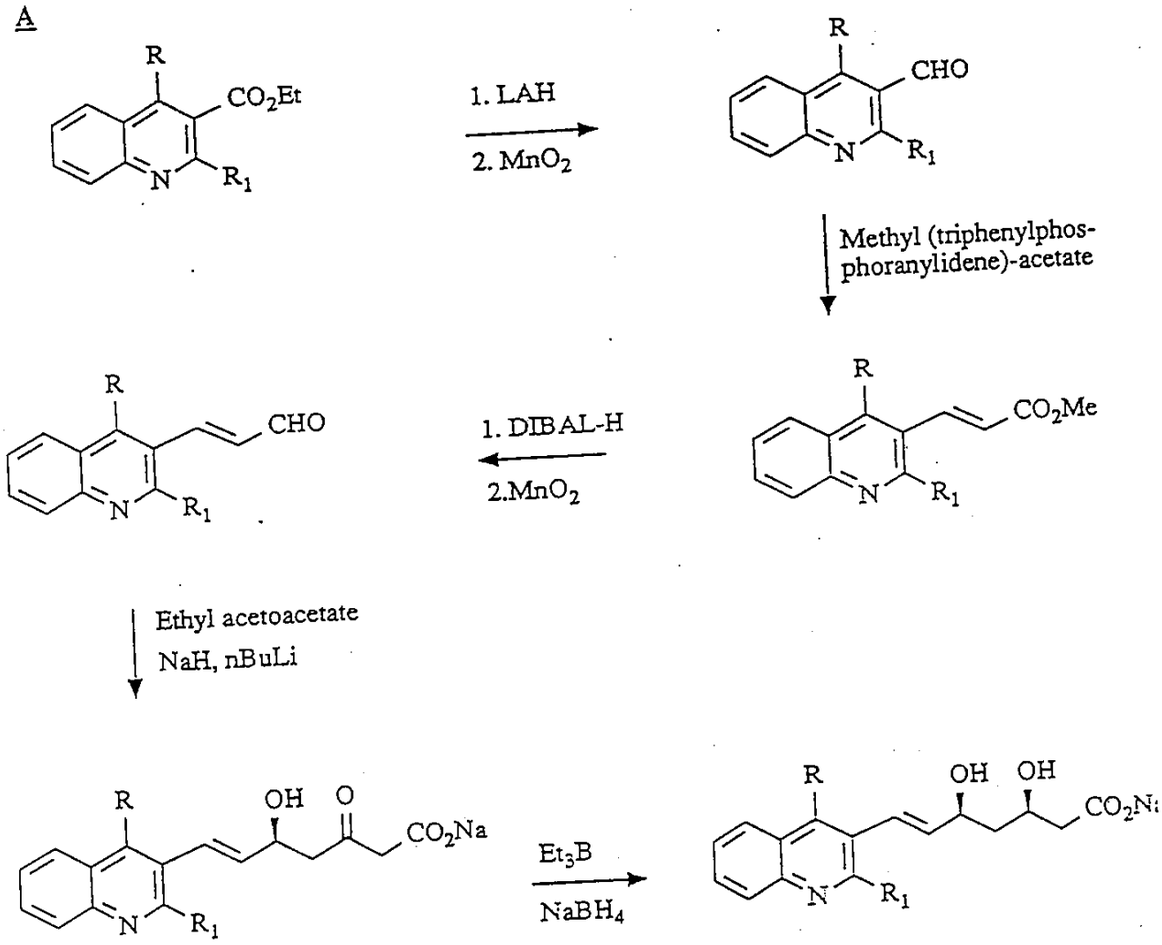


65-85%

R	R_1
i-Propyl	Me
Ph	i-Propyl
3,5-Dimethyl	4-Fluorophenyl
4-Fluorophenyl	

INTRODUCTION OF THE DIHYDROXY SIDECHAIN

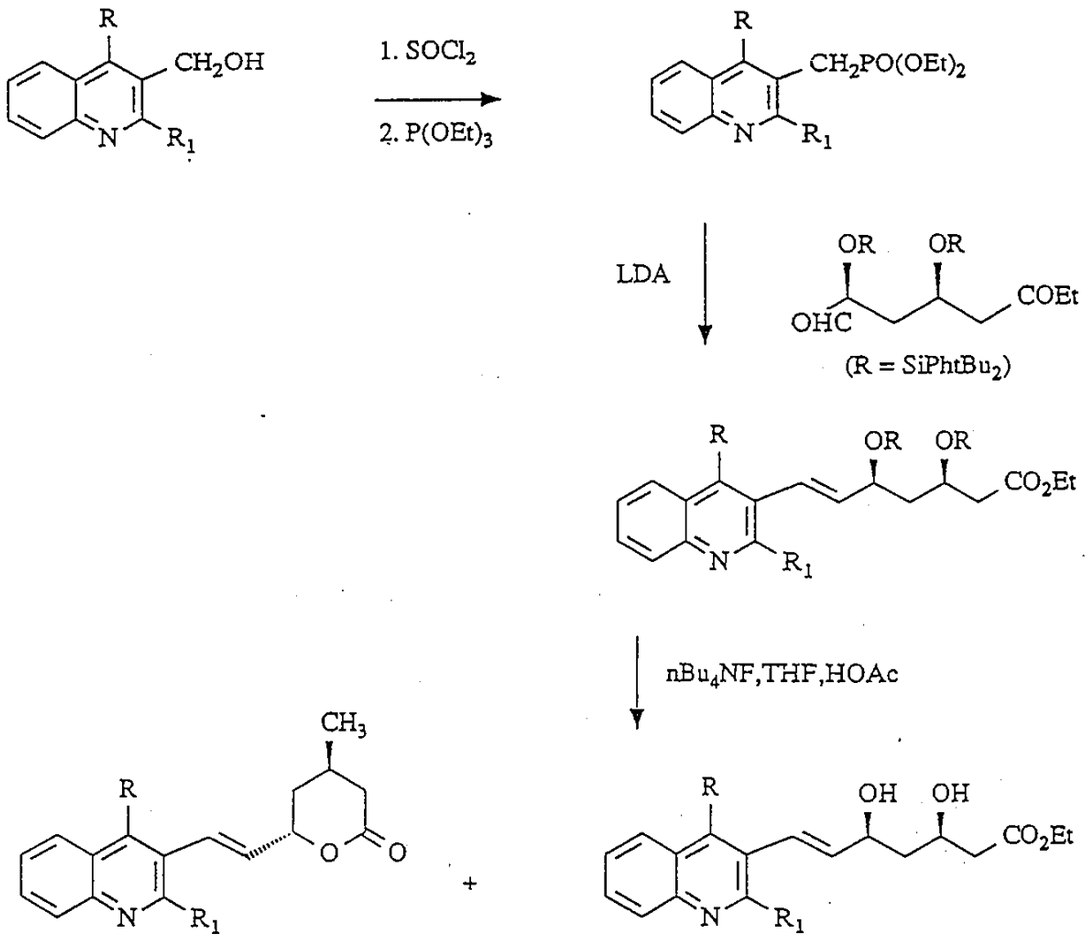
A



q6

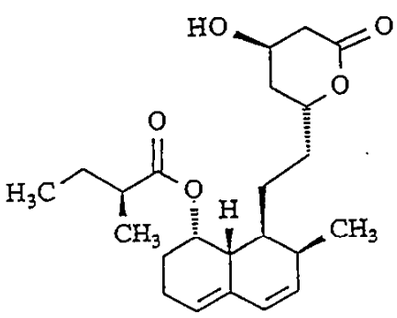
INTRODUCTION OF THE DIHYDROXY SIDECHAIN

B

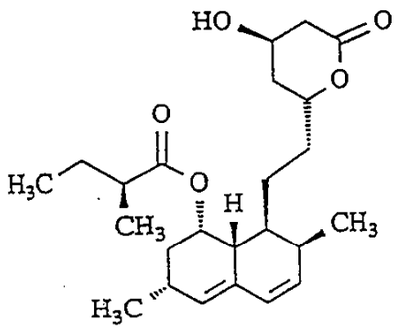


INHIBITORY EFFECT ON HMG-C0A REDUCTASE (Rat Liver Microsome)

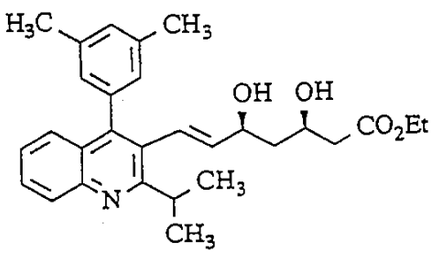
RELATIVE POTENCY*



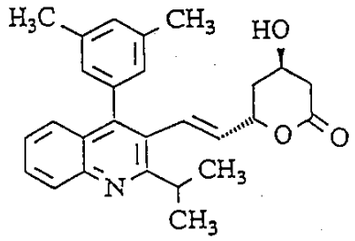
Compactin
1



Mevinoline
7.2



SDZ 63-366
0.64

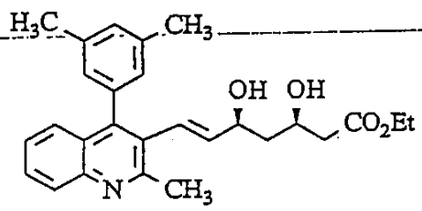


SDZ 63-549
0.14

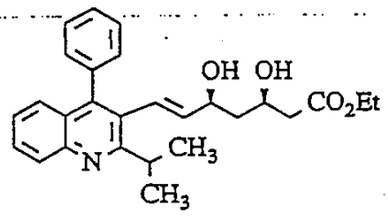
* The relative potency of the test compound was determined by comparing its IC_{50} value** with that of compactin, which was tested simultaneously and arbitrarily assigned a relative potency value of 1

** Method according to : Ackerman et.al. J. Lipid Res., 18 , 408-413 (1977)

RELATIVE POTENCY*



SDZ 63-548
0.27



SDZ 64-933
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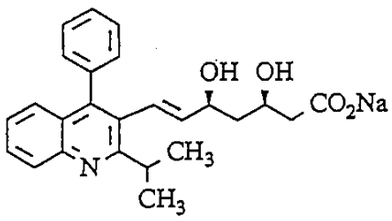

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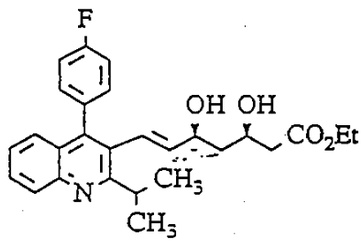
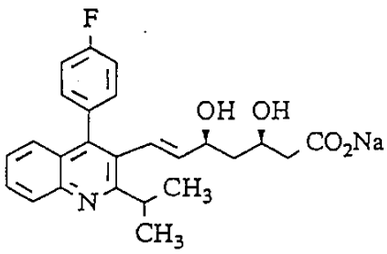
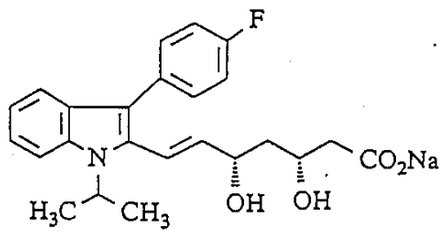


SDZ 64-935
2.46

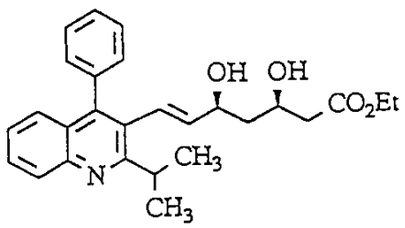


SDZ 64-936
1.9



XU 62-620
146

INHIBITORY EFFECT ON CHOLESTEROL SYNTHESIS (RATS) ED_{50} (mg/Kg)



SDZ 64-933

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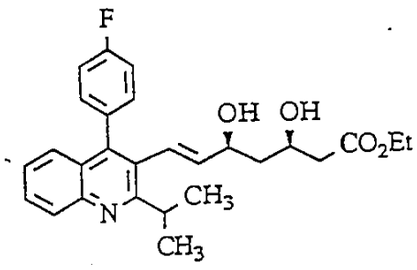
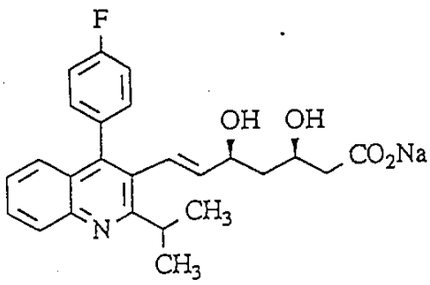


SDZ 64-935

0.49



SDZ 64936

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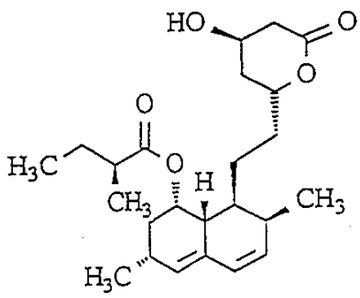

Mevinolin

0.38

CONCLUSION

1. QUINOLINE ANALOGS HAVE BEEN SYNTHESIZED AS NOVEL HMG-COA REDUCTASE INHIBITORS, BASED ON THE STRUCTURE AND SAR DATA OF XU 62-320

2. THESE ANALOGS ARE POTENT INHIBITORS OF HMG-COA REDUCTASE IN RAT MICROSOMAL ASSAYS AS WELL AS CHOLESTEROL BIOSYNTHESIS FROM C^{14}-ACETATE IN VIVO.

3. THE MOST ACTIVE COMPOUND (SDZ 64935) IS AS ACTIVE AS MEVINOLIN BUT IS FIVE FOLD LESS ACTIVE THAN XU 62-320 IN IN VIVO ASSAYS.

SANDOZ PATENT AND TRADEMARK DEPARTMENT

To: Dr. S. Wattanasin
Dr. F. Kathawala

From: Joanne M. Giesser

Date: June 13, 1989

Subject: Proposed publication "Quinolines as HMG-CoA Reductase Inhibitors" 5th SCI-RSC Medicinal Chemistry Symposium, Churchill College, Cambridge Sept. 10-13, 1989

The above-identified publication has been reviewed from a patent standpoint and is approved by the Patent and Trademark Department for publication.

Joanne M. Giesser

SANDOZ

Patent and Trademark Department
59 Route 10
E. Hanover, New Jersey 07936

Telex 240867
Telefax (201) 503-8807

June 15, 1989

SANDOZ LTD.
Patents and Trademarks Division
CH-4002
Basle, Switzerland

Re: Clearance for Poster Entitled
"QUINOLINES AS HMG-CoA REDUCTASE INHIBITORS"

Ref: 3700/RA

Dear Sirs:

Enclosed please find the Publication Clearance regarding the above-identified poster.

We look forward to receiving the corresponding number in due course.

Very truly yours,

Linda C. Rothwell

Linda C. Rothwell

LCR
Enc. Publication Clearance

BASLE

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

Address : COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
07/047,358	5/5/87	KATHAWALA	600-7025/CIP

PATENT AND
TRADEMARK DEPT.

JAN 6 - 1989

JMG

EXAMINER	
ART UNIT	PAPER NUMBER
121	6

DATE MAILED: 1/3/89

NOTICE OF ABANDONMENT

This application is abandoned in view of:

1. ☒ Applicant's failure to respond to the Office letter, mailed Nov. 11, 1988.
2. ☐ Applicant's letter of express abandonment which is in compliance with 37 C.F.R. 1.138.
3. ☐ Applicant's failure to timely file the response received _____ within the period set in the Office letter.
4. ☐ Applicant's failure to pay the required issue fee within the statutory period of 3 months from the mailing date of _____ of the Notice of Allowance.
   - ☐ The issue fee was received on _____.
   - ☐ The issue fee has not been received in Allowed Files Branch as of _____.

   In accordance with 35 U.S.C. 151, and under the provisions of 37 C.F.R. 1.316(b), applicant(s) may petition the Commissioner to accept the delayed payment of the issue fee if the delay in payment was unavoidable. The petition must be accompanied by the issue fee, unless it has been previously submitted, in the amount specified by 37 C.F.R. 1.17 (l), and a verified showing as to the causes of the delay.

   If applicant(s) never received the Notice of Allowance, a petition for a new Notice of Allowance and withdrawal of the holding of abandonment may be appropriate in view of Delgar Inc. v. Schuyler, 172 U.S.P.Q. 513.
5. ☐ Applicant's failure to timely correct the drawings and/or submit new or substitute formal drawings by _____ as required in the last Office action.
   - ☐ The corrected and/or substitute drawings were received on _____.
6. ☐ The reason(s) below.

[illegible] LEE
SUPERVISORY PRIMARY EXAMINER
[illegible] 121

PTO-1432 (REV. 5-83)

Exhibit No. 53 ID
Date 4-9-93
DIAsio Reporting

PATENT AND TRADEMARK DEPT.
OCT 21 1988

The impressed Mail Room date stamp acknowledges receipt on the date indicated of

- ☐ Communication
- ☐ Claim of Priority
- ☐ Not. of Appeal
- ☐ Appeal Brief
- ☐ Prel. Amendment
- ☐ Amendment
- XX Ext. of Time in duplicate
- ☐ Req. for Recon.
- XX Postcard: COM Stamp

MAIL ROOM OCT 20 19[illegible] PATENT AND TRADEMARK DEPT.

for Case No. 600-7025/CIP
Application of FAIZULLA G. KATHAWALA

Serial No. 07/047,358
Filed May 5, 1987

REV:lmc 10/11/88

BASLE

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
07/047,358	05/05/87	KATHAWALA	~~600-7025/CIP~~ 600-7025/CIP

07/047,358 5/5/87 KATHAWALA

GERALD D. SHARKIN
SANDOZ CORP.
59 ROUTE 10
EAST HANOVER, NJ 07936

PATENT AND TRADEMARK DEPT.
MAY 13 1988
JMG

EXAMINER	
BRISCOE,K	
BRISCOE,K	
ART UNIT	**PAPER NUMBER**
121	4

DATE MAILED: 05/11/88
5/11/88

This is a communication from the examiner in charge of your application.

COMMISSIONER OF PATENTS AND TRADEMARKS

August 11, 1988

☑ This application has been examined ☑ Responsive to communication filed on JAN. 19, 1988 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), ____ days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice re Patent Drawing, PTO-948.
3. ☑ Notice of Art Cited by Applicant, PTO-1449
4. ☐ Notice of Informal Patent Application, Form PTO-152
5. ☐ Information on How to Effect Drawing Changes, PTO-1474
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☑ Claims 1-23 and 26-32 are pending in the application.
   Of the above, claims _____ are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☑ Claims 1-23 and 26-29 are allowed.
4. ☑ Claims 30-32 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings which are acceptable for examination purposes until such time as allowable subject matter is indicated.
8. ☐ Allowable subject matter having been indicated, formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. These drawings are ☐ acceptable; ☐ not acceptable (see explanation).
10. ☐ The ☐ proposed drawing correction and/or the ☐ proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved. ☐ disapproved (see explanation). However, the Patent and Trademark Office no longer makes drawing changes. It is now applicant's responsibility to ensure that the drawings are corrected. Corrections MUST be effected in accordance with the instructions set forth on the attached letter "INFORMATION ON HOW TO EFFECT DRAWING CHANGES", PTO-1474.
12. ☐ Acknowledgment is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

Case No. 600-7025/CIP
Serial No. (047,358

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of :

FAIZULLA G. KATHAWALA : Art Unit: 121

Serial No. 07/047,358 : Examiner: K. BRISCOE

Filed: May 5, 1987 :

For: PYRIMIDINE DERIVATIVES :

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231, on October 11, 1988
[Date of Deposit]
Richard E. Vila
Name of applicant, assignee, or Registered Representative
/5/
Signature
October 11, 1988
Date of Signature

REQUEST FOR EXTENSION OF TIME

Honorable Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Dear Sir:

It is respectfully requested that the period for responding to the Office Action of May 11, 1988 or taking an appeal or further action in connection with the above-identified application, originally set to expire on August 11, 1988 , be extended for two (2) month(s) to October 11, 1988.

☐ A check in the amount of $ to cover the fee for this extension is enclosed.

☒ Please charge the extension fee of $170.00 required by 37 CFR 1.17(c) to Deposit Account No. 19-0134 in the name of Sandoz Corporation.

Respectfully submitted,

/5/
Richard E. Vila
Attorney for FAIZULLA G. KATHAWALA
(201) 503- 7852

JMG:lmc

SANDOZ CORP.
59 Route 10
E. Hanover, N.J. 07936

Enclosures: Postcard; COM Stamp

SUBMITTED IN DUPLICATE

BASILE

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

Address : COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
07/165,656	03/08/88	ANDERSON	P 500-7049-7DCA

GERALD D. SHARKEY
SANDOZ CORP.
59 ROUTE 10
E. HANOVER, NJ 07936

PATENT AND TRADEMARK DEPT.
JUN 15 1989
JMG

EXAMINER	
DENTZ B	
ART UNIT	PAPER NUMBER
121	17

DATE MAILED: 06/12/89

NOTICE OF ABANDONMENT

This application is abandoned in view of:

1. ☐ Applicant's failure to respond to the Office letter, mailed _____.
2. ☐ Applicant's letter of express abandonment which is in compliance with 37 C.F.R. 1.138.
3. ☐ Applicant's failure to timely file the response received _____ within the period set in the Office letter.
4. ☒ Applicant's failure to pay the required issue fee within the statutory period of 3 months from the mailing date of 1-3-89 of the Notice of Allowance.
   - ☐ The issue fee was received on _____.
   - ☐ The issue fee has not been received in Allowed Files Branch as of _____.

   In accordance with 35 U.S.C. 151, and under the provisions of 37 C.F.R. 1.316(b), applicant(s) may petition the Commissioner to accept the delayed payment of the issue fee if the delay in payment was unavoidable. The petition must be accompanied by the issue fee, unless it has been previously submitted, in the amount specified by 37 C.F.R. 1.17 (l), and a verified showing as to the causes of the delay.

   If applicant(s) never received the Notice of Allowance, a petition for a new Notice of Allowance and withdrawal of the holding of abandonment may be appropriate in view of Delgar Inc. v. Schuyler, 172 U.S.P.Q. 513.
5. ☐ Applicant's failure to timely correct the drawings and/or submit new or substitute formal drawings by _____ as required in the last Office action.
   - ☐ The corrected and/or substitute drawings were received on _____.
6. ☐ The reason(s) below.

DIRECT ANY INQUIRIES TO :
[redacted]
OR
MARCIA CAMPBELL
PUBLISHING DIVISION
(703) 557-[redacted]
8190

PTO-1432 (REV. 5-83)

Exhibit No. 54 ID
Date 4-9-93
DiAsio Reporting

85 (REV. 4-86)

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

NOTICE OF ALLOWANCE AND ISSUE FEE DUE

GERALD D. SHARKIN
SANDOZ CORP.
59 ROUTE 10
E. HANOVER, NJ 07936

PATENT AND TRADEMARK DEPT.
JAN 5 - 1989
JMG

April 3, 1989

All communications regarding this application should give the serial number, date of filing, name of applicant, and batch number.

Please direct all communications to the Attention of "OFFICE OF PUBLICATIONS" unless advised to the contrary.

The application identified below has been examined and found allowable for issuance of Letters Patent. PROSECUTION ON THE MERITS IS CLOSED.

SC/SERIAL NO.	FILING DATE	TOTAL CLAIMS	EXAMINER AND GROUP ART UNIT		DATE MAILED
07/165,656	03/08/88	017	DENTZ, B	121	01/03/89

1st named applicant: ANDERSON, PAUL L.

TITLE OF INVENTION: AZAINDOLE DERIVATIVES USEFUL AS CHOLESTEROL BIOSYNTHESIS INHIBITORS (AS AMENDED)

ATTY'S DOCKET NO.	CLASS-SUBCLASS	BATCH NO.	APPLN. TYPE	SMALL ENTITY	FEE DUE	DATE DUE
600-7044/CONT	514-300.000	P15	UTILITY	NO	$560.00	04/03/89

The amount of the issue fee is specified in 37 C.F.R. 1.18. If the applicant qualified for and has filed a verified statement of small entity status in accordance with 37 C.F.R. 1.27, the issue fee is one-half the amount for non-small entities. The issue fee due printed above reflects applicant's status as of the time of mailing this notice. A verified statement of small entity status may be filed prior to or with payment of the issue fee. However, in accordance with 37 C.F.R. 1.28, failure to establish status as a small entity prior to or with payment of the issue fee precludes payment of the issue fee in the amount so established for small entities and precludes a refund of any portion thereof paid prior to establishing status as a small entity.

THE ISSUE FEE MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE as indicated above. The application shall otherwise be regarded as ABANDONED. The issue fee will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the Patent and Trademark Office. Where an authorization to charge the issue fee to a deposit account has been filed before the mailing of the notice of allowance, the issue fee is charged to the deposit account at the time of mailing of this notice in accordance with 37 C.F.R. 1.311. If the issue fee has been so charged, it is indicated above.

In order to minimize delays in the issuance of a patent based on this application, **this Notice may have been mailed prior to completion of final processing.** The nature and/or extent of the remaining revision or processing requirements may cause slight delays of the patent. In addition, **if prosecution is to be reopened, this Notice of Allowance will be vacated and the appropriate Office action will follow in due course.** If the issue fee has already been paid and prosecution is reopened, the applicant may request a refund or request that the fee be credited to a deposit account. However, applicant may request that the previously submitted issue fee be applied. If abandoned, applicant may request refund or credit to a deposit account.

In the case of each patent issuing without an assignment, the complete post office address of the inventor(s) will be printed in the patent heading and in the Official Gazette. If the inventor's address is now different from the address which appears in the application, please fill in the information in the spaces provided on PTOL-85b enclosed. If there are address changes for more than two inventors, enter the additional addresses on the reverse side of the PTOL-85b.

The appropriate spaces in the ASSIGNMENT DATA section of PTOL-85b must be completed in all cases. If it is desired to have the patent issue to an assignee, an assignment must have been previously submitted to the Patent and Trademark Office or must be submitted not later than the date of payment of the issue fee as required by 37 C.F.R. 1.334. Where there is an assignment, the assignee's name and address must be provided on the PTOL-85b to ensure its inclusion in the printed patent.

Advance orders for 10 or more printed copies of the prospective patent can be made by completing the information in Section 4 of PTOL-85b and submitting payment therewith. If use of a deposit account is being authorized for payment, PTOL-85c should also be forwarded. The order must be for at least 10 copies and must accompany the issue fee. The copies ordered will be sent only to the address specified in section 1 or 1A of PTOL-85b.

[x] Note attached communication from the Examiner.

[ ] This notice is issued in view of applicant's communication filed

IMPORTANT REMINDER

Patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. See 37 CFR 1.20 (e)—(i).

U.S. Department of Commerce
Patent and Tradema... Office

PTOL-85 (REV. 2-85)

ISSUE FEE TRANSMITTAL

This form is provided in lieu of a formal transmittal and should be used for transmitting the Issue Fee. Sections 1A through 4 must be completed as appropriate.

1A. ENTOR(S) ADDRESS CHANGE	SC. SERIAL NO
ENTOR'S NAME	
eet Address	
, State and ZIP Code	
INVENTOR'S NAME	
eet Address	
y, State and ZIP Code	

☐ Check if additional changes are on reverse side

MAILING INSTRUCTIONS

All further correspondence including the Issue Fee Receipt the Patent, and advanced orders will be mailed to the addressee entered in section 1 on PTOL-85c, unless you direct otherwise by specifying the appropriate name and address in 1A below. (Note: See box 5 below for correspondence concerning maintenance fee payments.)

2A. The COMMISSIONER OF PATENTS AND TRADEMARKS is requested to apply the Issue Fee to the application identified below.

(Signature of party in interest of record)	(Date)

Note: The Issue Fee will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the Patent and Trademark Office.

SC/SERIAL NO.	FILING DATE	TOTAL CLAIMS	EXAMINER AND GROUP ART UNIT		DATE MAILED
[illegible]	03/06/88	017	DENTZ, B	121	01/03/89

1st named applicant: ANDERSON, PAUL L.

TITLE OF INVENTION: AZAINDOLE DERIVATIVES USEFUL AS CHOLESTEROL BIOSYNTHESIS INHIBITORS (AS AMENDED)

ATTY'S DOCKET NO.	CLASS-SUBCLASS	BATCH NO.	APPLN. TYPE	SMALL ENTITY	FEE DUE	DATE DUE
600-7044/CON	514-300.000	P15	UTILITY	NO	$560.00	04/03/89

Further correspondence to be mailed to the following:

2B. For printing on the patent front page, list the names of not more than 3 registered patent attorneys or agents OR, alternatively, the name of a firm having as a member a registered attorney or agent. If no name is listed, no name will printed.

1 _____
2 _____
3 _____

DO NOT USE THIS SPACE

3 ASSIGNMENT DATA (print or type)

(1) ☐ This application is NOT assigned.
(2) ☐ Assignment previously submitted to the Patent and Trademark Office.
(3) ☐ Assignment submitted herewith.

For Printing On The Patent: (Unless an assignee is identified below, no assignee data will appear on the patent. Inclusion of assignee data below is only appropriate when an assignment has been previously submitted to the PTO or is submitted herewith. Completion of this form is NOT a substitute for filing of an assignment as required by 37 C.F.R. 1.334).

(1) NAME OF ASSIGNEE:

(2) ADDRESS: (City & State or Country)

(3) STATE OF INCORPORATION, IF ASSIGNEE IS A CORPORATION:

4. The following fees are enclosed:
☐ Issue fee ☐ Advanced order ☐ Assignment recording

The following fees should be charged to deposit acc. no. _____
(PTOL-85c or additional copy of PTOL-85b must be enclosed)

☐ Issue fee
☐ Advanced order
☐ Assignment recording
☐ Any additional fees due

Number of advanced order copies requested. _____
(must be for 10 or more copies)

5. All correspondence relating to maintenance fees will be addressed to the correspondence address unless a separate "Fee Address" is provided to the Patent and Trademark Office (37 C.F.R. 1.363). A "Fee Address" may be submitted by the owner of record with the payment of the issue fee or thereafter by using form PTO-1537.

5c (REV 4 86)

ISSUE FEE TRANSMITTAL

U.S. Department of Commerce
Patent and Trademark Office

GERALD D. SHARKIN
SANDOZ CORP.
59 ROUTE 10
E. HANOVER, NJ 07936

2A. The COMMISSIONER OF PATENTS AND TRADEMARKS is requested to apply the Issue Fee to the application identified below.

(Signature of party in interest of record) | (Date)

Note: The Issue Fee will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the Patent and Trademark Office.

SC/SERIAL NO.	FILING DATE	TOTAL CLAIMS	EXAMINER AND GROUP ART UNIT		DATE MAILED
07/165,656	03/08/88	017	DENTZ, B	121	01/03/89

First Named Applicant: ANDERSON, PAUL L.

TITLE OF INVENTION: AZAINDOLE DERIVATIVES USEFUL AS CHOLESTEROL BIOSYNTHESIS INHIBITORS (AS AMENDED)

ATTY'S DOCKET NO.	CLASS-SUBCLASS	BATCH NO.	APPLN. TYPE	SMALL ENTITY	FEE DUE	DATE DUE
600-7044/CON	514-300,000	F15	UTILITY	NO	$560.00	04/03/89

1. Further correspondence to be mailed to the following:

2B. For printing on the patent front page, list the names of not more than 3 registered patent attorneys or agents OR, alternatively, the name of a firm having as a member a registered attorney or agent. If no name is listed, no name will printed.

1 _____
2 _____
3 _____

DO NOT USE THIS SPACE

3. ASSIGNMENT DATA (print or type)

(1) ☐ This application is NOT assigned.
(2) ☐ Assignment previously submitted to the Patent and Trademark Office.
(3) ☐ Assignment submitted herewith.

For Printing On The Patent: (Unless an assignee is identified below, no assignee data will appear on the patent. Inclusion of assignee data below is only appropriate when an assignment has been previously submitted to the PTO or is submitted herewith. Completion of this form is NOT a substitute for filing of an assignment as required by 37 C.F.R. 1.334).

(1) NAME OF ASSIGNEE:

(2) ADDRESS: (City & State or Country)

STATE OF INCORPORATION, IF ASSIGNEE IS A CORPORATION:

4. The following fees are enclosed:
☐ Issue fee ☐ Advanced order ☐ Assignment recording

The following fees should be charged to deposit acc. no. _____
(PTOL-85c or additional copy of PTOL-85b must be enclosed)

☐ Issue fee
☐ Advanced order
☐ Assignment recording
☐ Any additional fees due

Number of advanced order copies requested. _____
(must be for 10 or more copies

An Examiner's Amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the Issue Fee.

Authorization for this Examiner's Amendment was given in a telephone interview with Ms. Giesser on December 21, 1988.

Non-elected claims 18 and 19 have been canceled without prejudice to the filing of one or more divisional applications drawn thereto.

Claim 16, line 3, after "compound" --according to claim 1-- has been inserted.

Claim 16, last line "; said compound of claim 1" has been canceled.

Any inquiry concerning this communication should be directed to Examiner Dentz at telephone number 703-557-3572.

12/22/88;df

JOHN M. FORD
EXAMINER
GROUP ART UNIT 121

Wattanasin v. Picard et al. v. Fujikawa et al
patentee

102648

11 MAR 1992 **DECLARATION, MOTIONS DUE**

11 MAR 1992 - PS & MOS DUE 11 JUN 1992

Mar. 17, 92 - Designation of lead Counsel - Fujikawa et al
Mar. 18, 92 - Power to Inspect & make Copies - Fujikawa et al
Mar. 26, 92 - Suppl. Designation of Lead counsel (R.601(b)) - Fujikawa et al
Mar. 25, 92 - (R.602) - Notification of Interest (C/M 3-24-92) - Wattanasin
Mar. 24, 92 - Designation of lead atty. (C/M 3/23/92) - Wattanasin
Apr. 7, 92 - Power to inspect and Make Copies - Wattanasin
Apr. 8, 92 - Designation of Lead Attorney (C/M 4-6-92) - Picard et al
Apr. 8, 92 - Request (R.662(a)) For Entry of Adverse Judgmt. as to Picard et al. Cnts 1 & 2 of Cntf -
Apr. 10, 92 - Judgment adverse to Picard et al.
Jun. 11, 92 - Certificate of Service of Papers filed - Fujikawa et al.
Jun. 11, 92 - Notice of Filing (Sealed) P.S. - Fujikawa et al.
Jun. 11, 92 - Motion For Benefit (R.633(E)) - Fujikawa et al
Jun. 11, 92 - Motion to Add Counts (R.633(c)) - Fujikawa et al
Jun. 11, 92 - Motion For Benefit (R.633(E)) - Fujikawa et al
Jun. 11, 92 - Statement of Related applications - Fujikawa et al.
Jun. 15, 92 - Notice of Filing (Sealed) P.S. - Wattanasin
Jun. 15, 92 - Prelim. Motion (R.633(c)(1)) - Wattanasin
Jun. 15, 92 - Prelim Motion (R.635) (w/attach) - Wattanasin
Jun. 15, 92 - Contingent Preliminary Motion (R.633(e)) - Wattanasin
Jun. 15, 92 - Conti. Prelim. Mo. For Benefit (R.633(E)) - Wattanasin
Jun. 19, 92 - Power to inspect and Make Copies - Wattanasin
July 1, 92 - Oppos. to Contingent Prelim. Mo. (R.633(E)) & P/Mo. (R.635) - Fujikawa et al
July 1, 92 - Oppos. to the Continogent Prelim. Mo. For benefit (R.633(E)) - Fujikawa et al.
July 1, 92 - Motion For Benefit (R.633(j)) - Fujikawa et al.
July 1, 92 - Opposition to Prelim. Motion to Substitute a Count - Fujikawa et al.
July 1, 1992 - Oppos. to mo. to add count and to add claims - Wattanasin
July 7, 92 - Power to inspect - Wattanasin
July 16, 92 - Motion For Extension of time - Fujikawa et al.

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[SHEET 2]

3 1. Ext. of Time Granted (Reply due 7-21-92) Fujikawa et al 5/4
3 2. Jul. 21, 92 - Reply to the oppos. to mo. to add Cls. 3 & 4 - (Wattanasin)
3 3. Jul. 21 92 - Joint stip. to designate Inv 1 as corresponding to ct. etc. Wattanasin (cofm 7/21/92)
3 4. Jul. 27, 92 - Reply to oppos. to mo. to subst. Cl. - Wattanasin (cofm 7/21/92)
3 5. Jul. 27, 92 Motion to Correct Typographical Error etc. - (R. 635 + 638) (cofm 7/21/92)
3 6. Jul. 27, 92 - Reply to oppos. to motions - Wattanasin (cofm 7/21/92)
3 7. Jul. 27, 92 - Reply to oppos. to mo. for benefit - Wattanasin (R. 633) (cofm 7/21/92)
3 8. Jul. 27, 92 - second Cont. mo. for benefit - Wattanasin (R. 633) (cofm 7/21/92)
3 9. Jul. 27, 92 - Cont. Opposition to mo. for benefit - Wattanasin (cofm 7/21/92)
4 0. Aug 7, 92 - EIC proposes to set up new dec Fujikawa et al. Service of P.S. due 8/17/92
4 1. Aug. 3, 92 - Reply to belated oppos. to mo. for benefit - Fujikawa et al
4 2. Aug. 3, 92 - oppos. to mo. to correct typo error, etc. - Fujikawa et al
4 3. Aug. 11, 92 - Refiling of supplemental declaration - Fujikawa et al 5/31
4 4. Aug. 10, 92 - Response to Reply to oppos. to Mo. to add counts & Clms to appl'n - Wattanasin
4 5. Aug 21, 92 - Counts 1 + 2 are stricken & Ct 3 is added
4 6. Aug. 18, 92 - Power to Inspect & make copies - Fujikawa et al
4 7. Aug. 17, 92 - Request for ext. of time - Wattanasin (R. 635 + 645)
4 8. Aug. 21, 92 - Extension of time granted to 8/27/92 9/
4 9. Aug. 21, 92 - Comment on mo. for ext. of time - Fujikawa et al
5 0. Aug. 21, 92 - Request for Reconsideration - Fujikawa et al
5 1. Aug 17, 92 - Notice of Service - Fujikawa et al
5 2. Aug. 31, 92 - Acknowledgement & Clarification - Wattanasin (cofm 8/27/92)
5 3. Aug. 31, 92 Notification of Service of P. Stmt - Wattanasin (cofm 8/27/92)
5 4. Aug. 31, 92 - Response to Request for Reconsideration - Wattanasin (cofm 8/27/92)
5 5. Aug. 31, 92 - Response to Comment of mo. for ext. of time - Wattanasin (cofm 8/27/92)
5 6. Aug. 31, 92 - Notice of Filing Dec. of Supp. Preliminary Stmt. - Wattanasin (cofm 8/27/92)
5 7. Sep. 3, 92 - Modification of Request for Reconsid. etc. - Fujikawa et al
5 8. Sep. 21, 92 - Reconsideration granted to foregoing extent
5 9. Sept. 22, 92 - Jr. parties reply Brief due 6/15/93. 6/29
6 0. Sept. 30, 92 - Request for preservation of issues & Evidence - Fujikawa et al

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[SHEET 3]

6 1 Oct. 30, 92 Prod. of Invention - Wattanasin
6 2 Nov. 19, 92 Motion to Consolidate Record - Wattanasin
6 3 Nov. 19, 92 Motion for Ext. of time (with attachment) - Wattanasin
6 4 Nov. 19, 92 Notice of Intent to Rely - Wattanasin (cd-m 11/16/92)
6 5 Nov. 19, 92 TESTIMONY FOR Wattanasin, 12 vols., Rm. 10C06 (cd-m 11/16/92)
6 6 Nov. 19, 92 EXHIBITS FOR Wattanasin, 2 vols., Rm 10C06 (cd-m 11/16/92)
6 7 Dec. 10, 92 - Request for Extension of time - Fujikawa et al.
6 8 Dec. 7, 92 Request for Cross-Exam - Fujikawa
6 9 Dec. 15, 92 - Notice of Intent to Argue Abandonment, Suppression or Concealment - Fujikawa et al.
7 0 Dec. 14, 92 Notice of Deposition - Wattanasin, (cd-m 12/11/92)
7 1 DEC. 24, 192 - EXT. OF TIME APPROVED - TESTY due 2/25/93 3/11
7 2 Jan. 8, 93 M.S. for Additional Testy - Wattanasin
7 3 Jan. 13, 93 - Opposition to Motion for leave to present additional Testy. - Fujikawa et al
7 4 Feb. 1, 93 Notice of Intent to Rely - Fujikawa et al.
7 5 Feb. 1, 93 Official Records & Printed Publications TESTIMONY FOR Fujikawa (cd-m 1/28/93)
7 6 Feb. 1, 93 Reply to Opp. to M.S. for leave - Wattanasin
7 7 Feb. 5, 92 - Times remain as set in Paper No. 9
7 8 Feb. 18, 93 - Motion for Extension of time (R.645) (R635) - Fujikawa et al.
7 9 Feb. 19, 93 - Extension of time granted to 3/25/93 3/5
8 0 Feb. 25, 93 - Request for Cross-Examination - Fujikawa
8 1 Mar. 1, 93 Notice of Deposition - Fujikawa et al.
8 2 Feb. 24, 93 TESTIMONY FOR Wattanasin, (cd-m 2/22/93)
8 3 Mar. 19, 93 - Joint Request for Extension of time - Wattanasin & Fujikawa et al.
8 4 Mar. 19, 93 - Extension of time granted to 8/09/93 - R.B. due 8/18
8 5 Apr. 29, 93 - Notice of Deposition - Fujikawa et al
8 6 Apr. 6, 93 Notice of Deposition - Wattanasin
8 7 Apr. 22, 93 TESTIMONY FOR Fujikawa, 3 Vols. Room 10C06 (cd-m 4/22/93)
8 8 Apr. 28, 93 TESTIMONY FOR Fujikawa, 1 vol. Room 10C06
8 9 May 10, 93 TESTIMONY FOR Wattanasin, 1 vol. Room 10C06
9 0 May 17, 93 Motion to Consolidate Record - Fujikawa et al.

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[SHEET 4]

1	May 17, 93	RECORD FOR Fujikawa et. al., Room 10C06, 5 vols., 3 copies
2	May 17, 93	EXHIBITS FOR Fujikawa et. al. Room 10C06
3	May 19, 93	RECORD FOR Wattanasin, Room 10C06, 3 vols., 3 copies (C of M 5/17/93)
4	May 19, 93	EXHIBITS FOR Wattanasin Room 10C06
5	May 26, 93	Motion for Sanctions - (W/attach) - Fujikawa
6	June 1, 93	Receipt acknowledged paper no. 90 + 95
7	May 28, 93	Communication - Wattanasin
8	Jun. 4, 93	Request for extension of time - Wattanasin
9	June 8, 93	Extension of time granted to 9/04/93 RB, Lee (C of M 6/14/93)
10	Jun. 17, 93	Opposition to motion for sanctions - Wattanasin 9/20
11	Jun. 21, 93	Reply to oppos. to motions for sanctions - Fujikawa et al
12	June 23, 93	Times remain as set in Paper No. 99
13	July 19, 93	Motion for Extension of Time - Wattanasin (C of M 7/15/93)
14	July 22, 93	Extension of time approved to 7/16/93
15	July 19, 93	BRIEF FOR: Wattanasin, 1 orig., 3 copies, (C of M 7/16/93) Rm. 10C06
16	July 19, 93	Proposed Findings of Fact & Conclusions of Law - Wattanasin Rm. 10C06
17	Aug. 16, 93	BRIEF FOR: Fujikawa et. al., 1 orig., 3 copies Rm. 10C06
18	Aug. 16, 93	Oppo. to Proposed Findings of Fact - Fujikawa Rm. 10C06
19	Aug. 16, 93	Motion to Suppress Evidence - Fujikawa Rm. 10C06
20	Sept. 7, 93	Errata Sheet for Brief - Fujikawa Rm. 10C06
21	Sept. 7, 93	Errata Sheet for Findings of Fact - Fujikawa Rm. 10C06
22	Sept. 13, 93	REPLY BRIEF FOR Wattanasin, 1 orig., 3 copies (C of M 9/17/93)
23	Sept. 13, 93	Oppo. to M.S. to Suppress - Wattanasin
24	Sept. 13, 93	Reply to Oppo. to Proposed Findings of Fact - Wattanasin
25	Sept. 22, 93	Reply to Oppo. to M.S. to Suppress - Fujikawa
26	Sept. 22, 93	Extra copies of M.S. to Suppress + Findings of Fact - Wattanasin
27	Sep 16, 94	Final Hearing set for 11-22-94
28	Nov 22, 94	Appearance Record
29	Jan 31, 95	Final Hearing, judgment awarded to Wattanasin
30	Feb 28, 95	Request For Reconsideration of Final Decision - Fujikawa et al. (R. 658)

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[SHEET 5]

12 1 Mar. 17, 95 - Reply to Request for Reconsideration - Nattanasia
12 2 April 6, 95 - Reconsideration - Denied
12 3 June 2, 95 Appeal to Fed. Cir.
12 4 June 6, 95 - Notice forwarding certified list
12 5 Jul 11, 95 - Acknowledged Notice of Appeal
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