UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Aurobindo Pharma USA Inc.

Petitioners,

v.

Andrx Labs, LLC
Patent Owner

Case IPR2017-01648
U.S. Patent No. 6,866,866

DECLARATION OF JENNIFER DRESSMAN, PH.D.

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I, Jennifer Dressman, Ph.D., declare as follows:

1. My name is Jennifer Dressman.

I. QUALIFICATIONS

2. The opinions below are based on my background and experience, including my over 40 years of professional and educational experience in the fields of pharmaceutics and biopharmaceutics, including formulation of drugs for oral administration, *in vitro* pharmaceutical testing, and calculation and analysis of pharmacokinetic ("PK") parameters.

3. My qualifications as an expert in these areas are established by my *curriculum vitae*, which is attached hereto as Appendix A, and the publications cited therein. I have set forth below representative relevant experience.

4. I received a Bachelor of Pharmacy from the Victorian College of Pharmacy in Melbourne, Australia in 1976. I earned a Master of Science in Pharmaceutical Chemistry from the University of Kansas in 1979 and a Ph.D. in Pharmaceutical Chemistry also from the University of Kansas in 1981 under the supervision of Prof. Takeru Higuchi, who was known as the "father of physical pharmacy." *See* Takeru Higuchi biography, Kansas Historical Society, https://www.kshs.org/kansapedia/takeru-higuchi/16878 (last visited May 30, 2018).

5. While I was earning my graduate degrees, I was a research assistant at the University of Kansas. After I finished my Ph.D., I worked for one year as a Research Pharmacist at the Burroughs Wellcome Company in Greenville, North Carolina. I then worked for a year as a Senior Research Chemist at INTERx Research Corporation in Lawrence, Kansas, where I conducted research, *inter alia*, on predicting dosage form performance in the gastrointestinal tract.

6. From 1983 to 1994, I was an Assistant Professor, and then later an Associate Professor of Pharmaceutics with tenure at the University of Michigan. While there, I taught many courses, including, among others, undergraduate courses in pharmaceutics and a graduate course on principles of oral drug absorption. I also conducted research, most of which focused on understanding gastrointestinal physiology as it relates to oral drug absorption, and on designing formulations to improve the performance of orally administered drugs and dissolution tests to predict *in vivo* drug performance.

7. In 1994, I was appointed as a Professor of Pharmaceutical Technology at JW Goethe University in Frankfurt, Germany. Since that time, I have taught lectures, seminars, and practical courses in the fields of pharmaceutics, biopharmaceutics, pharmacokinetics, and pharmaceutical technology. Notable examples include "Biopharmaceutics and dosage form driven pharmacokinetics,"

"Design, manufacture and quality control of pharmaceutical dosage forms," "Utilization of drugs in pharmacy practice," and "Good manufacturing practice."

8. At JW Goethe University, the primary focus of my research has continued to be oral drug absorption and predicting *in vivo* drug performance using biorelevant dissolution testing and physiologically based pharmacokinetic ("PBPK") modeling. Biorelevant media are those that simulate conditions in the gastrointestinal tract before or after a meal has been ingested. They are specifically designed to be used in dissolution testing to predict the *in vivo* performance of drugs and drug formulations after oral administration.

9. In 2002, I was appointed the Director of the Institute of Pharmaceutical Technology at the JW Goethe University. In that capacity, I am responsible for over 30 staff dedicated to teaching and research activities in pharmaceutical technology. I also manage the budget and organization of the institute.

10. I am a named author on over 230 peer-reviewed publications and over 25 review articles in the fields of pharmaceutics and biopharmaceutics. Of these articles, approximately 60 have addressed the relationship between formulation and pharmacokinetics. I am also an author of 5 books and 10 book chapters in the area of pharmaceutics, including two books devoted to oral drug absorption and one book specifically on pharmaceutical dissolution testing. I am a named

inventor on over 20 patents, all of which relate to oral dosage forms. During my career, I have also supervised over 60 doctoral theses and have delivered well over 100 invited presentations.

11. I am also a member, and have served on various committees, of several professional organizations in the pharmaceutical field, including the American Association of Pharmaceutical Scientists, the International Association for Pharmaceutical Technology, and the Fédération Internationale Pharmaceutique. I also have served on the editorial boards of numerous preeminent journals in the pharmaceutical field. I am currently an associate editor of the European Journal of Pharmaceutics and Biopharmaceutics and the Journal of Pharmacy and Pharmacology.

12. Over the course of my career, I have also received various awards and other honors for my work in the pharmaceutical chemistry and technology fields. For example, in 1991, I was elected to be a Fellow of the American Association of Pharmaceutical Scientists; in 2010, I was elected to the College of Fellows of the Controlled Release Society; and in 2015, I was elected to be a Fellow of the Fédération Internationale Pharmaceutique. In 2010, I was awarded the Silver Medal of Honor from the International Association for Pharmaceutical Technology, and in 2008, I was awarded the Distinguished Scientist Award from the Fédération Internationale Pharmaceutique. In May 2017, I received the Nagai

International Woman Researcher of the Year Award from the Association of Pharmaceutical Science and Technology of Japan. In addition, in 2017, I received the award for the best academic paper in the field of pharmacokinetic modeling and simulation from SIMCYP.

II. SUMMARY OF OPINIONS

13. It is my opinion that claims 1-25 of U.S. Patent No. 6,866,866 (hereinafter "the '866 patent") are non-obvious under 35 U.S.C. § 103 over International Patent Application Publication No. WO 99/47125 (hereinafter "Cheng," Ex. 1002) in view of International Patent Application Publication No. WO 99/47128 (hereinafter "Timmins," Ex. 1003).

14. It is also my opinion that objective indicia further demonstrate the non-obviousness of claims 1-25 of the '866 patent, including addressing a long-felt but unmet need, copying by others, and unexpected results.

III. INFORMATION CONSIDERED

15. A list of the materials I have considered in rendering my opinions is attached hereto as Appendix B.

IV. A PERSON OF ORDINARY SKILL IN THE ART

16. I understand that Patent Owner has proposed a definition of a person of ordinary skill in the art ("POSA"), which defines a POSA as a person who, at the time of the invention, held a degree in pharmacy, chemistry, chemical

engineering, or a related field with at least three to five years of pharmacokinetics, biopharmaceutics, medicinal chemistry, pre-formulation, or formulation experience, research, or training. In addition, I understand that Patent Owner's proposed definition indicates that such a person would be familiar, at the time of the invention, with the methods used in formulating oral dosage forms, modified release dosage forms, and osmotic delivery, and have an understanding of the fundamental principles as to how osmotic dosage forms behave and function. Patent Owner Preliminary Response, 15-16. I agree with this definition.

17. I understand that Petitioner has proposed a slightly different definition of POSA. Petition at 11. Under either the Patent Owner's definition or the Petitioner's definition, I am at least a person of ordinary skill in the art, and have been since well before the November 3, 2000 filing date of the '866 patent. My opinions expressed herein are the same regardless of whether the Patent Owner's definition or the Petitioner's definition of a POSA applies.

V. LEGAL PRINCIPLES

18. I have been informed and understand that, under 35 U.S.C. § 103, a patent claim is considered obvious if the subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. The obviousness analysis involves several factual inquires, including: (i) the scope and content of the prior art; (ii) the differences between the prior art and the claim;

(iii) the level of ordinary skill in the art at the time of the invention; and (iv) the existence of objective indicia of non-obviousness ("secondary considerations").

19. In connection with obviousness, I have been informed and understand that there must have been some reason or motivation that would have led a person of ordinary skill in the art to combine or modify the relevant teachings in the prior art to obtain the claimed invention, and one of ordinary skill in the art must have had a reasonable expectation of success in doing so. I also understand that if a proposed modification would render the prior art being modified unsatisfactory for its intended purpose, then there can be no suggestion or motivation to make the proposed modification.

20. Furthermore, I understand that the rationale of "obvious to try" to support obviousness requires a finite number of identified, predictable solutions and a claimed invention is not obvious when a skilled artisan would have to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave no indication of which parameters were critical or direction as to which of many possible choices is likely to be successful. I also understand that it is incorrect to evaluate obviousness from a hindsight perspective using the teachings of the patent at issue as a guide.

21. I have also been informed and understand that objective indicia of non-obviousness (also known as "secondary considerations") can provide evidence

that a challenged claim is not obvious. Objective indicia may include satisfying a long-felt but unmet need, unexpected results, commercial success, and copying by others. I understand that for objective indicia to be given weight, there must be a nexus between the evidence and the claimed invention.

VI. CLAIM CONSTRUCTION

22. I understand that the parties in this proceeding have agreed that the term "T_{max}" recited in the claims should be construed as "the time period which elapses after administration of the dosage form at which the plasma concentration of the drug attains the highest plasma concentration of drug attained within the dosing interval (*i.e.*, about 24 hours)." Decision on Institution at 7; the '866 patent at col. 7, ll. 49–53; Petition at 24; and Patent Owner Preliminary Response at 18. I agree with this construction. Patent Owner also proposed constructions for the claimed terms "membrane," "dinnertime," and "at dinner." Patent Owner Preliminary Response at 16-18. The '866 patent also defines terms such as "AUC," "C_{max}," and "mean." '866 patent, col. 7, l. 40 – col. 8, l. 14. I agree with these constructions and definitions as well.

VII. BACKGROUND

A. State of the Art in November 2000

23. I understand that Petitioner has challenged the validity of claims 1-25 of the '866 patent, which issued from U.S. Patent Application No. 09/705,630

(hereinafter "the '630 application"), which application was filed November 3, 2000. At the time of filing of the '630 application in November 2000, metformin hydrochloride, a short-acting drug used to treat non-insulin-dependent diabetes mellitus (NIDDM), was marketed as Glucophage® by Bristol-Myers Squibb in the United States. *See* the '866 patent, col. 1 ll. 56-57, 61-63. At the time, there was no fixed dosage regimen for Glucophage® to manage hyperglycemia in patients with diabetes mellitus – instead, dosages were individualized to each patient using 500 mg, 850 mg, or 1,000 mg immediate release tablets based on both effectiveness and tolerance, while not exceeding the maximum recommended dose of 2,550 mg per day. *Id.* col. 1 l. 63 – col. 2 l. 2.

24. However, because metformin is a short-acting drug, patients had to take the medication two or three times each day. *Id.* at col. 2 ll. 4-6. Such frequent dosing typically led to reduced patient compliance and increased adverse events, including the potentially dangerous side-effects of anorexia, nausea, and vomiting. *See id.* at col. 1 ll. 14-18; col. 2 ll. 4-8; col. 20 ll. 16-18.

25. Thus, at the time of the filing of the '630 application, there was a need in the field for a safe and effective dosage form of metformin that would enable patients with type 2 diabetes to take their medication on a once-a-day basis, thereby improving patient compliance and reducing adverse events.

B. T_{max} and Other Pharmacokinetic Parameters of a Drug's Dosage Form

26. As explained above, T_{max} refers to "the time period which elapses after administration of the dosage form at which the plasma concentration of the drug attains the highest plasma concentration of drug attained within the dosing interval (i.e., about 24 hours)." Decision on Institution at 7; the '866 patent at col. 7, ll. 49–53; Petition at 24; and Patent Owner Preliminary Response at 18. A T_{max} for a single patient is a discrete variable – its value can only be one of the time points at which the patient's blood was sampled. T_{max} data for a population of patients is generally expressed as a median T_{max}, with a minimum T_{max} and maximum T_{max} reported (*i.e.*, "median T_{max} (minimum T_{max}, maximum T_{max})," *see*, *e.g.*, Timmins at Example 5), but can also be expressed as a mean T_{max}, as described in the '866 patent, *e.g.*, claim 1. For the former, the median T_{max} represents a T_{max} value in an ordered set of values where there is an equal number of values below and above the T_{max} value, or alternatively the arithmetic mean of the two middle values if there is no one middle number. Paper 12, Decision on Institution at 12, n6.

27. The minimum T_{max} is the single lowest T_{max} value obtained from the population of patients, while the maximum T_{max} is the single highest T_{max} value obtained from the population of patients. A mean T_{max} is the arithmetic average of all the individual T_{max} values reported for all the patients in the study. As

acknowledged by Dr. Akhlaghi, a mean T_{max} is a *single value*, not a range of values. Akhlaghi Deposition at 72:21-74:1. As also acknowledged by Dr. Akhlaghi, calculation of a single mean T_{max} value from a population of patients requires access to the underlying raw data (*i.e.*, the individual T_{max} recorded for each individual patient). Akhlaghi Deposition at 70:8-11; 71:11-21.

28. The T_{max} of a drug's dosage form does not provide any conclusive information, either expressly or inherently, about the *in vitro* dissolution profiles, or about the dosage form's further pharmacokinetic parameters, including width at 50% of the height of a mean plasma concertation/time curve, the ratio of mean C_{max} value to mean plasma level at about 24 hours after the administration, the mean C_{max} values, the ratio of the dosage form's mean $AUC_{0\text{-}24hrs}$ to an immediate release dosage form's mean $AUC_{0\text{-}24hrs}$, the dosage form's mean $AUC_{0\text{-}24hrs}$, the dosage form's mean $AUC_{0\text{-}24hrs}$ and mean C_{max} values, the dosage form's mean $AUC_{0\text{-}24hrs}$ and mean C_{max} values at the 1st day of administration and 14th day of administration, the mean $t_{1/2}$ of the claimed dosage form, or in general the precise shape of the plasma concentration/time curve. These other parameters would be important contributory information for a skilled person developing an oral dosage form of metformin in November 2000. For this reason, it is my opinion that such a person would not have focused on T_{max} in isolation. Such an approach could only

have been taken with the benefit of hindsight, which I understand is impermissible in the obviousness analysis.

C. The '866 Patent

29. The '866 patent, entitled "Controlled Release Metformin Compositions," issued from the '630 application. The named inventors are Chih-Ming Chen, Xiu-Xiu Cheng, Steve Jan, and Joseph Chou. The inventors of the '866 patent developed Fortamet®, a novel extended release dosage form of metformin. Results from clinical studies demonstrated that Fortamet® was comparable to immediate-release metformin in terms of efficacy and safety, while providing for a more convenient once-daily dosage regimen. *See* Apr. 27, 2004 Letter from the FDA Approving NDA 21-574 (hereinafter "the Fortamet® FDA Approval Letter," Ex. 2001); Fortamet® FDA Label (Rev. 02/10) at 8-12, 28 (Ex. 2002). The FDA approved Fortamet® for use in managing type 2 diabetes on April 27, 2004. *See* Fortamet® FDA Approval Letter (Ex. 2001). *See*, *also*, Patent Owner Preliminary Response at 6-7.

30. Claim 1, the only independent claim of the '866 patent, recites:

> 1. A controlled release oral dosage form for the reduction of serum glucose levels in human patients with NIDDM, comprising an effective dose of metformin or a pharmaceutically acceptable salt thereof and a controlled-release carrier to control the release of said metformin or pharmaceutically acceptable salt thereof from said dosage form, said dosage form being suitable for providing once-a-day oral administration of the metformin or

> pharmaceutically acceptable salt thereof, wherein following oral administration of a single dose, the dosage form provides a mean time to maximum plasma concentration (T_{max}) of the metformin from 5.5 to 7.5 hours after administration following dinner.

31. Claims 2-25 ultimately depend from claim 1 and recite additional limitations, including narrower ranges of mean T_{max}, the composition of the dosage form, *in vitro* dissolution profiles of the dosage form, and further pharmacokinetic parameters related to the dosage form, such as the width at 50% of the height of a mean plasma concentration/time curve, the ratios of the mean maximum plasma concentration (C_{max}) over the mean plasma concentration at 24 hours post-administration, the mean C_{max} values, the ratios of the mean $AUC_{0\text{-}24hrs}$ to an immediate release dosage form's $AUC_{0\text{-}24hrs}$, the mean $AUC_{0\text{-}24hr}$ values, the mean C_{max} and the mean $AUC_{0\text{-}24hr}$ values, the mean C_{max} and mean $AUC_{0\text{-}24hr}$ values at the 1st and 14th days of administration, and the mean half-life ($t_{1/2}$) values.

VIII. PRIOR ART RELIED ON BY PETITIONER

32. I understand that Petitioner has alleged that claims 1-25 of the '866 Patent are obvious over Cheng in view of Timmins. Petition at 40-53.

A. Cheng

33. Cheng is titled "Controlled Release Oral Tablet Having a Unitary Core." Cheng at title. Cheng discloses a "controlled release antihyperglycemic tablet … comprising a core containing the antihyperglycemic drug, a

semipermeable membrane coating the core and at least one passageway in the membrane." Cheng at Abstract.

34. Cheng teaches that a key feature of its tablet is that it "does *not* contain an expanding polymer." Cheng at Abstract (emphasis added). In fact, as acknowledged by Dr. Akhlaghi, the goal of Cheng is "to provide a controlled or sustained release formulation for an antihyperglycemic drug that does *not* employ an expanding polymer." Cheng at 3, ll. 3-6 (emphasis added); *see* Akhlaghi Deposition at 83:15-18.

35. Cheng also teaches that another key feature of its tablet is that it "provide[s] therapeutic levels of the drug throughout the day with peak plasma levels [(*i.e.*, T_{max})] being obtained between 8-12 hours after administration" following dinner. Cheng at 4, ll. 3-9. Again, as acknowledged by Dr. Akhlaghi, Cheng emphasizes that its disclosure is directed to "a controlled or sustained release formulation for an antihyperglycemic drug that obtains peak plasma levels approximately *8-12 hours after administration*;" and that "a controlled or sustained release formulation for an antihyperglycemic drug that can provide *continuous and non-pulsating therapeutic levels* of an antihyperglycemic drug to an animal or human in need of such treatment *over a twelve hour to twenty-four hour period*." Cheng at 3, ll. 7-17 (emphasis added); Akhlaghi Deposition at 85:8-19.

36. Thus, Cheng explicitly describes that its purpose is to provide a dosage form lacking an expanding polymer that provides a mean T_{max} value between 8-12 hours, which is longer than -- and outside the range of -- the mean T_{max} values recited in claim 1 of the '866 patent (*i.e.*, 5.5 to 7.5 hours). Cheng's Example 3 discloses a dosage form that provides a mean T_{max} of 10 hours. Cheng at Example 3, Figure 8.

B. Timmins

37. Timmins is titled "Biphasic Controlled Release Delivery System for High Solubility Pharmaceuticals and Method." Timmins discloses a "biphasic controlled release delivery system for pharmaceuticals which have high water solubility, such as the antidiabetic metformin [hydrochloride] salt, … which provides a dosage form that has prolonged gastric residence." Timmins at Abstract. Timmins teaches that the goal of its dosage form is to achieve "prolonged gastric residence," to maximize contact between released drug and the site of the absorption for metformin, which Timmins indicates is primarily in the upper small gastrointestinal ("GI") tract. Timmins at 14, ll. 6-12.

38. Timmins indicates that the prolonged gastric residence time of the dosage forms disclosed therein is due to the "swelling of the system." Timmins at 11, ll. 8-12. Timmins further teaches that its tablet "swells up to approximately three times its dry size following hydration" of the polymers used in the fabrication

of the tablet. Timmins at 30, ll. 13-16. Notably, the formulation of Example 3 of Timmins (which is used in Example 5) includes a swelling polymer (sodium carboxymethylcellulose). Timmins at Examples 3, 5.

39. Timmins also teaches that the formulations disclosed therein "will provide for an extended release formulation of drug with *minimal interpatient variability in pharmacokinetic parameters*." Timmins at 14, ll. 20-23 (emphasis added). Consistent with this teaching, Example 5 of Timmins states that when its dosage form was administered *in vivo* to patients, "[i]nterpatient variability in pharmacokinetic parameters was acceptable as illustrated by the mean parameters (%CV)" given for C_{max} and AUC. Timmins at Example 5; 34, ll. 24-29.

40. Timmins in Example 5 discloses administration to a group of patients[1] either a dosage form of metformin hydrochloride prepared according to Example 3 (*i.e.*, a dosage form that includes an expanding polymer) or Glucophage®. While the focus of Timmins is on improving gastric residence time, rather than T_{max}, Timmins does report that the median T_{max} value obtained for the patient group

[1] In Example 5, Timmins teaches that 24 patients were dosed with Example 3 or Glucophage® tablets following dinner. However, it is not clear from Timmins whether all 24 patients or a portion of the 24 patients (*e.g.*, 12 patients) received the dosage form of Example 3.

dosed with Example was 5 hours, with the lowest individual T_{max} value observed at 4 hours and the highest individual T_{max} value observed at 8 hours. Nowhere does Timmins mention a mean T_{max} value for Example 5, or even a range in which that mean T_{max} must fall. Timmins does not teach a mean T_{max} value between 5.5 to 7.5 hours, as I understand is required by independent claim 1 of the '866 patent.

41. Furthermore, as acknowledged by Dr. Akhlaghi, Timmins does not provide the individual T_{max} values for the other patients receiving the Example 3 dosage form, and thus a mean T_{max} value cannot be calculated from the data presented in Example 5. Akhlaghi Deposition at 80:19-81:1. While the Federal Circuit suggested that the single mean T_{max} value of Timmins would fall between approximately 4.67 hours and 6.33 hours, neither the Petitioner, Dr. Akhlaghi, nor the Federal Circuit provided any explanation as to *where* in that range the single mean T_{max} value of Timmins would be expected to fall. *Sciele Pharma, Inc. v. Lupin Ltd.*, 684 F.3d 1253, 1261 (Fed. Cir. 2012) (Ex. 1006) (hereinafter "the Federal Circuit opinion"). In fact, Dr. Akhlaghi stated that with respect to trying to determine where the single mean T_{max} value of Timmins falls, "everybody is guessing here." Akhlaghi Deposition at 80:19-81:1.

IX. DR. AKHLAGHI CANNOT OPINE RELIABLY ON THE '866 PATENT DUE TO HER LACK OF EXPERTISE IN THE RELEVANT FIELD AND LACK OF UNDERSTANDING OF THE DISCLOSURE OF TIMMINS

42. While Petitioner's declarant Dr. Akhlaghi has expertise in the area of clinical pharmacology, after review of her declaration, accompanying CV and deposition testimony, it is my opinion that she does not have the appropriate experience and understanding of the prior art to offer an opinion on the alleged obviousness of design and development of a controlled release dosage form, which is the field of the '866 patent.

43. First, I have read Dr. Akhlaghi's deposition transcript, and I believe that she conceded that she is not an expert in formulation development of controlled release dosage forms. Akhlaghi Deposition at 24:5-16; 33:16-34:4. Additionally, she admitted that she has never developed the same kinds of dosage forms that are the subject of Timmins (*i.e.*, expanding polymer-based dosage forms) or Cheng (*i.e.*, osmotic pump dosage forms). Akhlaghi Deposition at 33:16-22 ("Q: Your CV doesn't indicate that you've ever designed or developed an osmotic pump dosage form. Correct? A: I did not develop an osmotic pump dosage form. Q: And your CV doesn't indicate that you've ever designed an expanding polymer dosage form? A: I have not done it"). This is consistent with my review of Dr. Akhlaghi's CV (Exhibit 1020), which does not suggest that she

has expertise in developing such solid oral dosage forms. Without this background, I do not believe Dr. Akhlaghi is able to reliably opine on what a person skilled in the art in November 2000 would understand from the teachings of Timmins and Cheng.

44. Furthermore, during her deposition, Dr. Akhlaghi was unable to convey a clear understanding of the subject matter of the claims of the '866 patent. For example, although Dr. Akhlaghi initially stated that the subject matter of the '866 patent relates only to pharmacokinetic parameters, and not formulation development, she subsequently admitted that her conclusion that there was a motivation for a person skilled in the art to combine Timmins and Cheng to arrive at the '866 patent's claims was based on a motivation to develop a controlled release dosage form of metformin. Akhlaghi Deposition at 24:5-16, 32:20-33:15; *cf.* 86:2-22. In my opinion, her statements are contradictory and cannot be reconciled with the specification and claims of the '866 patent.

45. It is my opinion that the '866 patent is directed to the design and development of a controlled release oral dosage form of metformin or a pharmaceutically acceptable salt thereof for the reduction of serum glucose levels in human patients with NIDDM. In fact, this is explicitly the subject matter of claim 1. '866 Patent at clam 1 (reciting "a controlled release oral dosage form for the reduction of serum glucose levels in human patients with NIDDM, comprising

an effective dose of metformin or a pharmaceutically acceptable salt thereof and a controlled-release carrier to control the release of said metformin or pharmaceutically acceptable salt thereof from said dosage form").

46. Additionally, during her deposition, Dr. Akhlaghi advanced unsupportable opinions regarding the mean T_{max} value of Timmins. Her opinions are inconsistent with basic principles of pharmacokinetics and statistics that would be well understood by those skilled in the art in November 2000. For example, Dr. Akhlaghi initially stated that she relied on the Federal Circuit opinion (Ex. 1006) for the proposition that Example 5 of Timmins provided a mean T_{max} value that falls somewhere in the range of 4.67 to 6.33 hours. Akhlaghi Deposition at 77:13-20; *see* Ex. 1019, ¶ 72. However, Dr. Akhlaghi later stated that the *mean* T_{max} value in Timmins's Example 5 could actually fall *anywhere* in the range of 4 to 8 hours, and that it is possible that all of the patients in Example 5 of Timmins dosed with its Example 3 dosage form had measured T_{max} values of 4 hours, or alternatively that all of the patients had measured T_{max} values of 8 hours. Akhlaghi Deposition at 79:9-15 ("Q: And a single mean Tmax from Timmins could fall anywhere between 4.6 and 6.33 hours. Right? A: It can fall between 4 to 8 hours. We are assuming it is falling between 4.67 based on the median data. But honestly, the range is 4 to 8. Maybe they had everybody in 8. Maybe they had everybody at 4. Maybe they had everybody at 6"). This is not consistent with the

statistical summary provided by Timmins, which states that the median T_{max} was 5 hours with a range of 4-8 hours. Statistically speaking, if the median value is 5 hours, it is simply not possible that all subjects could have had a T_{max} of either 4 hours or 8 hours as proposed by Dr. Akhlaghi. *See* Akhlaghi Deposition at 79:13-15; *cf.* Timmins at 34 (reporting a minimum T_{max} of 8 hours). In my opinion, Dr. Akhlaghi was somewhat confused as to the information provided in Timmins and how a person of ordinary skill in the art would understand Timmins in November 2000. A person of ordinary skill in the art would have possessed the requisite knowledge to interpret Timmins as I do herein.

47. Dr. Akhlaghi also stated that Timmins's Example 5's mean T_{max} value cannot be 5 hours. Akhlaghi Deposition at 79:19-80:15 ("Q: Right. So the single mean Tmax value from Timmins could be 5 hours. Right? . . . A: It cannot be 5 hours"). This was especially odd to me, as a mean T_{max} of 5 hours falls squarely within the range of possible T_{max} values of 4.67 to 6.33 hours proposed by the Federal Circuit and relied upon by Dr. Akhlaghi. Furthermore, as a person skilled in the art would immediately understand, a mean T_{max} of 5 hours is not only possible, but also certainly probable, based on the data presented in Timmins. There are numerous of distributions that would provide a mean T_{max} of 5 hours that are consistent with the data presented in Timmins.

48. Finally, Dr. Akhlaghi stated that she calculated the mean T_{max} value in Example 5 of Timmins to be 5.75 hours, but presented no data or explanation on how she obtained this value. Akhlaghi Deposition at 72:8-12 ("Q: So what is the single mean Tmax value you calculated from the data presented in Timmins? A: It was around 5.75, or something like that. And depends on, you know, how you set your confidence values").[2] However, Dr. Akhlaghi stated that it is simply not possible to calculate the mean T_{max} value of Timmins without "guessing," since Timmins does not provide the raw T_{max} data. Akhlaghi Deposition at 80:19-81:1; 70:8-11. To the best of my knowledge, these data have not been disclosed to Dr. Akhlaghi, so it would not be possible for her to pinpoint the mean value of T_{max} at 5.75 hours. Accordingly, I disagree with Dr. Akhlaghi's statement that she was able to identify "the single mean T_{max}" of 5.75 hours from the data presented in Timmins, *i.e.*, the actual "true" mean T_{max} value that would be based on the original raw data set.

49. These statements, combined with my review of Dr. Akhlaghi's deposition transcript and Declaration, indicate that Dr. Akhlaghi does not have

[2] I note that I did not have the benefit of reviewing Dr. Akhlaghi's purported calculation. Had this been provided to me, I could provide additional opinions on its validity.

sufficient understanding of all aspects of the '866 patent to reliably offer an opinion from the point of view of a person skilled in the art in November 2000.

X. CLAIMS 1-25 ARE NOT OBVIOUS IN VIEW OF CHENG AND TIMMINS

50. As described in further detail below, after my review of the materials in Appendix B, including Cheng, Timmins, the Petition, and Dr. Akhlaghi's declaration (Ex. 1019), it is my opinion that claims 1-25 would not have been obvious to a person skilled in the art in November 2000 based on Cheng and Timmins for a number of reasons.

51. **First**, a person skilled in the art in November 2000 would not read Timmins to teach that a particular mean T_{max} value or range is preferable. Instead, such a person would understand from Timmins that the main concern is to achieve the optimal release pattern of metformin in the gastrointestinal tract, whereas the time at which metformin reaches maximum plasma concentration is, at most, of peripheral interest to Timmins.

52. **Second**, my review of Timmins and Cheng indicates that a POSA would not have been motivated to combine those references in a way that would produce the compositions claimed in the '866 patent. This is because these references have distinct and incompatible goals such that the modifications to Cheng proposed in the Petition and by Dr. Akhlaghi would render Cheng

inoperative for its intended purpose. As I explain below, Timmins does not teach a mean T_{max} at all, but rather instructs persons skilled in the art to extend gastric retention for maximal absorption of metformin in the upper GI tract.

53. **Third**, even if a POSA were so motivated, she would not have had any reasonable expectation of success in arriving at the dosage forms recited in the claims of the '866 patent by combining Cheng and Timmins. More specifically, a POSA would not have had any reasonable expectation of success from modifying the osmotic pump dosage forms recited in Cheng having a mean T_{max} range of 8-12 hours with the teachings from the biphasic, swelling dosage forms in Timmins (*see* Timmins at 11:8-15 and Example 3; which does not teach a mean T_{max} at all, as described below) to arrive at a dosage form as claimed having a mean T_{max} range of 5.5-7.5 hours, which is outside the mean T_{max} range described and preferred in Cheng.

54. **Fourth**, even if a POSA did make the combination of Cheng and Timmins, the Petition and Dr. Akhlaghi fail to establish why this would produce a composition having a mean T_{max} value in the claimed range. This is because, as acknowledged by Dr. Akhlaghi, Timmins does not teach a range of mean T_{max} values. Instead, a POSA would understand that the mean T_{max} of Timmins to be a *single value*. While the Petition and Dr. Akhlaghi rely on the Federal Circuit opinion for the proposition that this single value must fall between 4.67 and 6.33

hours, Timmins does not specify *where* the mean T_{max} will fall within that range. Neither the Petitioner nor Dr. Akhlaghi explain why a POSA would expect that single mean T_{max} to fall within the ranges recited in claims 1-3 or 23-24 of the '866 patent, as opposed to elsewhere in the range of 4.67 to 6.33 hours, or why such a person would target the claimed ranges. Finally, accepting Dr. Akhlaghi's testimony that a POSA would expect the raw T_{max} data from Timmins to be a normal distribution, that person would in fact expect a mean T_{max} that would likely be less than 5.5 hours. However, the Petitioner and Dr. Akhlaghi fail to give any explanation of *why* such a person would arrive at the claimed compositions based on the disclosure of Timmins.

55. **Fifth**, a POSA could only have targeted a mean T_{max} in the claimed ranges with the benefit of hindsight, which I understand is impermissible in the obviousness analysis.

56. **Finally**, with respect to the dependent claims, neither the Petition nor Dr. Akhlaghi explain why a POSA would have been motivated to achieve the limitations in those claims. Instead, they simply assert that those limitations are "inherent." However, I have been informed and understand that the limitations in the dependent claims cannot be found to be inherently obvious except where those limitations necessarily, or always, flow from the claims or the prior art. Because Dr. Akhlaghi testified that those limitations "might or might not" be present in the

compositions falling within the scope of claim 1, I believe those claims therefore cannot be found to be inherently obvious. In view of this failure, the Petition and Dr. Akhlaghi's lack of an explanation of why a POSA would have been motivated to arrive at those claims supports my conclusion that those claims would not have been obvious to a POSA in November 2000. Moreover, even if Dr. Akhlaghi's contention that she was able to calculate the true, intrinsic mean T_{max} value of 5.75 hours were to be founded, a contention with which I disagree, the combination of Cheng and Timmins would still fail to provide a dosage form with a mean T_{max} between 6.0 and 7.0 hours, as is recited in claims 2 and 23.

A. Independent Claim 1 is Not Obvious Over Cheng and Timmins

57. Claim 1, the only independent claim of the '866 patent, is directed to, *inter alia*, a controlled release oral dosage form for the reduction of serum glucose levels in human patients with NIDDM, comprising an effective dose of metformin or a pharmaceutically acceptable salt thereof and a controlled-release carrier and having a mean T_{max} of 5.5-7.5 hours after administration following dinner. It is my opinion that this subject matter would not have been obvious to a POSA in November 2000 based on the combination of Cheng and Timmins for at least the reasons set forth below.

58. ***First***, a POSA would not read Timmins to teach that any particular mean T_{max} or range of mean T_{max} values was preferable. Instead, Timmins teaches

that its goal is to provide a dosage form of metformin that releases the active ingredient in the upper GI tract by way of a "gastroretentive" formulation (*i.e.*, a formulation with prolonged residence time in the stomach). *See* Timmins 13:6-23. Based on this understanding, if a POSA were motivated to modify the formulations of Cheng based on the teaching of Timmins, they would produce a dosage form with prolonged residence in the stomach and extended release in the upper GI tract, rather than aiming for one with a particular mean T_{max} value. Importantly, a POSA in November 2000 would understand that gastric retention is not a proxy for mean T_{max}. In addition to the gastric retention time, the pattern of release from the dosage form (slow or fast, continuous or pulsatile) will also be a key determinant of this parameter. Thus, it would be entirely possible for a POSA to design a controlled release dosage form of metformin based on Cheng with extended release in the upper GI tract that would have a mean T_{max} value outside of the ranges claimed in the '866 patent.

59. While Timmins reports a median T_{max} for the gastroretentive formulation disclosed in Example 3, a POSA would understand this disclosure to be incidental to the main purpose of that reference. This is reinforced by the fact that Timmins only mentions T_{max} twice. Further, if given the task of designing a dosage form of metformin with a particular mean T_{max}, a POSA in November 2000 could not do so based on the *median* T_{max} value alone. This is because the raw T_{max}

data is not presented in Timmins – it only conveys to a POSA that half of the population had a T_{max} at or below 5 hours, and the other half of the population had a T_{max} at or above 5 hours, with at least one patient having a T_{max} of 4 hours and at least one patient having a T_{max} of 8 hours.

60. ***Second***, it is my opinion that a POSA would not have been motivated to combine Cheng with Timmins as alleged in the Petition and by Dr. Akhlaghi. As I discuss above, Cheng explicitly describes that its purposes are to provide a dosage form *without any expanding polymer* and with a mean T_{max} value of *8 to 12 hours*. I note that Dr. Akhlaghi agrees on this point. Akhlaghi Deposition at 83:15-18 ("Q: So you understand that Cheng aims to provide a controlled-release formulation that does not employ an expanding polymer. Right? A: That what i[t] says here"); 85:17-19 ("Q: So you understand that Cheng aims to provide a mean Tmax of 8 to 12 hours. Right? A: Sure"). On the other hand, Timmins explicitly teaches that the key feature of its dosage form is the inclusion of one or more expanding, swelling hydrophilic polymers (*e.g.*, sodium carboxymethylcellulose in Example 3) to obtain its goal of "prolonged gastric residence." Dr. Akhlaghi also agreed with this conclusion during her deposition. Akhlaghi Deposition at 85:4-7 ("Q: And just to make the record clear, so you understand that Timmins does disclose a dosage form of metformin that includes an expanding polymer. Right? A: Yes"). Thus, with respect to dosage form components, the teachings of Cheng

and Timmins are actually *mutually exclusive*, and it is my opinion for at least this reason that a person skilled in the art in November 2000 would not be motivated to combine them.

61. The Petition alleges that a POSA would have simply combined the teachings of Cheng with Timmins's Example 5 to arrive at the claims of the '866 patent. Petition at 41, 45-46. However, I have been informed and understand that there cannot be a motivation to combine two references when doing so would render the prior art unsatisfactory for its intended purpose. That is exactly the case here – Example 3 of Timmins uses a swelling hydrophilic polymer (*i.e.*, an expanding polymer, sodium carboxymethylcellulose), while Cheng explicitly states that its goal is to provide a dosage form *without any expanding polymer*.

62. Dr. Akhlaghi and the Petition suggest that a POSA would have simply reduced the T_{max} range of 8 to 12 hours from Cheng in view of Timmins's Example 5 to arrive at the claimed T_{max} range in the '866 patent. Petition at 45-49; Ex. 1019, ¶¶ 185-96. However, Cheng specifically emphasizes that the ability of its composition to provide once-a-day administration of metformin, as well as the improved bioavailability profile obtained thereby, are contingent upon the dosage form providing a peak plasma level between 8 to 12 hours after administration. Cheng at 4, ll. 4-9 (stating that "the dosage form will be administered once a day, ideally with or after a meal and most preferably with or after the evening meal, and

provide therapeutic levels of the drug throughout the day with peak plasma levels being obtained between 8-12 hours after administration"). Thus, a POSA certainly would not have reduced the mean T_{max} value of Cheng's dosage form in view of Timmins as alleged by the Petitioner, because doing so would render Cheng unsatisfactory for its intended purpose of providing a formulation having a mean T_{max} value of 8 to 12 hours to meet its stated goals of achieving an once-a-day administration of metformin with an improved bioavailability profile.

63. For this reason as well, I do not believe that there can be a motivation to combine Cheng and Timmins as suggested in the Petition and by Dr. Akhlaghi, because this would render Cheng unsatisfactory for its intended purpose.

64. ***Third***, even if a POSA were to combine Cheng and Timmins, she would not have had any reasonable expectation of success in arriving at the claimed compositions.

65. The Petition relies on arguments submitted by Patentee in response to an enablement rejection during prosecution of the '866 patent, which state, *inter alia*, that "pharmaceutical formulators know that controlled release technologies can be manipulated … to provide a formulation which upon in-vivo testing will provide the T_{max} range of the *present invention*." Petition at 3 (citing Ex. 1010) (emphasis in original removed and emphasis added). However, the context of these statements must be taken into account. The Patentee was explaining the

formulation flexibility within the *same* claimed controlled release formulation of the '866 patent, an interpolative flexibility that would enable a controlled release oral dosage form having a mean T_{max} value *within* the context of the limitations recited in claim 1, *e.g.*, a once-a-day, controlled release oral dosage form as described in the '866 patent (1) comprising a controlled-release carrier and metformin or a pharmaceutical salt thereof and (2) having a mean T_{max} in the range of 5.5-7.5 hours after administration following dinner. That is, based on the teachings of the '866 patent, a POSA would be able to vary the parameters or components of the *same controlled release dosage form* recited in claim 1 to achieve the full range of the mean T_{max} of 5.5-7.5 hours, without undue experimentation.

66. These statements do not suggest that a POSA could reasonably expect to successfully arrive at the claimed dosage form's target T_{max} range of 5.5-7.5 hours by combining the teachings from the two very different dosage forms in Cheng (osmotic dosage forms) and Timmins (biphasic, matrix-based dosage forms), which have *mutually exclusive components*. *Supra*, ¶ 60. Even Dr. Akhlaghi stated that this would not be routine. Akhlaghi Deposition at 117:9-15. The extrapolation of the formation flexibility to modify the T_{max} range of 8-12 hours of Cheng in view of Timmins down to the T_{max} range of 5.5-7.5 hours of the '866 patent was not being argued by the Patentee. Thus, in my opinion,

Petitioner's contentions above have taken Patentee's statements out of context. The Patentee's statements do not suggest that there is a reasonable expectation of success in combining two prior art references describing two dosage forms with different controlled release mechanisms and mutually exclusive compositions.

67. The Petition and Dr. Akhlaghi also argue that "[d]rug release from the tablet of Example 3 [of Cheng] could easily be increased by the POSA, for example, merely by adding a second laser drilled hole." Petition at 46; Ex. 1019, ¶ 193. I disagree that doing so would necessarily produce a dosage form with a T_{max} in the claimed range. While adding a second laser-drilled hole might be expected to provide some increase in the release of metformin from the dosage form of Cheng, a POSA in November 2000 would not have been able to predict in advance how much that release rate might change. This is because osmotic dosage forms rely upon the influx of water from the biological fluid through the membrane to begin to dissolve the drug and excipients on the interior of the dosage form, thus creating an osmotic pressure inside the dosage form and expelling the dissolved components (including the active drug) through holes in the membrane. While the laser-drilled hole(s) certainly contribute to the rate of release, pores formed by the hydrophilic additives in the coating of a tablet are also expected to have some contribution to the rate of release. Furthermore, the diameter and location of the hole could also have an impact on the extent to which release of the drug from the

dosage form is altered. Thus, a POSA could not predict in advance whether a second laser-drilled hole in the dosage form of Cheng would produce an adequate reduction of mean T_{max} into the range claimed in the '866 patent on the one hand, or overshoot the desired rate of release on the other hand.

68. In fact, even Dr. Akhlaghi admitted that it would be desirable, but not routine, for a POSA to achieve a particular mean T_{max} value that they had targeted. Akhlaghi Deposition at 117:9-15. Based on this admission, I do not believe that the Petition or Dr. Akhlaghi have established that a POSA would have had a reasonable expectation of success in arriving at the claimed dosage forms by combining Cheng and Timmins.

69. In summary, in my opinion, a POSA would not have had any reasonable expectation of success in combining the osmotic dosage form in Cheng (which does *not* contain a swelling polymer) and the biphasic, matrix-based dosage form in Timmins (which *does* contain a swelling polymer) to arrive at the claimed controlled release dosage form.

70. ***Fourth***, even if a POSA were to combine the teachings of Cheng and Timmins, the Petition and Dr. Akhlaghi fail to establish why the alleged combination would have produced a dosage form having a mean T_{max} value in the claimed range. This is because neither the Petition nor Dr. Akhlaghi offers any

explanation of why a POSA in November 2000 would understand Timmins to teach or suggest a mean T_{max} value that falls within the claimed range.

1. A POSA Would Understand Timmins to Teach Increased Gastric Residence Time, Not a Particular Mean T_{max} Value or Range Thereof

71. As discussed above, Timmins is primarily concerned with providing a dosage form having prolonged residence in the upper GI tract and is not concerned with providing a particular mean T_{max} value. As also discussed above, any teachings in Timmins regarding T_{max} values are merely incidental to its main purpose of providing a gastroretentive dosage form. Thus, even if a POSA were to combine Cheng and Timmins, she would not have focused on any particular mean T_{max} value. In view of this understanding, I see no reason advanced by the Petition or Dr. Akhlaghi that would lead such a person to produce a dosage form with a mean T_{max} value in the claimed range.

2. A POSA Would Not Read Timmins to Teach a T_{max} Value in the Claimed Range

72. Petitioner and Dr. Akhlaghi appear to suggest that Example 5 of Timmins teaches a mean T_{max} *range* of 4.67 to 6.33 hours. Petition at 45-46; Ex. 1019, ¶ 182-83. I disagree with this reading of Timmins because it is based on purely theoretical statistical calculations and does not take into account the pharmacokinetic experience and knowledge of a POSA.

73. As the Federal Circuit opinion indicates, based on the full range of theoretical statistical possibilities, the mean T_{max} of Timmins lies somewhere between 4.67 and 6.33 hours. This does not suggest that Timmins discloses an actual mean T_{max} of either 4.67 hours or 6.33 hours, or any other single mean T_{max} value. Dr. Akhlaghi agrees, as she must, that Timmins discloses no single mean T_{max} value. Akhlaghi Deposition at 79:3-8. Instead, a POSA could only determine that, statistically, the mean T_{max} of Timmins falls somewhere between these two values, but neither Dr. Akhlaghi nor the Federal Circuit offered any information on *where* in the range that would occur. Akhlaghi Deposition 78:3-6 ("Q: Right. But the Federal Circuit does not say where that possible mean Tmax exactly falls in terms of a single value. Correct? A: No, it does not"); Akhlaghi Deposition at 80:19-81:1.

74. Taking the arguments in the Petition and Dr. Akhlaghi's Declaration about Timmins at face value, I understand them to amount to an allegation that a POSA in November 2000 reading Timmins would target a mean T_{max} value somewhere in the range of 4.67 hours and 6.33 hours. But no document I have reviewed explains *why* a POSA would choose a value that would fall in the claimed ranges of the '866 patent. This alleged set of possible mean T_{max} values is not based on a POSA's reasonable reading of Timmins, but merely on statistical possibilities. There are a large number of possible combinations of T_{max} values for

the 24 patients reported in Timmins that would provide a median of 5 hours, a minimum of 4 hours, and a maximum of 8 hours, as reported therein. There would be no reason for a POSA in November 2000 to infer that a mean T_{max} value within the mean T_{max} range recited in claim 1 should be considered as a potential target. Neither the Petition nor Dr. Akhlaghi explain why a POSA would target one falling within that claimed range.

75. In contrast, it is my opinion that a POSA reviewing Example 5 in Timmins is likely to associate the data with an approximately normal distribution of T_{max}, as is commonly observed in the field. Distributions of T_{max} values that are representative of those commonly observed in the field are reported in Basson *et al.*, *Why Rate of Absorption Inferences in Single Dose Bioequivalence Studies are Often Inappropriate*, Pharmaceutical Research, Vol. 15, No. 2, 1998, 276-279 (hereinafter "Basson," Ex. 2004), using several sets of pharmacokinetic data generated at Eli Lilly & Company. Table II in Basson shows the T_{max} distributions of three dosing studies using two antibiotic drugs and one antiviral drug, respectively, showing the number of patients with a T_{max} at each tested interval. As shown in Basson's Table II, in a typical T_{max} distribution, most patients will have T_{max} values in the middle of the distribution, (*e.g.*, 3-5 quarter hours in Study 1; 2-3 quarter hours in Study 2; and 3-6 third hours in Study 3), with just a few patients at the lower edge and the higher edge of the distribution. In fact, all of these

distributions approximate a so-called "normal" distribution (which is also referred to as a bell-shaped curve or a "Gaussian" distribution).

76. Furthermore, I note that Dr. Akhlaghi stated that a POSA would expect the distribution of T_{max} to be a normal distribution. Akhlaghi Deposition at 67:5-67:16 ("Q: Sure. My question is: A person skilled in the art in November, 2000, would need a lot of information about the patient population in order to determine what type of distribution they might see for Tmax values. Right? A: Well, if you're referring to person of ordinary skill in the art, as we have defined in our declarations between us, like, my side or Dr. Moore's side or basically Aurobindo's side versus your side, I think those persons of ordinary skill in the art probably would assume normal distribution, because that's the most—that's the easiest distribution"). As explained in more detail below, such a normal distribution will likely result in a mean T_{max} *outside* the claimed mean T_{max} range.

77. I have also been informed and understand that a claim can be found to be obvious according to the rationale of "obvious to try" if there are a finite number of identified, predictable solutions to a problem from which a POSA could choose. Here, Timmins is primarily concerned with providing dosage forms having prolonged upper GI tract residence, and does not provide sufficient information for a POSA to calculate the mean T_{max} value that would be obtained from the data in Example 5. Dr. Akhlaghi opined that a POSA would be left to

guess the mean T_{max} value of Timmins's Example 5 among myriad statistically possible mean T_{max} values. It is my opinion that this is not a "finite number of identified, predictable solutions." According to Dr. Akhlaghi, a POSA in November 2000 designing a controlled release dosage form of metformin based on Timmins would have been able to choose virtually *any* mean T_{max} value, as they would principally be attempting to produce a dosage form with increased residence time in the upper GI tract. Even if such a person were to attempt to target a mean T_{max} that falls within the statistically possible range of options in Timmins, they would have a choice of any mean T_{max} value consistent with the data presented in Timmins that falls between 4.67 hours and 6.33 hours. Thus, it is my opinion that the claims of the '866 patent are not obvious, even under an "obvious to try" rationale.

78. The distribution of T_{max} values that would be required to provide a mean T_{max} value at the upper end of the possible values of Timmins alleged by the Petitioner (*i.e.*, 6.33 hours) could only be produced by a non-normal, *e.g.*, a highly skewed or even bimodal, distribution of T_{max} values. For instance, to reach a mean T_{max} value of 6.33 hours from the teachings provided in Example 5 of Timmins,[3]

[3] This calculation assumes that 24 patients in Example 5 of Timmins were dosed with the dosage form of Example 3 of Timmins.

one patient would have to have a T_{max} of 4 hours, 12 patients would have to have a T_{max} of 5 hours, and the remaining 11 patients would all have T_{max} values of 8 hours.[4] However, such a bimodal distribution of the T_{max} values, where half of the patients are at the low end of the T_{max} distribution profile (T_{max} of 4 or 5 hours) and the other half of the patients are at the high end of the T_{max} distribution profile (T_{max} of 8 hours) with no patients having T_{max} values in between (*e.g.*, 6 or 7 hours), would be considered to be implausible by a person of ordinary skill in pharmacokinetics.

79. The T_{max} distribution described above (where one patient has a T_{max} of 4 hours, 12 patients have a T_{max} of 5 hours, and the remaining 11 patients all have a T_{max} of 8 hours) is a highly unlikely bimodal distribution and is not at all consistent with an essentially bell-shaped T_{max} distribution observed in the overwhelming majority of pharmacokinetic studies of oral dosage forms.

80. In fact, such an odd-shaped T_{max} distribution alleged by the Petitioner is inconsistent with the teachings of Timmins itself. As described above, Timmins teaches that "[t]he formulations of [its] invention will provide for an extended release formulation of drug with *minimal interpatient variability in pharmacokinetic parameters*." Timmins at 14, ll. 20-23 (emphasis added). Thus,

[4] ((4 * 1) + (12 * 5) + (11 * 8)) / 24 = 6.33.

given this "minimal interpatient variability," a POSA would expect that the T_{max} distribution in Example 5 of Timmins would likely be an essentially bell-shaped distribution similar to the ones described in Basson. And since half of the patients in Example 5 of Timmins have a T_{max} value of 4 or 5 hours,[5] in view of the minimal interpatient variability taught by Timmins, a POSA would have found it reasonable to assume that the majority of the patients will have had T_{max} values at or close to 5 hours (*i.e.*, 4, 5, or 6 hours). Even Dr. Akhlaghi conceded that the mean T_{max} value of Timmins is around 5. Akhlaghi Deposition at 71:2-8; 80:6-10 ("Q: Right. But the arithmetic mean Tmax— A: See, if you have somebody with 8 and your median is 5, you cannot have somebody with 1 hour and then add them up to reach, like, 4 hours. It has to be hovering around 5 at least").

81. Timmins's Example 5 teaches that when its dosage form was administered *in vivo* to patients, "[i]nterpatient variability in pharmacokinetic

[5] Timmins at Example 5 has a median T_{max} value of 5 hours and a minimum T_{max} of 4 hours. The median value represents the middle number of an ordered set of numbers for an odd set of values, or the average of the two middle numbers for an even set of values. In other words, there are an equal number of values above or equal to and below or equal to the median. Assuming 24 patients, this means that at least half of the patients must have had a T_{max} value of 4 or 5 hours.

parameters was acceptable as illustrated by the mean parameters (%CV)" given for C_{max} (13%) and AUC (21%). Timmins at Example 5; 34, ll. 24-29. These %CV values show that metformin hydrochloride formulated in Example 3 of Timmins is not a drug with high variability. *See* Ex. 2005 at 23 (FDA Guidance for Industry) (defining drug products having more than 30% CV as drugs with high variability).

82. Thus, in view of Timmins's teachings, a POSA will understand that the T_{max} values in Timmins's Example 5 will likely have an essentially bell-shaped distribution, not the odd and unexpected bimodal distribution implicitly alleged by the Petitioner.

83. An illustrative example of a T_{max} value distribution in Example 5 of Timmins which is consistent with the commonly observed bell-shaped distribution that Dr. Akhlaghi admitted a POSA would expect is as follows: six patients have a T_{max} of 4 hours, 10 patients have a T_{max} of 5 hours, four patients have a T_{max} of 6 hours, three patients have a T_{max} of 7 hours, and one patient has T_{max} of 8 hours. Such a distribution of T_{max} results in a mean T_{max} of 5.29 hours.[6] Such a mean T_{max} value, consistent with the bell-shaped T_{max} distribution familiar to the POSA and with Timmins's own teachings about the lack of variability in pharmacokinetics, falls outside the claimed mean T_{max} range of 5.5-7.5 hours.

[6] ((6 * 4) + (10 * 5) + (4 * 6) + (3 * 7) + (1 * 8)) / 24 = 5.29.

84. In summary, the Petition and Dr. Akhlaghi have failed to explain why a POSA would read Timmins to have a mean T_{max} value falling in the claimed range of 5.5 to 7.5 hours, or the ranges recited in certain dependent claims, or why a POSA reading Timmins would have had any motivation to target these ranges as claimed. In fact, a POSA would understand that Timmins most likely teaches a mean T_{max} value less than the claimed range of 5.5 to 7.5 hours, *e.g.*, 5.29 hours.

3. The Remaining Rationales Presented in the Petition and Dr. Akhlaghi's Declaration Would Not Provide a Dosage Form Having a T_{max} in the Claimed Range

85. The Petition and Dr. Akhlaghi argue that a POSA would have been motivated to reduce the mean T_{max} value of 8 to 12 hours disclosed by Cheng to "approach the drug profile of Glucophage, the industry standard drug." *See* Petition at 22-23 (quoting Ex. 1006). However, it was well-known in the art that when administered in the fed state, Glucophage® provided a T_{max} value well below 5 hours. Timmins at Example 5 (showing that administration of Glucophage® provided a median T_{max} value of 3.5 hours with a lowest T_{max} value of 1 hour and a highest T_{max} value of 5 hours); Ex. 1012 at Table 1 (showing that Glucophage® has a T_{max} of around 3 hours). Thus, even if one were to assume that that a POSA would have modified the dosage form in Cheng (a controlled release tablet) to approach the T_{max} of Glucophage®, there is no teaching or motivation in the prior

art to lead a POSA to arrive at a dosage form with a mean T_{max} value within the claimed range of 5.5-7.5 hours.

86. ***Fifth***, my review of the Petition and Dr. Akhlaghi's declaration suggest that their obviousness allegations rely on hindsight information only disclosed in the challenged patent itself that would not have been available to a POSA in November 2000.

87. For example, Dr. Akhlaghi cited the occurrence of peak gluconeogenesis at 2 am as a motivation for a POSA in November 2000 to achieve the claimed mean T_{max}. *See* Ex. 1019, ¶ 124. However, Dr. Akhlaghi provides no citation or data to support this teaching, other than relying on the hindsight information in the '866 patent itself. Akhlaghi Deposition at 120:1-122:1. I have been informed and understand that it is impermissible to rely upon a patent's specification when attempting to establish a motivation to combine prior art references to render the claims obvious. This is because the patent's specification would not have been available to a person skilled in the art, who instead would have to rely on the prior art.

88. Additionally, Dr. Akhlaghi in her deposition stated that the dosage form of Timmins was more desirable than that of Cheng, and that Cheng was *not* an advance over Timmins. *See* Akhlaghi Deposition at 122:22-123:7. Based on these statements, it appears to me that Dr. Akhlaghi admitted that a person skilled

in the art would not have been motivated to modify Timmins based on Cheng. As Timmins is primarily concerned with providing a dosage form having prolonged residence in the upper GI tract, without hindsight information disclosed in the '866 patent regarding a mean T_{max} range of 5.5-7.5 hours, a POSA would not have focused on the T_{max} information in Timmins's Example 5. Instead, it appears that Dr. Akhlaghi relied on hindsight to combine these references.

89. Finally, Dr. Akhlaghi admitted that her search for the prior art was based on information obtained from the '866 patent, and thus was tainted with hindsight information. Akhlaghi Deposition at 42:15-43:4 ("Q: And your process for finding prior art relevant to the '866 patent involves searching for patents in publications that had pharmacokinetic parameters similar to those recited in the claims of the '866 patent. Right? . . . A: It had pharmacokinetics and some of them only had dissolution data. It was basically using the terms that would be applicable here, like 'metformin,' 'controlled release' in general, and then that may yield some patents").

90. I understand that a finding of obviousness cannot be based on hindsight information. Thus, as described above, the obviousness case alleged by the Petitioner relies on information only disclosed in the challenged patent itself and it is my opinion that such an obviousness allegation is improper.

91. In summation, because of at least the reasons I set forth above, it is my opinion that claim 1 would not have been obvious to a person skilled in the art in November 2000 based on Cheng and Timmins.

B. Dependent Claims 2-25 Are Not Obvious Over Cheng and Timmins

92. I understand that claims 2-25 depend from independent claim 1 and thus include all the limitations recited in claim 1. It is my opinion that claims 2-25 are not obvious in view of Cheng and Timmins for at least the reasons explained above with respect to claim 1.

93. In addition, it is my opinion that these dependent claims are not obvious over Cheng and Timmins for the following additional reasons.

1. Claims 2-3 and 23-24 Are Not Obvious Over Cheng and Timmins

94. Claims 2-3 and 23-24 recite narrower mean T_{max} ranges (*i.e.*, 6.0-7.0 hours or 5.5-7.0 hours) than that recited in claim 1. '866 Patent at claims 2-3, 23-24. Because, as explained above, Cheng and Timmins even in combination fail to teach the broader mean T_{max} range of 5.5-7.5 hours recited in claim 1, they also fail to teach these narrower mean T_{max} ranges. Thus, it is my opinion that claims 2-3 and 23-24 are non-obvious in view of Cheng and Timmins at least for this additional reason.

95. Furthermore, both the Petition and Dr. Akhlaghi's Declaration state, in their invalidity claim charts for claims 2 and 3, that "[t]he Tmax value 6.33 hours taught by Timmins is within the claimed range. . . ." Petition at 50-51; Ex. 1019 at 73. However, as admitted by Dr. Akhlaghi, Timmins does *not* teach a mean T_{max} of 6.33 hours. Akhlaghi Deposition at 79:6-8. For this additional reason, it is my opinion that the Petition and Dr. Akhlaghi have failed to establish that claims 2 and 3 are obvious over Cheng and Timmins.

96. Claims 2 and 23 recite mean T_{max} range of 6.0-7.0 hours. During her Deposition, Dr. Akhlaghi alleged that she calculated a mean T_{max} value from Timmins's Example 5 of 5.75 hours. Akhlaghi Deposition at 72:8-12; 75:2-6. If of this were true, it would mean that claims 2 and 23 cannot be obvious over the combination of Timmins and Cheng, because the combination of those references would provide a dosage form of metformin with a mean T_{max} *below the range* of 6.0 to 7.0 hours recited in those claims. Thus, it is my opinion that claims 2 and 23 are not obvious over Cheng and Timmins at least for this additional reason.

2. Claims 4-5 Are Not Obvious Over Cheng and Timmins

97. Claims 4-5 recite specific dissolution profiles of the claimed dosage forms. '866 Patent at claims 4-5. The Petition and Dr. Akhlaghi simply state that "[t]he claim limitations are those needed for an *in vitro* release rate to produce a Tmax in the range claimed . . . ." Petition at 51-52; Ex. 1019 at 73-74. However,

neither the Petition nor Dr. Akhlaghi provide any explanation or data to support the notion that the dissolution profiles recited in claim 4 or 5 are needed to provide a dosage form having the mean T_{max} values recited in claim 1. I understand that the allegation in the Petition essentially boils down to a contention that the dissolution profiles recited in claims 4 and 5 are inherent in a controlled release dosage form of metformin of claimed 1.

98. I understand that for a limitation to be found inherently obvious, it must be the *natural result* flowing from the operation as taught, or a property that is *necessarily present* from the disclosure of the prior art.

99. I note that Dr. Akhlaghi was unable in her deposition to say whether the dissolution profiles recited in claims 4 and 5 are different. Akhlaghi Deposition at 95:20-96:13; 99:9-14. It is my opinion that the differences in the dissolution profiles recited in claims 4 and 5 include the following: (i) claims 4 and 5 expressly state that different percentage ranges of metformin are released after 2 hours, 4 hours, and 8 hours; (ii) the minimum percentages of metformin released after 12 hours, 16 hours, and 20 hours differ; and (iii) the dosage form recited in claim 5 generally has a faster dissolution compared with the dosage form recited in claim 4: 20-40% metformin release (claim 5) vs. 10-45% metformin release (claim 4) after 4 hours; 45-90% metformin release (claim 5) vs. 30-90% metformin release (claim 4) after 8 hours; at least 60% metformin release (claim 5) vs. at least

50% metformin release (claim 4) after 12 hours; at least 70% metformin release (claim 5) vs. at least 60% metformin release (claim 4) after 12 hours; and at least 80% metformin release (claim 5) vs. at least 70% metformin release (claim 4) after 20 hours.

100. Furthermore, it is entirely possible for two dosage forms with the same T_{max} to have quite different dissolution profiles. Consider the case where a sustained release product with slow continuous release is compared with an enteric coated product which does not begin to release until it enters the small intestine. These two dosage forms could very well have the same T_{max} values but will not have the same dissolution profiles under the conditions required by claims 4-5. Therefore, it is my opinion that the dissolution profiles recited in claims 4-5 are *not* inherently present based on a dosage form having a mean T_{max} as recited in claim 1. Moreover, neither Petitioner nor Dr. Akhlaghi offers any evidence or reasoning as to why a POSA would have been motivated to combine Cheng and Timmins to achieve the limitations in claims 4-5. For at least these additional reasons, it is my opinion that claims 4 and 5 are not obvious over the combination of Cheng and Timmins.

3. Claims 6-24 Are Not Inherently Obvious Over Cheng and Timmins

101. Regarding the dependent claims, I understand that the Petition and Dr. Akhlaghi appear to rely on inherent obviousness, stating that "[o]nce [a] POSA modelled a dosage form with a metformin release rate meeting the T_{max} taught by Timmins, all of the PK parameters listed in the claims 2-25 of the '866 patent would be inherently produced." Petition at 46-47, 50-59; Ex. 1019, ¶¶ 194, 74-75. I disagree with this assertion.

102. I understand that for a limitation to be found inherently obvious, it must be the *natural result* flowing from the operation as taught, or a property that is *necessarily present* from the disclosure of the prior art. This is not the case here —dependent claims 6-24 recite additional limitations that might or might not be present in a dosage form that meets the limitations of claim 1.

103. As explained above, T_{max} refers to "the time period which elapses after administration of the dosage form at which the plasma concentration of the drug attains the highest plasma concentration of drug attained within the dosing interval (i.e., about 24 hours)." '866 Patent at col. 7, ll. 49-53. However, T_{max} of a drug's dosage forms does not provide any concrete information, either expressly or inherently, about the additional limitations recited in the dependent claims, including the dosage form's other pharmacokinetic parameters such as *in vitro*

dissolution profiles, width at 50% of the height of a mean plasma concertation/time curve, the ratio of mean C_{max} value to mean plasma level at about 24 hours after the administration, the mean C_{max} values, the ratio of the dosage form's mean $AUC_{0\text{-}24hrs}$ to an immediate release dosage form's mean $AUC_{0\text{-}24hrs}$, the dosage form's mean $AUC_{0\text{-}24hrs}$, the dosage form's mean $AUC_{0\text{-}24hrs}$ and mean C_{max} values, the dosage form's mean $AUC_{0\text{-}24hrs}$ and mean C_{max} values at the 1st day of administration and 14th day of administration, and the mean $t_{1/2}$ of the claimed dosage form (*i.e.*, the PK parameters recited in claims 6-24). I note that Dr. Akhlaghi agreed. 93:17-94-4 ("Q: So it is possible that different dosage forms with similar mean Tmax values would display different PK curves? A: Different PK curves in terms of AUC, yes. Tmax probably will go back to dissolution. Q: And a person skilled in the art would understand that determination of a mean Tmax value does not necessarily also determine the other PK parameters, like AUC and Cmax. Right? A: Yes."); 110:11-16 ("Q: . . . So two dosage forms that fall within the scope of Claim 1 might fall within the scope of the limitations of Claims 6 through 24. Right? A: Might or might not. That, again, goes back to your first again. It's 100 percent. It's like lots of uncertainty here.").

104. For at least this additional reason, it is my opinion that claims 6-24 are not obvious over the combination of Cheng and Timmins.

4. Claims 6-7 and 23-24 Are Not Obvious Over Cheng and Timmins

105. Claims 6-7 recite specific peak widths at 50% of the height of a mean plasma concentration/time curve of the metformin of the claimed dosage forms. '866 Patent at claims 6-7. Claims 23-24 depend from claim 6. '866 Patent at claims 23-24. As discussed above, the Petition and Dr. Akhlaghi simply state that "[o]nce [a] POSA modelled a dosage form with a metformin release rate meeting the T_{max} taught by Timmins, all of the PK parameters listed in the claims 2-25 of the '866 patent would be inherently produced." Petition at 46-47; Ex. 1019, ¶ 194. However, neither the Petition nor Dr. Akhlaghi provide any explanation or data in support of the notion that the PK curves described in claims 6-7 or 23-24 would be arrived at by a POSA in November 2000 combining Timmins and Cheng. Moreover, neither Petitioner nor Dr. Akhlaghi offers any evidence or reasoning as to why a POSA would have been motivated to combine Cheng and Timmins to achieve the limitations in claims 6-7 and 23-24.

106. Particularly, the Petition and Dr. Akhlaghi have not shown any reason or data to support that a dosage form made by the combination of Cheng and Timmins and having a mean T_{max} value in the claimed range will inherently or necessarily exhibit the specific widths at 50% of the height of a mean plasma concentration/time curve of the metformin recited in claims 6-7. I note that the

parameter "50% of the height of a mean plasma concentration/time curve of the metformin" is an indirect measure of the duration of action of the formulation, *i.e.*, it can be used to interpret whether the extended release dosage form also extends the duration of action of the drug. A mean T_{max}, on the other hand, cannot provide such information, since the controlled-release carrier could have various release kinetics, leading to different plasma profile shapes albeit with the same T_{max}.

107. For at least this additional reason, it is my opinion that claims 6-7 and 23-24 are not obvious over the combination of Cheng and Timmins.

5. Claims 8-10 Are Not Obvious Over Cheng and Timmins

108. Claims 8-10 recite specific ratios of mean C_{max} to mean plasma level at about 24 hours after the administration of the claimed dosage forms. '866 Patent at claims 8-10. As discussed above, the Petition and Dr. Akhlaghi merely allege that "[o]nce [a] POSA modelled a dosage form with a metformin release rate meeting the T_{max} taught by Timmins, all of the PK parameters listed in the claims 2-25 of the '866 patent would be inherently produced." Petition at 46-47; Ex. 1019, ¶ 194. However, neither the Petition nor Dr. Akhlaghi provide any reason or data to support the notion that the PK curves described in claims 8-10 would be arrived at by a POSA in November 2000 combining Timmins and Cheng. Moreover, neither Petitioner nor Dr. Akhlaghi offers any evidence or reasoning as

to why a POSA would have been motivated to combine Cheng and Timmins to achieve the limitations in claims 8-10.

109. Particularly, neither the Petition nor Dr. Akhlaghi have shown any reason or data to support that a dosage form made by the combination of Cheng and Timmins and having a mean T_{max} value in the claimed range will inherently or necessarily exhibit the specific ratios of mean C_{max} value to mean plasma level at about 24 hours after the administration recited in claims 8-10. I note that the parameter "ratio of mean C_{max} value to mean plasma level at about 24 hours after the administration" is another indirect measure of the duration of action of the formulation, *i.e.*, it can be used to interpret whether the extended release dosage form also extends the duration of action of the drug. A mean T_{max}, on the other hand, cannot provide such information.

110. For at least this additional reason, it is my opinion that claims 8-10 are not obvious over the combination of Cheng and Timmins.

6. Claims 11-12 Are Not Obvious Over Cheng and Timmins

111. Claims 11-12 recite specific mean C_{max} values of the claimed dosage forms. '866 Patent at claims 11-12. As discussed above, the Petition and Dr. Akhlaghi simply state that "[o]nce [a] POSA modelled a dosage form with a metformin release rate meeting the T_{max} taught by Timmins, all of the PK parameters listed in the claims 2-25 of the '866 patent would be inherently

produced." Petition at 46-47; Ex. 1019, ¶ 194. However, neither the Petition nor Dr. Akhlaghi provide any explanation or data in support of the notion that the PK curves described in claims 11-12 would be arrived at by a POSA in November 2000 combining Timmins and Cheng. Moreover, neither Petitioner nor Dr. Akhlaghi offers any evidence or reasoning as to why a POSA would have been motivated to combine Cheng and Timmins to achieve the limitations in claims 11-12.

112. Particularly, the Petition and Dr. Akhlaghi have not shown any reason or data to support that a dosage form made by the combination of Cheng and Timmins and having a mean T_{max} in the claimed range will inherently or necessarily exhibit the specific mean C_{max} values recited in claims 11-12. A mean T_{max} value can be the same even when the values of C_{max} are different. For instance, when the percentage of drug absorbed is reduced in conjunction with a reduction of the dose, a reduction in the total amount of the drug absorbed is observed, *i.e.*, a decrease in bioavailability. On the other hand, similar C_{max} values do not imply that T_{max} values would be the same, since different types of dosage forms, *e.g.*, immediate release, delayed release, extended release, could all produce the same C_{max} but would be expected to have very different T_{max} values.

113. For at least this additional reason, it is my opinion that claims 11-12 are not obvious over the combination of Cheng and Timmins.

7. Claims 13-14 Are Not Obvious Over Cheng and Timmins

114. Claims 13-14 recite specific ratios of the claimed dosage form's mean $AUC_{0\text{-}24hrs}$ to an immediate release dosage form's $AUC_{0\text{-}24hrs}$. '866 Patent at claims 13-14. The Petition and Dr. Akhlaghi simply state that "[o]nce [a] POSA modelled a dosage form with a metformin release rate meeting the T_{max} taught by Timmins, all of the PK parameters listed in the claims 2-25 of the '866 patent would be inherently produced." Petition at 46-47; Ex. 1019, ¶ 194. However, neither the Petition nor Dr. Akhlaghi provide any explanation or data in support of the notion that the PK curves described in claims 13-14 would be arrived at by a POSA in November 2000 combining Timmins and Cheng. Moreover, neither Petitioner nor Dr. Akhlaghi offers any evidence or reasoning as to why a POSA would have been motivated to combine Cheng and Timmins to achieve the limitations in claims 13-14.

115. Particularly, the Petition and Dr. Akhlaghi have not shown any reason or data to support that a dosage form made by the combination of Cheng and Timmins and having a mean T_{max} value in the claimed range will inherently or necessarily exhibit the specific ratios of the claimed dosage form's mean $AUC_{0\text{-}24hrs}$ to an immediate release dosage form's $AUC_{0\text{-}24hrs}$ recited in claims 13-14. This parameter (ratio of the claimed dosage form's mean $AUC_{0\text{-}24hrs}$ to an immediate release dosage form's $AUC_{0\text{-}24hrs}$) describes the bioavailability of the claimed

dosage form relative to the bioavailability of the immediate release dosage form. Parameters contributing to bioavailability include, among others, dose, rate of release, site of release, and permeability at the site of release, whereas T_{max} exclusively reflects the balance between rate of absorption and rate of elimination. Therefore, there is only a peripheral connection between T_{max} and relative bioavailability, so knowing the mean T_{max} value of a particular formulation therefore could not automatically lead a POSA to be able to make a prediction of relative bioavailability as recited in claims 13-14.

116. For at least this additional reason, it is my opinion that claims 13-14 are not obvious over the combination of Cheng and Timmins.

8. Claims 15-17 Are Not Obvious Over Cheng and Timmins

117. Claims 15-17 recite specific mean $AUC_{0\text{-}24hrs}$ values of the claimed dosage form. '866 Patent at claims 15-17. As discussed above, the Petition and Dr. Akhlaghi simply state that "[o]nce [a] POSA modelled a dosage form with a metformin release rate meeting the T_{max} taught by Timmins, all of the PK parameters listed in the claims 2-25 of the '866 patent would be inherently produced." Petition at 46-47; Ex. 1019, ¶ 194. However, neither the Petition nor Dr. Akhlaghi provide any explanation or data in support of this notion that the PK curves described in claims 15-17 would be arrived at by a POSA in November 2000 combining Timmins and Cheng. Moreover, neither Petitioner nor Dr.

Akhlaghi offers any evidence or reasoning as to why a POSA would have been motivated to combine Cheng and Timmins to achieve the limitations in claims 15-17.

118. Particularly, the Petition and Dr. Akhlaghi have not shown any reason or data to support that a dosage form made by the combination of Cheng and Timmins and having a mean T_{max} value in the claimed range will inherently or necessarily exhibit the specific mean $AUC_{0\text{-}24hrs}$ values recited in claims 15-17. *See, e.g.*, Akhlaghi Deposition at 114:6-13; 116:2-15. This parameter (mean $AUC_{0\text{-}24hrs}$) describes the bioavailability of the claimed dosage form. As already explained above, parameters contributing to bioavailability include, among others, dose, rate of release, site of release, and permeability at the site of release, whereas a mean T_{max} exclusively reflects the balance between rate of absorption and rate of elimination. Therefore, there is only a peripheral connection between mean T_{max} and bioavailability, so knowing the mean T_{max} of a particular formulation could not invariably allow a POSA in November 2000 to a prediction of bioavailability.

119. I also note that Dr. Akhlaghi admitted that she has offered no opinion of why claims 15-17 would have been obvious to a POSA in November 2000 apart from inherency. Akhlaghi Deposition at 114:6-13; 116:2-15.

120. For at least this additional reason, it is my opinion that claims 15-17 are not obvious over the combination of Cheng and Timmins.

9. Claims 18-20 Are Not Obvious Over Cheng and Timmins

121. Claims 18-20 recite specific mean $AUC_{0\text{-}24hrs}$ and mean C_{max} values of the claimed dosage form. '866 Patent at claims 18-20. As discussed above, the Petition and Dr. Akhlaghi simply state that "[o]nce [a] POSA modelled a dosage form with a metformin release rate meeting the T_{max} taught by Timmins, all of the PK parameters listed in the claims 2-25 of the '866 patent would be inherently produced." Petition at 46-47; Ex. 1019, ¶ 194. However, neither the Petition nor Dr. Akhlaghi provide any explanation or data in support of the notion that the PK curves described by claims 18-20 would be arrived at by a POSA in November 2000 combining Timmins and Cheng. Moreover, neither Petitioner nor Dr. Akhlaghi offers any evidence or reasoning as to why a POSA would have been motivated to combine Cheng and Timmins to achieve the limitations in claims 18-20.

122. Particularly, the Petition and Dr. Akhlaghi have not shown any reason or data to support that a dosage form made by the combination of Cheng and Timmins and having a mean T_{max} value in the claimed range will inherently or necessarily exhibit the specific mean $AUC_{0\text{-}24hrs/inf}$ and mean C_{max} values recited in claims 18-20. Claims 18-20 recite a combination of the mean $AUC_{0\text{-}24hrs/inf}$ and mean C_{max} values, which are discussed above in connection with claims 11-12 and 15-17. As I discussed above, knowing the mean T_{max} value of a particular

formulation could not automatically enable a POSA in November 2000 to a prediction of either the AUC or mean C_{max} values.

123. I also note that Dr. Akhlaghi admitted that she has offered no opinion of why claims 18-19 would have been obvious to a POSA in November 2000 apart from inherency. Akhlaghi Deposition at 116:2-15.

124. For at least this additional reason, it is my opinion that claims 18-20 are not obvious over the combination of Cheng and Timmins.

10. Claim 21 Is Not Obvious Over Cheng and Timmins

125. Claim 21 recites specific mean $AUC_{0\text{-}24hrs}$ and mean C_{max} values at the 1st day of administration and 14th day of administration of the claimed dosage form. As discussed above, the Petition and Dr. Akhlaghi simply state that "[o]nce [a] POSA modelled a dosage form with a metformin release rate meeting the T_{max} taught by Timmins, all of the PK parameters listed in the claims 2-25 of the '866 patent would be inherently produced." Petition at 46-47; Ex. 1019, ¶ 194. However, neither the Petition nor Dr. Akhlaghi provide any explanation or data in support of the notion that the PK curve described in claim 21 would be arrived at by a POSA in November 2000 combining Timmins and Cheng. Moreover, neither Petitioner nor Dr. Akhlaghi offers any evidence or reasoning as to why a POSA would have been motivated to combine Cheng and Timmins to achieve the limitations in claim 21.

126. Particularly, the Petition and Dr. Akhlaghi have not shown any reason or data to support that a dosage form made by the combination of Cheng and Timmins and having a mean T_{max} value in the claimed range will inherently or necessarily exhibit the specific mean $AUC_{0\text{-}24hrs}$ and mean C_{max} values at the 1st day of administration and 14th day of administration recited in claim 21. Claim 21 recites a combination of the mean $AUC_{0\text{-}24hrs}$ and mean C_{max} values, which are discussed above in connection with claims 18-20, at certain date of the administration. As noted above, knowing the mean T_{max} of a particular formulation could not automatically enable a POSA in November 2000 to a prediction of either the $AUC_{0\text{-}24hrs}$ or mean C_{max} values, let alone their values at certain days after a series of once-a-day administrations.

127. For at least this additional reason, it is my opinion that claim 21 is not obvious over the combination of Cheng and Timmins.

11. Claim 22 Is Not Obvious Over Cheng and Timmins

128. Claim 22 recites specific mean $t_{1/2}$ of the claimed dosage form. As discussed above, the Petition and Dr. Akhlaghi simply state that "[o]nce [a] POSA modelled a dosage form with a metformin release rate meeting the T_{max} taught by Timmins, all of the PK parameters listed in the claims 2-25 of the '866 patent would be inherently produced." Petition at 46-47; Ex. 1019, ¶ 194. However, neither the Petition nor Dr. Akhlaghi provide any explanation or data in support of

the notion that the half-life described in claim 22 would be arrived at by a POSA in November 2000 combining Timmins and Cheng. Moreover, neither Petitioner nor Dr. Akhlaghi offers any evidence or reasoning as to why a POSA would have been motivated to combine Cheng and Timmins to achieve the limitations in claim 22.

129. Particularly, the Petition and Dr. Akhlaghi have not shown any reason or data to support that a dosage form made by the combination of Cheng and Timmins and having a mean T_{max} value in the claimed range will inherently or necessarily exhibit the specific mean $t_{1/2}$ recited in claim 22. Since T_{max} value reflects both absorption and elimination, a knowledge of the T_{max} value cannot be used to pinpoint the mean $t_{1/2}$ (a measure of elimination) in the absence of further information, *i.e.*, the absorption rate constant. Thus, it is my opinion that the mean $t_{1/2}$ as claimed is not an inherent property of a drug's dosage form having a certain mean T_{max} range.

130. For at least this additional reason, it is my opinion that claim 22 is not obvious over the combination of Cheng and Timmins.

XI. OBJECTIVE INDICIA SUPPORT THE NON-OBVIOUSNESS OF THE CHALLENGED CLAIMS

131. I understand that objective indicia (sometimes referred to as "secondary considerations") may support non-obviousness of the claimed invention. As explained in more detail below, it is my opinion that the non-

obviousness of claims 1-25 of the '866 patent is reinforced by evidence of addressing a long-felt but unsolved need, copying by others of the claimed invention, and unexpected results. These objective indicia are demonstrated by Fortamet®, Patent Owner's commercial embodiment of the dosage forms claimed in the '866 patent.

132. ***First,*** as taught by the '866 patent, prior to the instant invention, there was a long-felt, unmet need for controlled release metformin dosage forms that allowed for safe and effective once-a-day dosing for the treatment of type 2 diabetes, improving patient compliance and reducing potentially dangerous side-effects observed with multiple daily doses (*e.g.*, anorexia, nausea, and vomiting). *See* '866 patent col. 1, ll. 14-18, 51-55; col. 2, ll. 6-16. Previous work on controlled or sustained release formulations suffered from the fact that the absorption of metformin was decreased and slightly delayed by food intake. *Id.* col. 2, ll. 17-33. There was a need for dosage forms that provided sustained, continuous, and non-pulsating metformin release where the dosage form could be administered once-a-day while providing therapeutic levels of the drug throughout the day with peak plasma levels being obtained at a desirable time.

133. The invention claimed in the '866 patent met this need by providing controlled release once-a-day dosage forms of metformin that provide effective control of blood glucose levels. Importantly, because the claimed dosage forms

provide a mean time to maximum plasma concentration (T_{max}) of metformin from 5.5 to 7.5 hours after administration following dinner, these dosage forms provide for the highest blood plasma levels of drug at the time when the patient needs it most (*i.e.*, around 2 a.m.), when the body is producing the most glucose. *See id.* col. 8, l. 66 – col. 9, l. 12. The claimed dosage forms are thus superior to the dosage forms of the prior art and solved the long-standing problems associated with known metformin tablets prior to the instant invention.

134. ***Second,*** I understand that the invention claimed in the '866 patent has been the subject of extensive copying by others. Since the FDA's approval of Fortamet® in 2004, at least five generic manufacturers have filed Abbreviated New Drug Applications ("ANDAs") seeking approval for bioequivalent copies of the claimed dosage forms. I also understand that a significant portion of the ANDAs describe products that use virtually identical metformin concentrations, semipermeable membrane compositions and patient instructions as the Fortamet® extended release tablet. Patent Owner Preliminary Response at 32; Exs. 1008-1009. Such copying is strong evidence of the non-obviousness of the claimed invention.

135. I note that Dr. Akhlaghi failed to properly consider copying by others. While Dr. Akhlaghi was aware that a number of generic pharmaceutical companies (including Aurobindo) have applied to market generic forms of Fortamet®, she

stated that she did not consider the applications to be "copying." Akhlaghi Deposition at 56:15-57:19. I disagree. As described above, a significant portion of the ANDAs contain products that use virtually identical metformin concentrations, semipermeable membrane compositions and patient instructions as the Fortamet® extended release tablet. Such development of the generic version of Fortamet® is clearly "copying" the claimed invention. The fact that Dr. Akhlaghi did not properly consider this objective indicium of non-obviousness indicates to me that her analysis was flawed.

136. ***Third***, the invention of the '866 patent provided unexpected results. There is nothing in Cheng or Timmins that would suggest to a POSA the unexpected improvement in bioavailability of the metformin drug provided by the claimed dosage forms. '866 Patent at col. 5, ll. 1-7; col. 16, l. 28 – col. 19, l. 29. Nor does Cheng or Timmins suggest developing a dosage form in which metformin is formulated to achieve a mean T_{max} of 5.5 to 7.5 hours, as claimed in the '866 patent. These unexpected results confirm that the invention claimed in the '866 patent was a non-obvious advance over the prior art. Patent Owner Preliminary Response at 32-33; '866 Patent at col. 5, ll. 1-7; col. 16, l. 28 – col. 19, l. 29.

137. It is also my opinion that there is a nexus between these objective indicia and the invention claimed in claims 1-25. Fortamet®, Patent Owner's

commercial embodiment of the dosage forms claimed in the '866 patent, has a T_{max} of 6.1 hours when administered with food, which is within the T_{max} ranges of 5.5-7.5 hours, 6.0-7.0 hours, and 5.5-7.0 hours recited in the claims of the '866 patent. Ex. 2002 at 6. Furthermore, I understand that the PK parameters listed in a number of claims 6-24 are also obtained by administration of Fortamet® as claimed. *See, e.g.*, Ex. 2002. Additionally, the Fortamet® composition corresponds to the specific composition recited in claim 25, which describes the key components of an osmotic pump formulation. Ex. 2002 at 4. Because Fortamet® embodies these claims and is the embodiment to which these objective indicia relate, there is a clear connection between these objective indicia and the claimed invention in claims 1-25.

138. Accordingly, it is my opinion that these numerous objective indicia of non-obviousness further support the patentability of the challenged claims 1-25.

XII. COMPENSATION

139. I am being compensated at a rate of $500/hour for the time I spend on this matter. My compensation is not dependent upon and in no way affects the substance of my statements in this Declaration.

140. I have no financial interest in Patent Owner. I similarly have no financial interest in the '866 patent.

XIII. AVAILABILITY FOR CROSS EXAMINATION

141. In signing this declaration, I recognize that the declaration will be filed as evidence in a contested case before the Patent Trial and Appeal Board of the United States Patent and Trademark Office. I also recognize that I may be subject to cross examination in the case and that cross examination will take place within the United States. If cross examination is required of me, I will appear for cross examination within the United States during the time allotted for cross examination.

XIV. JURAT

142. I declare 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.

Dated: May 31st, 2018

Jennifer Dressman, Ph.D.

Appendix A. CV of Dr. Jennifer Dressman

Prof. Dr. Jennifer Dressman (nee Boehm)

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Permanent Residency: Germany

EDUCATION

1976 Bachelor of Pharmacy, Victorian College of Pharmacy, Melbourne, Australia

1979 Master of Science in Pharmaceutical Chemistry, The University of Kansas

1981 Doctor of Philosophy in Pharmaceutical Chemistry, The University of Kansas

POSITIONS HELD

1977-1981	Teaching and Research Assistantships, The University of Kansas
1981-1982	Research Pharmacist II, Burroughs Wellcome Co., Greenville, North Carolina
1982-1983	Senior Research Chemist, INTERx Research Corp., Lawrence, Kansas
1983-1989	Assistant Professor of Pharmaceutics, The University of Michigan
1989-1994	Associate Professor of Pharmaceutics, The University of Michigan
1994-	Professor of Pharmaceutical Technology, JW Goethe University, Frankfurt
2002-	Director, Institute of Pharmaceutical Technology, JW Goethe University, Frankfurt

HONOURS & AWARDS

1976	1. Pharmacy Board of Victoria Prize 2. Australian Government Post-Graduate Award 3. C.J. Tonkin Scholar
1977-80	4. Intersearch Scholar
1987	5. Ebert Prize (Best paper in J. Pharmaceutical Sciences, Paper #15)
1988	6. American Association of Pharmaceutical Scientists (AAPS) Procter & Gamble Thesis Research Award
1989	7. National Institute of Hygienic Sciences, Tokyo, Japan Visiting Scientist (February/March)
1990	8. Phi Lambda Upsilon Honorary Member
1991	9. Elected AAPS Fellow
1992	10. University of Paris XI Visiting Professor
1994	11. University of Cincinnati Parke-Davis Distinguished Scientist Award
1998	12. Universite d'Auvergne (Clermont-Ferrand) Visiting Professor (March)
2003	13. Phoenix Prize (Paper #74)
2006	14. WHO Research group designated "WHO Collaborating Center for Research on Bioequivalence"
2006	15. University of North Carolina GlaxoSmithKline Distinguished Speaker in Drug Delivery
2006	16. Institute of Food Technologists, USA Food Expo Innovation Award for Fortefiber® (US Patent 5,789,393)
2008	17. Federation Internationale Pharmaceutique Distinguished Scientist Award
2010	18. Silver Medal of Honour, APV 19. Elected to the College of Fellows, CRS 20. Best Paper 2010 Award, European Journal of Pharmaceutics and Biopharmaceutics
2015	21. Elected to Fellow, Federation Internationale Pharmaceutique
2016	22. "Outstanding Personality with a Foreign Background" – recognition by the City of Frankfurt.
2016	23. recognized as a "Highly Cited Researcher" in the field of Pharmacology and Toxicology by HCR Clavirate Analytics (formerly Thomas Reuters)

2017 24. The Nagai "International Woman Scientist of the Year 2017"
Association of Pharmaceutical Sciences and Technologies
25. Election to Fellow of the APSTJ
26. Most Informative Scientific Report Award 2017
SimCyp (paper # 185)

PROFESSIONAL INVOLVEMENT

Association Memberships
- American Association of Pharmaceutical Scientists (Charter Member)
- APV
- Federation Internationale Pharmaceutique

Committees

1987-1989 - National Cancer Institute
Developmental Therapeutics Contracts Review Committee

1996- - Royal Pharmaceutical Society International Advisory Panel

1996- - FIP Working Group 4 (formerly Dissolution, now BCS&Biowaiver)

1997 - 2000 - Executive Committee, APV

Controlled Release Society

1989-1991 - Controlled Release Society (CRS) Member, Board of Governors
2004/5 - CRS President

American Association of Pharmaceutical Scientists (AAPS)

1992 Chair, Pharmaceutics and Drug Delivery Section
Member, Executive Council

1993 Member, Strategic Planning Committee
Member, Awards Committee
Member, Task Force-Use of Women in Clinical Research

1994-1998 Member-At-Large
Member, Management Committee and Executive Council

2001 Chair, Strategic Alliance Committee

2002-2003 Chair, PDD Fellows Committee

WHO

Since 2003 Technical Advisor to Quality and Safety: Medicine
Since 2006 Collaborating Centre for Research on Bioequivalence

FIP

Since 2009 Member, Board of Pharmaceutical Sciences
Since 2010 Chair, Focus Group "BCS and Biowaiver"
2012-2018 Member, Executive Council, Board of Pharmaceutical Sciences

Editorial Boards

1993-1998 - Biopharmaceutics and Drug Disposition
1995-2000 - Pharmaceutical Research
1995- - European J. of Pharmaceutics and Biopharmaceutics
1996-2004 - Pharmaceutical Technology

1998- - Dissolution Technologies
1998- - European J. of Pharmaceutical Sciences
2001- - Journal of Pharmaceutical Sciences
2001- - Journal of Pharmacy and Pharmacology
2011- - Saudi Pharmaceutical Journal

Associate Editorships
Since 2012 - European J. of Pharmaceutics and Biopharmaceutics
Since 2014 - Journal of Pharmacy and Pharmacology

PUBLICATIONS

Peer Reviewed Research Articles

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An *in vitro* study of the adsorption of drugs by activated charcoal.
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2. JJ Boehm, TCK Brown, RC Oppenheim
Flavored activated charcoal as an antidote.
Austr. J. Pharm. Sci. **7**:119 (1978)

3. JJ Boehm, TCK Brown, RC Oppenheim
Reduction of pheniramine toxicity using activated charcoal.
Clin. Toxicol. **12**:523 (1978)

4. JB Dressman, KJ Himmelstein, T Higuchi
Simultaneous self-association and diffusion of phenol in isooctane.
J. Pharm. Sci. **71**:1226-1230 (1982)

5. JB Dressman, KJ Himmelstein, T Higuchi
Diffusion of phenol in the presence of a complexing agent, tetrahydrofuran.
J. Pharm. Sci. **72**:12-17 (1983)

6. JB Dressman, RI Poust
Stability of allopurinol and of five antineoplastics in suspension.
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7. JB Dressman, GL Amidon
Radiotelemetric method for evaluating enteric coatings *in vivo*.
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8. JB Dressman, D Fleisher, GL Amidon
Physicochemical model for dose-dependent drug absorption.
J. Pharm. Sci. **73**:1274-1279(1984)

9. JJ Boehm, DM Dutton, RI Poust
Shelf life of unrefridgerated succinylcholine chloride injection.
Am. J. Hosp. Pharm. **41**:300 (1984)

10. JJ Boehm, RI Poust
Hydrolysis of succinylcholine chloride in pH range 3.0 to 4.5.
Chem. Pharm. Bull. **32**:1113 (1984)

11. JB Dressman, GL Amidon, D Fleisher
Absorption potential: estimating the fraction absorbed for orally administered compounds.
J. Pharm. Sci. **74**:588-589 (1985)

12. CA Youngberg, J Wlodyga, S Schmaltz, JB Dressman
Radiotelemetric determination of gastrointestinal pH in four healthy beagles.
Am. J. Vet. Res. **46**:1516-21 (1985)

13. JH Meyer, JB Dressman, A Fink, GL Amidon
Effect of size and density on canine gastric emptying of nondigestible solids.
Gastroenterology **89**:805-813 (1985)

14. JB Dressman, L Shtorhyn, D Diokno

Effects of product formulation on *in vitro* activity of pancreatic enzymes.
Am. J. Hosp. Pharm. **42**:2502-2506 (1985)

15. JB Dressman, D Fleisher
Mixing-tank model for predicting dissolution rate control of oral absorption.
J. Pharm. Sci. **75**:109-116 (1986) **(Ebert Prize)**

16. CY Lui, GL Amidon, RR Berardi, D Fleisher, C Youngberg, JB Dressman
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J. Pharm. Sci. **75**:271-274 (1986)

17. JH Meyer, Y Gu, J Elashoff, T Reedy, JB Dressman, GL Amidon
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18. GL Amidon, AE Merfeld, JB Dressman
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19. AE Merfeld, AR Mlodozeniec, MA Cortese, JB Rhodes, JB Dressman, GL Amidon
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20. CA Youngberg, RR Berardi, WF Howatt, ML Hyneck, GL Amidon, JH Meyer, JB Dressman
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21. SS Ozturk, BO Palsson, JB Dressman
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Pharm. Res. **5**:272-282 (1988)

22. SS Ozturk, BO Palsson, B Donohoe, JB Dressman
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23. JH Meyer, J Elashoff, V Porter-Fink, JB Dressman, GL Amidon
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24. RR Berardi, JB Dressman, GH Elta, GJ Szpunar
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25. KC Meadows, JB Dressman
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26. SS Ozturk, JB Dressman, BO Palsson
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31. AG Ozturk, SS Ozturk, BO Palsson, TA Wheatley, JB Dressman
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50. LJ Naylor, V Bakatselou, N Rodriguez-Hornedo, ND Weiner, JB Dressman
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51. L Henderson, GJ Brewer, JB Dressman, DJ DuRoss, SZ Swidan, CH Adair, JL Barnett, RR Berardi
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53. S Swidan, C Reppas, JL Barnett, DE Greenwood, AM Tallman, SW Tobey, JB Dressman
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54. GM Derbin, BO Palsson, JF Mansfield, TA Wheatley, JB Dressman
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55. LM Henderson, GJ Brewer, JB Dressman, SZ Swidan, DJ DuRoss, CH Adair, JL Barnett, RR Berardi.
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61. C Reppas, G Eleftheriou, P Macheras, M Symilldes, D Greenwood, JB Dressman
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62. C Reppas, DE Greenwood, JB Dressman
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63. AS Uch, U Hesse, JB Dressman
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65. E Galia, J Horton, JB Dressman
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66. E Nicolaides, E Galia, C Efthymiopolos, JB Dressman, C Reppas
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67. R Löbenberg, J Krämer, V Shah, GL Amidon, JB Dressman
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68. JB Dressman, C Reppas.
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Europ. J. Pharm. Sci. **11**(Supp 2): S73-S80 (2000)

69. V Loi, TA Wheatley, C Reppas, JB Dressman
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Pharmaceutical Technology **24** (3):1-5 (2001)

70. MW Rudolph, S Klein, TE Beckert, H-U Petereit, JB Dressman
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9. C Becker, J Dressman, GL Amidon, HE Junginger, S. Kopp, KK Midha, VP Shah, S. Stavchansky, DM Barends
Biowaiver monographs for immediate release dosage forms: Ethambutol Dihydrochloride
J. Pharm. Sci. **97**:1350-1360 (2008)

10. J. Arnal, I. Gonzalez-Alvarez, M. Bermejo, J Dressman, GL Amidon, HE Junginger, S. Kopp, KK Midha, VP Shah, S. Stavchansky, DM Barends
Biowaiver monographs for immediate release dosage forms: Aciclovir
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11. G. Granero, M. Longhi, C. Becker, J Dressman, GL Amidon, HE Junginger, S. Kopp, KK Midha, VP Shah, S. Stavchansky, DM Barends
Biowaiver monographs for immediate release dosage forms: Acetazolamide
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12. A Stosik, HE Junginger, S Kopp, KK Midha, VP Shah, S Stavchansky, J Dressman, DM Barends
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13. C Becker, J Dressman, GL Amidon, HE Junginger, S Kopp, KK Midha, VP Shah, S. Stavchansky, DM Barends
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14. J Polli, HE Junginger, S Kopp, KK Midha, VP Shah, S. Stavchansky, J Dressman, DM Barends
Biowaiver monographs for immediate release dosage forms: Diclofenac potassium and sodium
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15. S Grube, P Langguth, GL Amidon, HE Junginger, S Kopp, KK Midha, VP Shah, S Stavchansky, JB Dressman, DM Barends.
Biowaiver monographs for immediate release dosage forms: Quinidine Sulfate
J. Pharm. Sci. **98**: 2238-2251 (2009)

17. C Becker, J Dressman, GL Amidon, HE Junginger, S Kopp, KK Midha, VP Shah, S. Stavchansky, DM Barends
Biowaiver monographs for immediate release dosage forms: Rifampicin
J. Pharm. Sci. **98**: 2252-2267 (2009)

18. E Jantratid, S Strauch, C Becker, J Dressman, GL Amidon, HE Junginger, S Kopp, KK Midha, VP Shah, DM Barends
Biowaiver monographs for immediate release dosage forms: Doxycycline hyclate
J. Pharm. Sci. **99**:1639-1653 (2010)

19. G Granero, M Longhi, M Mora, H Junginger, KK Midha, VP Shah, S Stavchansky, J Dressman, D Barends.
Biowaiver monographs for immediate release dosage forms: Furosemide
J. Pharm. Sci. **99**:2544-2566 (2010)

20. S Strauch, E Jantratid, J Dressman, GL Amidon, HE Junginger, S Kopp, KK Midha, VP Shah, DM Barends
Biowaiver monographs for immediate release dosage forms: Mefloquine Hydrochloride
J. Pharm. Sci. **100**: 11-21 (2011)

21. M Olivera, R Manzo, GL Amidon, HE Junginger, S Kopp, KK Midha, VP Shah, S Stavchansky, J Dressman, DM Barends
Biowaiver monographs for immediate release dosage forms: Ciprofloxacin Hydrochloride
J. Pharm. Sci. **100**: 22-33 (2011)

22. C Rediguieri, V Porta, D Nunes, T Nunes, S Kopp, HE Junginger, KK Midha, VP Shah, S Stavchansky, J Dressman, DM Barends
Biowaiver monographs for immediate release dosage forms: Metronidazol
J. Pharm. Sci. **100**:1618-1627 (2011)

23. M Koeppe, R Cristofoletti, E Fernandes, S Storpirtis, HE Junginger, S Kopp, KK Midha, VP Shah, S Stavchansky, J Dressman, DM Barends
Biowaiver monographs for immediate release dosage forms: Levofloxacin
J. Pharm. Sci. **100**:1628-1636 (2011)

24. S Strauch, E Jantratid, HE Junginger, S Kopp, KK Midha, VP Shah, S Stavchansky, J Dressman, DM Barends
Biowaiver monographs for immediate release dosage forms: Lamivudine
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25. A Silva, R Cristofoletti, E Fernandes, S Storpirtis, HE Junginger, S Kopp, KK Midha, VP Shah, S Stavchansky, J Dressman, DM Barends
Biowaiver monographs for immediate release dosage forms: Stavudine
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26. S Strauch, J Dressman, P Langguth, B Abrahamsson, JE Polli, VP Shah, DM Barends
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27. A Nair, P Langguth, B Abrahamsson, S Kopp, JE Polli, VP Shah, DM Barends, J Dressman
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28. J Dressman, A Nair, M Zimmer, P Langguth, B Abrahamsson, S Kopp, JE Polli, VP Shah, DM Barends
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29. I Shohin, J Kulinich, G Ramenskaya, B Abrahamsson, S Kopp, P Langguth, JE Polli, VP Shah, DW Groot, DM Barends, J Dressman
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31. R Cristofoletti, A Nair, B Abrahamsson, DW Groot, S Kopp, P Langguth, JE Polli, VP Shah, J Dressman. Biowaiver Monographs for Immediate Release Solid Oral Dosage Forms: Efavirenz
J. Pharm. Sci. **102**: 318-328 (2013)

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33. IE Shohin, JI Kulinich, GV Ramenskaya, B Abrahamsson, S Kopp, P Langguth, JE Polli, VP Shah, DW Groot, DM Barends, J Dressman.
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34. N Charoo, A Shamsher, LY Lian, B Abrahamsson, R Cristofoletti, DW Groot, S Kopp, P Langguth, JE Polli, VP Shah, J Dressman
Biowaiver Monograph for Immediate-Release Solid Oral Dosage Forms: Bisoprolol Fumarate
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35. A Dahan, GL Amidon, B Abrahamsson, R Cristofoletti, DW Groot, S Kopp, P Langguth, JE Polli, VP Shah, J Dressman
Biowaiver Monograph for Immediate-Release Solid Oral Dosage Forms: Codeine Phosphate
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36. N Charoo, R Cristofoletti, A Graham, P Lartey, B Abrahamsson, DW Groot, S Kopp, P Langguth, JE Polli, VP Shah, J Dressman.
Biowaiver monograph for immediate-release solid oral dosage forms: Fluconazole
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37. J Gajendran, J Krämer, VP Shah, J Polli, P Langguth, M Mehta, DW Groot, R Cristofoletti, B Abrahamsson, J Dressman
Biowaiver Monographs for Immediate-Release Solid Oral Dosage Forms: Nifedipine
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38. M Petrusesvka, S Berglez, I Krisch, I Legen, K Megusar, L Peternal, B Abrahamsson, R Cristofoletti, DW Groot, S Kopp, P Langguth, M Mehta, J Polli, VP Shah, J Dressman
Biowaiver Monographs for Immediate Release Solid Oral Dosage Forms: Levetiracetam
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39. N. Goodarzi, M.A. Barazesh, B. Abrahamsson,. R. Cristofoletti, D.W. Groot, P. Langguth, J.E. Polli, A. Parr, V.P. Shah, M. Mehta, J. Dressman
Biowaiver Monographs for Immediate Release Solid Oral Dosage Forms: Ribavirin
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40. R. Verbeeck, I. Kanfer, R. Löbenberg, B. Abrahamsson, R. Cristofoletti, D.W. Groot, P. Langguth, J.E. Polli, A. Parr, V.P. Shah, M. Mehta, J. Dressman.
Biowaiver Monographs for Immediate Release Solid Oral Dosage Forms: Enalopril
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41. D. Thambavita, P. Galappatthy, U. Mannapperuma, R.L. Jayakody, B. Abrahamsson, R. Cristofoletti, D.W. Groot, P. Langguth, J.E. Polli, A. Parr, V.P. Shah, M. Mehta, Jennifer Dressman.
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42. M. Höfsäß, J. de Souza, N. Silva-Barcellos, K. Bellavinha, B. Abrahamsson, R. Cristofoletti, D.W. Groot, A. Parr, P. Langguth, J.E. Polli, V.P. Shah, M. Mehta, T. Tajiri, Jennifer Dressman.
Biowaiver Monographs for Immediate Release Solid Oral Dosage Forms: Folic Acid
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43. G. Plöger, B. Abrahamsson, R. Cristofoletti, D.W. Groot, A. Parr, P. Langguth, J.E. Polli, V.P. Shah, M. Mehta, T. Tajiri, Jennifer Dressman.
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Books

1. P. Macheras, C. Reppas and J.B. Dressman
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2. J. Dressman, H. Lennernäs
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3. J. Dressman, J. Krämer
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4. J. Dressman, C. Reppas
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5. J. Dressman
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2. JB Dressman, G Ridout, RH Guy
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3. JB Dressman, K Yamada
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5. AS Uch, JB Dressman
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6. JB Dressman
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7. A. Glomme, J. März, J.B. Dressman
Predicting the intestinal solubility of poorly soluble drugs
Pharmacokinetic Profiling in Drug Research
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8. S Klein, JB Dressman, C Reppas
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Ed: GL Amidon, L Lesko, K Midha, V Shah
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9. J. Alsenz, K. Schamp, K. Beltz and J. Dressman
In vitro tests for Lipid formulations
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10. C. Wagner, J. Dressman
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Chapter 12 in
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Editors: Jianling Wang and Laszlo Urban

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S. Diebold, J.B. Dressman
Hydrodynamik kompendialer Lösungsgeschwindigkeitstestapparaturen
Pharm Ind **63** (2):94-104 (2001)

SM Diebold, JB Dressman
Entgasung und Wiedersättigung von wässrigen Medien für Lösingsgeschwindigkeittest
Die Pharmazeutische Industrie **60**:354-359 (1998)

S. Klein, M. Rudolph, JB Dressman
"Perorale Mesalazin-Präparate"
Deutsche Apotheke Zeitung **142** (28): 3404-3410 (2002).

C. Notheis, T. Zöller, J. Dressman, S. Klein
Aut idem bei Metoprolol retard
DAZ **143** (28): 48-55(2003)

S. Bido, S. Csorvasi, M. Sander, M. Spree, JB Dressman
Nahrungsmittelinteraktionen
PZ- Prizma **11** (4): 208-213 (2004)

PATENTS

Lipid Osmotic Pump (assigned to Merck & Co.)
US 4,685,918
Issued 1987

Controlled Release Dosage Form (assigned to the University of Michigan)
US 4,976,949
Issued 1990

Pharmaceutical Compositions and Uses of Water-Soluble, High Viscosity Cellulose Ethers (assigned to the Dow Chemical Co.)
US 5,576,306
Issued 1996

Pharmaceutical Compositions and Uses of Water-Soluble, High Viscosity Cellulose Ethers (assigned to the Dow Chemical Co.)
US 5,789,393
Issued 1998

Use of a Copolymer for producing a pharmaceutical product for the therapy of ulcerative colitis, and a pharmaceutical product provided for the inventive use
(assigned to Röhm GmbH)
WO 01/68057
Date of Publication: 20. September, 2001

Pharmaceutical Formulation for the active ingredient Budesonide
(assigned to Röhm GmbH)
WO 2003/080032
Date of Publication: 02.October, 2003

Mehrschichtige Arzneiform
(assigned to Röhm GmbH)
WO 2004/039357
Date of Publication: 13 May, 2004

Multiparticulate Form of Medicament, Comprising at Least Two Differently Coated Forms of Pellet
(assigned to Röhm GmbH)
US 6,897,205 B2
Date of Patent May 24, 2005

Arzneiform, enthaltend den Wirkstoff Cholylsarcosine
(assigned to Röhm GmbH)
WO 2005/120467
Date of Publication: 12. December, 2005

Multilayer Dosage Forms, which contain active substances and which comprise a neutral core, and an inner and outer coating consisting of methacrylate copolymers and methacrylate monomers
(assigned to Röhm GmbH)
US 2006/0204576 A1
Publication Date: September, 2006

Pharmacetical composition for controlled release of β-lactam antibiotics in combination with β-lactamase inhibitors
(assigned to Next Pharma)
WO2006072424 A1

Publication date: July, 2006

Carboxyalkylcellulose esters for administration of poorly soluble pharmaceutically active agents
(assigned to Eastman Chemical)
WO2007056205 A3
Publication date: May, 2007

Multiparticulate form of medicament, comprising at least two differently coated forms of pellet.
(assigned to Evonik Röhm GmbH)
EP 1 248 599 B1
Publication Date: 05.12.2007

Pharmazeutische Zusammensetzungen, enthaltend Mischungen aus Polymeren und in Wasser schlecht löslichen Stoffen.
(assigned to Evonik GmBH)
WO 2007/090721 A1

Multilayer Dosage Forms, which contain active substances and which comprise a neutral core, and an inner and outer coating consisting of methacrylate copolymers and methacrylate monomers
(assigned to Evonik Röhm GmbH)
E P155 6016 B1
Publication Date: September, 2008

Multiparticulate Form of Medicament, Comprising at Least Two Differently Coated Forms of Pellet
(assigned to Evonik Röhm GmbH)
US 7,438,929 B2
Publication Date: October, 2008

Process for preparing instant forms of aqueous mixed micellar solutions as physiological buffer systems for use in the analysis of in vitro release
(assigned to Boehringer Ingelheim)
WO2008040799 A3
Publication date: April, 2008

Biorelevant compositions
(assigned to Phares Pharmaceutical Research)
WO2013144374 A1
Publication date: October, 2013

Last updated 2016

MASTERS AND DOCTORAL THESES SUPERVISED

1. Carole A. Youngberg (Masters 1985)
Radiotelemetric determination of gastrointestinal pH in man and dog.

2. Kem C. Meadows (Doctorate 1988)
Intestinal uptake mechanism of purine bases and analogues.

3. Lambros C. Dermentzoglou (Doctorate 1989)
Changes in upper gastrointestinal pH with aging: implications for drug absorption.

4. Paul J. Sirois (Doctorate 1989)(Procter and Gamble Thesis Research Award)
Size and density discrimination of nondigestible solids during emptying from the canine stomach: a hydrodynamic correlation.

5. Sandra Witham (Doctorate 1989)
Joint Adviser with GL Flynn
Esterase hydrolysis of an homologous series of PABA esters in hairless mouse and human skin homogenates.

6. Vassiliki Bakatselou (Doctorate 1990)
Dissolution of steroid compounds at physiological bile salt concentrations.

7. Asuman G Ozturk (Masters 1990), Bioengineering
Joint advisor with Bernhard Palsson (Chem Eng)
Studies on the release of drugs from pellets coated with ethylcellulose-based films.

8. Tanya L Russell (Doctorate 1991)
pH related changes in oral drug absorption in the elderly.

9. Lori J McDonald Naylor (Doctorate 1993)
Dissolution mechanisms of poorly soluble compounds in simple and mixed micelle systems.

10. Vanaja Mummaneni (Doctorate 1993)
Oral absorption of histamine-2 receptor antagonists.

11. Christopher N TenHoor (Doctorate 1993)
Limitations to the oral absorption of cyclosporine A.

12. Dale E Greenwood (Doctorate 1994)
Small intestinal pH and buffer capacity: implications for dissolution of ionizable compounds.

13. Sabena Mithani (Doctorate 1998)
Joint advisor with Nair Rodriguez
Dissolution and precipitation of dipyridamole: Effect of pH and bile salt concentration

14. Dirk Hörter (Doctorate 1999)
Löslichkeit, Freisetzungsverhalten und galenische Präformulierung schwer wasserlöslicher Antimykotika unter Berücksichtigung der gastrointestinalen Physiologie.

15. Antje Uch (Doctorate 1999)
Intestinal uptake of azole antifungals in rats - method development, Validation and determination of uptake mechanisms

16. Eric Galia (Doctorate 1999)
Physiologically based dissolution tests - experiences with poorly soluble substances

17. Steffen Diebold (Doctorate 2000)
Hydrodynamik und Lösungsgeschwindigkeit: Untersuchungen zum Einfluss der Hydrodynamik auf die Lösungsgeschwindigkeit schwer wasserlöslicher Arzneistoffe

18. Markus Rudolph (Doctorate 2002)
Entwicklung und in vitro Charackterisierung von peroralen multipartikulären Arzneiformen zur Optimierung der Therapie der Colitis ulcerosa und des Morbus Crohn

19. Karen Schamp (Doctorate 2002)
Lipidartige Formulierungen zur Verbesserung der Bioverfügbarkeit schwerlöslicher Arzneistoffe

20. Annette Scholz (Doctorate 2002)
The influence of hydrodynamics on the dissolution of poorly soluble drugs

21. Kerstin Westerhoff (Doctorate 2002)
Joint supervisor with Prof. Dr. Manfred Schubert-Zsilavecz

22. Erika Stippler (Doctorate 2004)
Development of BCS-conform dissolution testing methods

23. Christian Leuner (Doctorate 2004)
Solid dispersions improve the biopharmaceutical properties of itraconazole

24. Alexander Glomme (Doctorate 2004)
Biorelevante Löslichkeit schwerlöslicher Arzneistoffe

25. Martin Wunderlich (Doctorate 2004)
Biorelevante in vitro Methoden zur Vorhersage des in vivo Verhaltens von schlecht wasserlöslichen, schwach basischen Arzneistoffen

26. Sandra Klein (Doctorate 2005)
Biorelevant dissolution test methods for modified release dosage forms

27. Thomas Fürst (Doctorate 2005)
Formulation of cholylsarcosine for bile salt replacement therapy

28. Ekarat Jantratid (Doctorate 2005, Mahidol University, Bangkok)
Feasibility Studies on Biowaiver Extension of in vivo Bioequivalnce of Class III drugs based on the Biopharmaceutics Clasiification System
Joint Supervisor

29. Matthias Fischbach (Doctorate 2006)
Vorhersage des *in vivo* Verhaltens von Arzneiformen mit modifizierter Wirkstofffreisetzung

30. Markus Vogt (Doctorate 2007)
Zur Auflösung covermahlener Formulierungen schwerlöslicher Arzneistoffe

31. Marc Lindenberg (Doctorate 2007)
A biopharmaceutics classification scheme for development

32. Karen Beltz (Doctorate 2008)
Bestimmung von Auswahlkriterien und formulierungsrelevanten Parametern zur Formulierung schwerlösicher Arzneistoffe in Lipidsysteme

33. Kevin Kiehm (Doctorate 2009)
Devlopment of a novel screening tool for the prediction of oral drug absorption based on surface activity profiling

34. Corina Becker (Doctorate 2009)
Preparation of Biowaiver Recommendations for Antituberculosis Drugs

35. Kathrin Nollenberger (Doctorate 2009)
Löslichkeitsverbesserung schwerlöslicher Arzneistoffe durch Schmelzextrusion mit Polymethacrylaten

36. Julia Boni (Doctorate 2009)
Improvements to biorelevant dissolution testing

37. Frank Seiler (Doctorate 2009)
Controlled Release Solid Dosage Forms by Melt-Extrusion

38. Thomas Zöller (Doctorate 2010)
Verbesserung des Auflösungsverhaltens schwer löslicher schwacher Säuren mit Hilfe von festen Lösungen und Cyclodextrinen

39. Niels Janssen (Doctorate 2011)
Entwicklung von biorelevanten Medien zur Simulation des oberen Magen-Darm-Traktes

40. Steffen Paulekuhn (Doctorate 2011)
Bildung und Analyse pharmazeutischer Salze schwer löslicher, schwach basischer Wirkstoffe

41. Anna-Christine Petereit (Doctorate 2011)
Prediction of biological membrane penetration of poorly soluble drugs using surface activity profiling

42. Stephanie Strauch (Doctorate 2011)
Application of Biowaiver Tools to Combat High-Burden Diseases

43. Yasushi Shono (Doctorate 2011)
Forecasting food effects on the intestinal absorption of poorly soluble compounds based on biorelevant dissolution testing coupled with *in silico* simulation technology

44. Kirstin Thelen (Doctorate 2012)
Physiologically based models to simulate the gastrointestinal transit and absorption process of orally administered drugs

45. Daniel Jünemann (Doctorate 2012)
Analytics of dissolution testing of products containing nanosized drugs with a view to predicting plasma profiles

46. James Butler (Doctorate 2012)
The optimal use of in vitro tools for the prediction of in vivo oral dosage form behavior

48. Murat Kilic (Doctorate 2013)
Die Lipidtoolbox für Arzneimittel-ein systematischer Ansatz für die Entwicklung von oralen Lipidformulierungen schwerlöslicher Arzneistoffe

49. Marc Hugo (Doctorate 2013)
Einfluss von Lösungsmittel, Hilfsstoff und Wirkstoff auf die Eigenschaften von sprühgetrockneten festen Dispersionen

50. Marcel Arndt (Doctorate 2013)
Biorelevante Freisetzungsmedien zur Simulation von Magen- und Darmsaft des nüchternen Hundes

51. Christian Wagner (Doctorate 2013)
Predicting the Oral Absorption of Poorly Soluble Drugs

52. Anita Nair (Doctorate 2013)
Improving Quality of Essential Medicines: A Biowaiver Approach

53. Thomas Taupitz (with Sandra Klein) Doctorate 2014
Anwendung neuer ternärer Cyclodextrinformulierungen für schwer lösliche Wirkstoffe: Verbesserung der *in vitro* Performance und Vorhersage des *in vivo* Verhaltens

54. Atsushi Kambayashi Doctorate 2014
Predicting Oral Pharmacokinetic Profiles of Solid Dosage Forms Containing Poorly-Soluble Weak Acid Drugs

55 Mark Berlin (Doctorate 2015)
Predicting absorption of poorly soluble, weakly basic drugs

56. Alexander Fuchs (Doctorate 2016)
Entwicklung einer neuen Generation von biorelevanten Medien zur Simulation des nüchternen humanen Dünndarms: FaSSIFv3

58. Susanne Beyer (Doctorate 2017)

59. Cord Andreas (Doctorate 2017)
Biorelevant dissolution tests to elucidate food effects on release from modified release dsage forms

60. Rodrigo Cristofoletti (Doctorate 2017)
Going beyond the traditional BE borders: using in vitro and in silico tools to improve the assessment and extrapolation of therapeutic equivalence

61. Simone Hansmann (Doctorate 2018)
Simulation of oral abdsorption with physiologically based pharmacokinetic models with a focus on weakly basic active pharmaceutical ingredients

Current Graduate (Doctoral) students:

Dieter Bischoff ABD
Yang Fei ABD
Keiichi Otsuka
Christine Janas ABD
Aaron Ruff ABD
Gerlinde Born
Julian Thinnes ABD
Andreas Kozwara ABD
Martin Höfsass
Lukas Klumpp
Rafel Leal Paraiso

Daniel Price
Chara Litou
Ioannis Loisios-Konstantinidis
Yaser Mansuroglu

POSTDOCTORAL FELLOWS and HABILITATION CANDIDATES

University of Michigan
Christos Reppas 1988-1991
Sahar Swidan 1991-1994

University of Frankfurt
Edmund Kostewicz 2000-2002, 2009-
Javed Ali (BOYSCAST Fellow 2005)
Ekarat Jantratid 2006-2009
Sandra Klein 2005-2010
Matthias Wacker 2012-
Christoph Saal 2012-
Bassam al Meslmani 2014-2015
Yoshi Miyaki 2015-2017
Kalpa Nagasekar 2016-2018
Ayahisa Watanabe 2017-2018

INVITED PRESENTATIONS

1979

Victorian College of Pharmacy, Melbourne, Australia
'Pharmacy studies at the University of Kansas'.

Ohio State University, Pharmaceutics Graduate Student Meeting, Columbus, OH
'Effects of self-association on the interphase transport of phenol'.

1983

* Higuchi Research Seminars, Lake of the Ozarks, MO
'A physicochemical model for dose dependent drug absorption'.

SmithKline Board of Governors Meeting, Sanibel Island, FL
'Gastrointestinal pH profile: implications for dosage form design'.

1984

Menley & James, Philadelphia, PA
'Gastric emptying considerations in dosage form design'.

Victorian College of Pharmacy, Melbourne, Australia
'Research interest of pharmaceutics faculty at The University of Michigan'.

Burroughs Wellcome Co., Greenville, NC
'Gastric emptying considerations in dosage form design'.

** 26th Annual National Industrial Pharmaceutical Conference, Madison, WI
'Drug absorption and dosage form design: thiazides and beyond'.

Warner Lambert Co., Ann Arbor, MI
'Modeling gastrointestinal drug absorption'.

* The University of Michigan, Biannual Pharmaceutics Seminar, Ann Arbor, MI
'Gastric emptying considerations in dosage form design'.

Purdue University, West Lafayette, IN
'Modeling gastrointestinal drug absorption'.

1985

The Upjohn Co., Kalamazoo, MI
'Gastrointestinal transit considerations in dosage form design'.

Syntex, Palo Alto, CA
'Gastrointestinal transit considerations in dosage form design'.
'Models for drug absorption'.

Sterling Winthrop Research Institute, Rensselaer, NY
'Role of gastrointestinal physiology in drug absorption'.

Victorian College of Pharmacy, Melbourne, Australia
'Drug absorption and dosage form design'.
'Role of gastrointestinal physiology in drug absorption'.

* Higuchi Research Seminars, Lake of the Ozarks, MO
'Comparison of human with canine gastrointestinal physiology'.

1986

** Arden House Conference On Oral Controlled Release Products, Harriman, NY
'Predicting bioavailability from oral controlled release products'.

* Higuchi Research Seminars, Lake of the Ozarks, MO
'Mechanisms of release from enteric coated dosage forms'.
Pfizer Central Research, Groton, CT
'Recent developments in GI absorption modeling'.

1987

FH Faulding & Co., Adelaide, Australia
'Gastrointestinal physiology and enteric-coated dosage form design'.

University of Toronto, Toronto, Canada
'Recent developments in GI absorption modeling'.

Mc Neil Consumer Products Co.
'Changes in gastrointestinal pH: Ramifications for dosage form design'.

** Eastern Regional Pharmaceutical Technology Meeting, Newark, NJ
'Aspects of GI physiology important to dosage form design'.

1988

* Drug Delivery and the Gastrointestinal Tract, Davos, Switzerland
'Gastrointestinal transit and the onset, rate and extent of drug delivery'.

SmithKline and French Laboratories,, Uper Marion, PA
'Gastric emptying and dosage form design'.

Sterling Winthrop Research Institute, Rensselaer, NY
'pH related changes in oral drug absorption'.

** Pharmaceutical Technology Conference, East Rutherford NJ
'Predicting release kinetics from enteric coated dosage forms'.

* The University of Michigan, Biannual Pharmaceutics Seminar, Ann Arbor, MI
'Current trends in oral controlled release dosage forms'.

1989

Merrell Dow, Cincinnati, OH
'Effects of supplemental fiber on blood glucose levels in dogs'.

Kyoto University, Kyoto, Japan
'Current trends in oral controlled release dosage forms'.
Kanazawa University, Kanazawa, Japan
'Current trends in oral controlled release dosage forms'.

Meiji University, Tokyo, Japan
'Current trends in oral controlled release dosage forms'.

National Institute of Hygienic Sciences, Tokyo, Japan
'Gastrointestinal physiology and drug absorption'.

** Food and Drug Administration/Pharmaceutical Manufacturers Association Workshop on Animal Models for Oral Drug Absorption,Washington DC
'Species differences in gastrointestinal physiology'.

** Controlled Release Society, 16th Int Symp Contr Rel Bioact Mat, Chicago, IL
'Current trends in oral controlled release dosage forms'.

Eli Lilly & Co., Indianapolis, IN
'Gastrointestinal physiology and drug absorption'.

1990

SmithKline & French Laboratories, Upper Marion, PA
'Species differences in GI physiology'.

** University of Wisconsin, 9th Annual Update Conference in Pharmaceutics, Madison, WI
'Animal models for oral drug absorption'.

University of California, San Francisco, CA
'Importance of gastrointestinal pH in drug absorption'.

** AAPS, Eastern Regional Meeting, New Brunswick, NJ
'Current trends in oral controlled release dosage form research'.

The Upjohn Co, Kalamazoo, MI
'Animal models for oral drug absorption'.

The University of Michigan, Ann Arbor, MI
'The importance of gastrointestinal pH in drug absorption'.

1991

** AAPS Indiana Discussion Group, Indianapolis, IN
'Upper gastrointestinal pH and drug absorption'.

ETH-Zentrum, Zurich, Switzerland
'Gastrointestinal pH and drug absorption'.

JW Goethe University, Frankfurt, Germany
'Gastrointestinal pH and oral drug delivery'.

University of Athens, Athens, Greece
'Upper gastrointestinal pH and drug absorption'.

University of Paris XI, Chatenay-Malabry, France
'Physiological considerations in the design of oral controlled release dosage forms'.

Butler University, Indianapolis, IN
'Effects of gastrointestinal pH on drug absorption'.

Warner Lambert, Morris Plains, NJ
'Upper gastrointestinal pH and motility drug absorption'.

** Philadelphia Pharmaceutical Forum, Philadelphia, PA
'Dissolution of poorly soluble drugs in the gastrointestinal tract'.

McNeil Laboratories, Spring House, PA
'Practical considerations in designing 24 hour acting oral dosage forms'.

** University of Wisconsin, 33rd Annual International Industrial Research Conference, Madison, WI
'Effects of particle size on dissolution (and biologic disposition/ consequences)'.

Johnson and Johnson 5th Drug Delivery Symposium, New Brunswick, NJ
'New aspects of gastrointestinal drug delivery'.

SmithKline Beecham, King of Prussia, PA
'Gastrointestinal pH and drug absorption'.

University of Sydney, Sydney, Australia
'Gastrointestinal pH and drug absorption'.

1992

University of Paris IX, Paris, France
'Gastrointestinal absorption of peptides'.

SmithKline Beecham, Worthing, England
'Role of upper gastrointestinal physiology in drug absorption'.

University of Basel, Basel, Switzerland
'Role of upper gastrointestional pH in drug absorption'.

JW Goethe University, Frankfurt, Germany
'Role of upper gastrointestinal pH in drug absorption'.

** GTRV meeting, Paris, France
'Opportunities for peptide absorption in the gastrointestinal tract'.

1993

SmithKline Beecham, Philadelphia
'Challenges in formulations of cimetidine'.

** Fine Particle Society, Chicago
'Role of gastrointestinal physiology in drug absorption'.

DuPont-Merck, Delaware
'Limitations to oral drug absorption'.

** Delaware Discussion Group, Delaware
'Gastrointestinal absorption: Animal models and limitations to absorption'.

The University of Michigan
University Seminars
'Hydroxypropylmethylcellulose: a cholesterol lowering agent'.

1994

University of Cincinnati, Ohio
'Routes of administration: their effect on therapeutic efficacy'
'Dissolution rate limited absorption from the gastrointestinal tract.'

** 2nd European Congress on the Pharm. Sci., Berlin
Predicting dissolution of poorly soluble drugs in the gastrointestinal tract.

1995

University of Uppsala, Uppsala, Sweden
Physiologically based dissolution tests

Martin Luther Universität, Halle
Dissolution as a rate-limiting step to oral drug absorption

** Workshop on the Evaluation of orally administered highly variable drugs and drug formulations
AAPS-FDA joint Workshop, Washington DC
Examples of variability imposed by GI physiology

Warner-Lambert, Ann Arbor, MI
Predicting the dissolution of poorly soluble drugs in the GI tract

Friedrich Alexander Universität, Erlangen, Germany
Reproducibility of release from ethylcellulose coated dosage forms

Hoechst, GmbH, Frankfurt, Germany
Predicting absorption of drugs from the gastrointestinal tract

Astra Hässle, Sweden
Physiologically-based dissolution tests

University of Copenhagen
Predicting absorption of poorly soluble drugs from the gastointestinal tract.

1996

** APGI; Paris
Improving bioavailability by colonic administration

Bayer AG; Leverkuchen
The role of gastrointestinal physiology in drug absorption

DuPont-Merck; Wilmington, Delaware
The role of gastrointestinal physiology in drug absorption

** EUFEPS; Edinburgh
a priori prediction of oral drug absorption: are we almost there?

** FIP Workshop on Dissolution Testing; Frankfurt am Main
Physiological aspects for dissolution test design

** APV Colon Workshop; Düsseldorf
Geeignete Arzneiformen für die Therapie von Morbus Crohn und Colitis Ulcerosa

1997

** APV, Präformulierung in der Arzneimittelentwicklung, Fulda
Permeabilitäts- und Absorptionsmodelle

* GlaxoWellcome, Ware, England
PALS Conference, Keynote Speaker
Poorly absorbed low solubility drugs: the challege

** AAPS Workshop on the Scientific Basis for and applications of the Biopharmaceutics Classification System and in vitro-in vivo correlations, Washington DC
Physiological aspects of the design of dissolution tests

** CRS Local Chapter, Athens, Greece
Reproducibility of release from prolonged release dosage forms

** Fourth International Conference on Drug Absorption, Edinburgh, Scotland
Whole animal models for oral drug absorption

** 24th International Symposium of the CRS, Stockholm, Sweden
Dissolution in the gastrointestinal tract: regional differences

University of Tokyo, Tokyo, Japan
A priori prediction of drug absorption: are we almost there?

* Capsugel, Biopharmaceutics Drug Classification and International Drug Regulation, Tokyo, Japan
Physiological aspects of in vitro dissolution and in vitro/in vivo correlations.

Daiichi Pharmaceutical Company, Tokyo, Japan
A priori prediction of drug absorption: are we almost there?

Sankyo Pharmaceutical Company, Tokyo, Japan
Physiological aspects of the design of dissolution tests

Otsaka Phamaceutical Company, Tokushima, Japan
Physiological aspects of the design of dissolution tests

Fujisawa Pharmaceutical Company, Osaka, Japan
Physiological aspects of the design of dissolution tests

* University of Kanazawa, Kanazawa, Japan
A priori prediction of drug absorption: are we almost there?

** Swedish Academy of Pharmaceutical Sciences, Malmo
Physiological aspects of the design of dissolution tests

Universität Freiburg
Absorptionsuntersuchungen im Dünn- und Dickdarm

1998

** APV/AAPS/CRS/EUFEPS/FDA, Frankfurt/Main
Biopharmaceutics classification system and in vitro/in vivo correlations
Dissolution tests for IR Products

1999

** APV, Bad Soden
Dissolution für Praktiker
Praxisrelevante Methodeentwicklung unter Maßgabe physiologischer Gegebenheiten

Elan, Dublin
1. Whole animal models for oral drug absorption
2. Physiologically relevant dissolution testing

Universität Heidelberg
Untersuchung der Permeabilität von Antimykotika mit dem intestinalen Ringmodell.

** Helsinki, Finland
XV Helsinki University Congress of Drug Research
A decision tree for dissolution testing of immediate release products

** Melbourne, Australia
Dissolution '99, sponsored by FIP
Designing the dissolution test for an immediate release product: choice of medium

Heinrich Heine Universität, Düsseldorf
Lösungsverhalten als absorptionsbestimmender Schritt

** CRS, Hong Kong
JB Dressman, C Reppas
Physiological basis of the design of dissolution tests
CRS Asian meeting, Hong Kong December 1999 (C Reppas, speaker)

2000

**Universität Greifswald
Verbesserung der peroralen Bioverfügbarkeit schwer wasserlöslicher Substanzen

**Universität Saarland
Physiological dissolution tests
„Cell culture and other alternative methods for drug delivery research"

Vertex, Cambridge MA
Physiological aspects of drug absorption

2002

**University of Vienna
Die Bioäquivalenz - ist sie von Dissolution-Tests verhersagbar?
Montag, den 21.01.02

*+FIP, Mumbai, India
FIP, Bangalore, India
Setting up Dissolution tests for ER products: which media?

Aventis, Paris , March 18, 2002
Use of biorelevant dissolution media in developing new drugs

**CRS International symposium on scientific and regulatory aspects of dissolution and bioequivalence, Athens 12-14 April, 2002
Media simulating the upper GI tract

**AAPS, Washington DC, 16.09.2002
Orally administered dosage forms for targeted drug delivery in the GI tract

Bristol-Myers Squibb NJ, 19.09.2002
Oral delivery of poorly soluble drugs - how low can you go?

**Royal Pharmaceutical Society of Great Britain
British Pharmaceutical Conference, 23.09.2002
Biopharmaceutics: predicting properties, preventing problems: predictive dissolution systems

**AAPS, Annual Meeting and Exposition, Toronto, 13.11.02
Solubilizing options for toxicology studies:getting the drug in solution and keeping it there

**APV Dissolution Workshop für Fortgeschrittene, Nürnberg, 11/11.12.2002
Biorelevant dissolution testing

2003

**Federation Internationale Pharmaceutique (FIP) Workshop "Dissolution Technology and Biopharmacy"
Selection of a dissolution test medium, March 2003 (Bangkok)

**Federation Internationale Pharmaceutique (FIP) Workshop "Dissolution Technology and Biopharmacy"
Selection of a dissolution test medium and IVIVC, March 2003 (Ho Chi Minh City)

**APV Seminar:"Pellets – Grundlagen und aktuelle Entwicklungen"
"Biopharmazeutische Aspekte"; June 2003 (Bielefeld)
**CRS Symposium
Man, Animal and Glass: Are there correlations for oral drug absorption?
Controlled Release Society, July 2003 (Glasgow)

**FIP Symposium
Issues and Challenges in dissolution/in vitro release of drug products
Federation Internationale Pharmaceutique, September 2003 (Sydney)

**Dissolution workshop
"*Designing Dissolution Tests.I. General Aspects*
October 2003 (Brussels)
Industrial seminar
Development of in vitro methods that predict in vivo behavior for CR formulations with insoluble drugs
Alza Corp., October 2003 (Palo Alto)

Industrial Seminar
Characterization and development of poorly soluble drugs
TransForm Pharmaceuticals, October 2003 (Boston)

*Meeting of "Quality and Safety: Pharmaceuticals" Division
Dissolution/in vitro Release from Oral IR Drug Products"WHO, October 2003 (Geneva)

Industrial Seminar
Development of in vitro methods that predict in vivo behaviour of IR and CR formulations
Pfizer, November 2003 (Sandwich)

2004

***in vitro in vivo* correlations for oral drug products
Workshop onScientific and Regulatory Aspects of Bioequivalence: A to Z
FIP/AAPS/Indian Pharmaceutical Association, February 2004 (Goa, India)

**Dissolution enhancement of poorly soluble substances by hot melt extrusion
CRS Workshop, February 2004 (Mumbai, India)

**Development of in vitro methods that predict in vivo behaviour of CR formulations
CRS Workshop, February 2004 (Mumbai, India)

*Solubility: How low can you go?
European Drug Absorption Network, March 2004 (Leuven, Belgium)

Dissolution test to predict oral drug product behaviour
Merck Medicinal Chemists' Seminar, March 2004 (Bad Dürkheim)

**Development of in vitro methods that predict in vivo behaviour of CR formulations
CRS Annual Meeting, July 2004 (Honolulu, USA)
**Switchability of Drug Products: *Scientists vs. Lawmakers?*

2005

Applications of biorelevant dissolution testing

Strategies in Oral Drug Delivery 2005**
Garmisch-Patenkirchen (organized by the Drug Delivery Foundation in USA)

Prediction of the intestinal solubility of poorly soluble drugs
6th International Symposium on advances in Technology and business potential of new drug delivery systems**
CRS, Mumbai, India

Applications of biorelevant dissolution testing to poorly soluble compounds and their formulations
Soliqs, Ludwigshafen

1) Designing dissolution tests
2) Role of GI physiology in oral drug absorption
Dr. Reddy's, Hyderabad, India

Formulierungssyteme für Colonfreigabe
Effizienzsteigerung beim Filmcoating**
Würzburg (organized by the APV)

In vitro assessment of drug release from multi-particulate systems in relation to their in vivo behaviour
Modified Release Forum*
Heidelberg (organized by Colorcon)

Applications of biorelevant dissolution testing
Mahidol University, Bangkok, Thailand

Can we predict oral drug absorption in humans?
F. Hoffmann-LaRoche, Basel
F. Hoffmann-LaRoche, Nutley

Dissolution tests – how they relate to in vivo drug performance
Center for Drug Evaluation Research, Food and Drug Administration, USA

In vivo fate of colloids after oral administration
Colloidal drug carriers and the product applications**
Berlin (organized by the APV)

1) Freigabeprüfung für Qualitätskontrolle nach dem Arzneibuch
2) Methodenentwicklung für neue Arzneistoffe
Dissolution für Praktiker**
Nürnberg (organized by the APV)

2006

Can we predict oral drug absorption in humans?
Vertex, Boston, USA

Can we predict oral drug absorption in humans?
Unilever, Vlaardingen, The Netherlands

** *Using dissolution tests to predict performance of oral solid dosage forms*
Nagai Foundation, Tokyo, Japan

** *Can we predict oral drug absorption in humans?*
Nagai Foundation, Tokyo, Japan

Using dissolution tests to predict performance of poorly soluble drugs
Sankyo, Tokyo, Japan

Can we predict oral drug absorption in humans?
Astellas, Tokyo, Japan

** *in vitro dissolution systems: biorelevant dissolution tests and a priori prediction of plasma profiles*
EUFEPS Conference on "When poor solubility becomes an issue: from early stage to proof of principle", Verona, Italy

** *Factors affecting oral drug absorption in humans*
CRS Annual Meeting Workshop on Role of intestinal and hepatic transporters on oral bioavailability, Vienna, Austria

** *Can we predict oral drug absorption?*
University of North Carolina at Chapel Hill, USA

Biorelevant dissolution tests: state of the art
GlaxoSmithKline, Research triangle Park, USA

Use of biorelevant media in dissolution testing
Eli Lilly & Co., Indianapolis, USA

Zweckorientierte Methodenentwicklung für neue Arzneistoffe
Dissolution mit dem Ziel Biowaiver
Dissolution für Fortgeschrittene**
Dresden (organized by the APV)

2007

***Methodenentwicklung für neue Arzneistoffen*
University of Mainz, Mainz, Germany

Vorhersage des in vivo Verhaltens von MR-Produkte mittels biorelevanten Dissolutiontests
Grünenthal, Aachen, Germany

***Soluble Cellulose as Dietary Fiber in Human Nutrition and Health*
ACS, Chigaco, USA

Why do dissolution Testing?
***BCS based Biowaivers*
WHO Prequalification Workshop, Kiev, Ukraine

Design of dissolution testing in predicting drug absorption and optimizing formulation
F.Hoffmann-LaRoche, Nutley, NJ. USA and Basel, Switzerland

The Drug Absorption Process
Merck Inc, West Point Pennsylvania, USA

Dissolution Methods for Melt Extrusion Products
Leitstritz and Röhm Symposium, Nürnberg, Germany

****Solubility: how to predict it, how to measure it***
PhysChem Forum 4, Brussels, Belgium

****Methodenentwicklung für neue Arzneistoffe***
Tipps und Tricks
Dissolution für Praktiker**
Dresden (organized by the APV)

2008

Dissolution testing of oral dosage forms
Dr. Reddy's, Hyderabad India

Design of dissolution testing with a view to establishing IVIVC
Dr. Reddy's, Hyderabad India

Updated biorelevant media for dissolution testing of oral dosage forms
EDAN, Leuven Belgium

****Increasing Bioavailability: Biopharmaceutical aspects***
APV 6th World Meeting Barcelona (Plenary Lecture)

****Bioequivalence of oro-dispersible tablets: are standard tests appropriate for in vitro characterization?**
EUFEPS conference "New Regulations in Bioequivalence"
Bad Homburg, Germany

Biowaiver possibilities – A comparison of regulations in the US, Japan, EU and at the WHO
The role of biopharmaceutics in drug development
Invited lectures at the US-FDA, Washington DC

*In vitro-in Vivo relationships for melt extrusion dosage forms
Opening of the BASF Research Center, Ludwigshafen

****Overview of current FIP solid dosage forms White Paper**
FIP and RPSGB symposium: Special Dosage forms – what's new with release?
London

****Overview of biorelevant media and USP IV dissolution testing for drug development**
AAPS Symposium: Application of biorelevant USP dissolution methods in pharmaceutical development.
AAPS Annual Meeting, Atlanta USA

2009

*Development of on vitro in vivo correlations for novel dosage forms
National and Kapodistrian University of Athens
March, 2009

****Acceptable Predictivity and Biopharmaceutics tools**
FDA/AAPS/U-Wisconsin Workshop "Applied Biopharmaceutics and QbD for dissolution/release specification setting
Rockville, MD (USA)
June 2009

*Controlled release dosage forms: when and how?
Janssen NV, Beerse Belgium,

June 2009

*In vitro-in silico-in vivo tools to predict oral drug absorption
Novartis, Basel, Switzerland
September 2009

**Physicochemical parameters to predict oral drug absorption
Plenary Lecture
"First World Conference on physicochemical methods in drug discovery and development"
Rovinj, Croatia, September 2009

**Overview of strategies for formulation of poorly water soluble drugs
APV seminar "Modern concepts in pharmaceutical profiling and preformulation"
Berlin, October 2009

Predicting oral drug absorption: combining biorelevant media with pharmacokinetic simulation models
Merck & Co. West Point, PA (USA)
October 2009

**1) Why Dissolution is performed
2) BCS classification, screening of API properties
3) Bioequivalence of generic products: biowaivers
APV "Workshop on dissolution"
Wiesbaden, December 2009

2010

**Application of biorelevant dissolution testing to predicting plasma profiles
Mahidol University, Thailand, March 2010

*Poorly soluble compounds in oral formulations - proven and new solutions for pharmaceutical development
R.P.Scherer Symposium
Frankfurt am Main, June 2010

**The Challenge of Poorly Soluble Drugs: Formulation options
Drug Transport and Delivery Symposium
Swedish Academy of Pharmaceutical Sciences
Gothenburg June2010

Freigabeprüfung oraler Darreichungsformen 2010
BfARM, Bonn July, 2010

**Product approval using the Biowaiver in the EMA Guideline
APV workshop on the European Medicines Agency Guideline on Bioequivalence of Immediate release dosage forms, Titisee, June 2010

**Why is dissolution testing still needed?: Biorelevant dissolution testing"
FIP Annual Meeting Lisbon August 2010

**Approving generics without human bioequivalence studies – how far are we?– *In which cases can human studies be waived? The ground rules*
FIP Annual Meeting Lisbon August 2010

Poorly soluble compounds in oral formulations - proven and new solutions for pharmaceutical development

Grünenthal GmbH Aachen, September 2010

Biorelevant dissolution testing:an Update
Grünenthal GmbH Aachen, September 2010

Biorelevant *in vitro* methods for prediction of the *in vivo* performance of poorly soluble and weakly basic drugs
Novartis AG Basel, September 2010

**Standards for Essential Drugs: Biowaivers based on the BCS
PSWC 2010 New Orleans November 2010

**Advances in Dissolution Methodology and Application of IVIVC to biowaivers
PSWC 2010 New Orleans November 2010

**Predicting food effects from dissolution tests
PK-PD Expertentreffen 2011 (Heppenheim, April 2011)
Arbeitsgemeinschaft für Angewandte Humanpharmakologie e.V.

**Predicting bioequivalence from in vitro dissolution tests
International Symposium on BA/BE of oral drug products
FIP and Japanese Pharmaceutical Society (Kobe, Japan, June 2011)

Predicting bioequivalence from in vitro dissolution tests combined with PBPK modelling
Bayer Pharma AG (Wuppertal, September 2011)

**1) Freisetzungsprüfungen für Qualitätskontrolle. I. Schnellfreisetzende Produkte
2) Freisetzungsprüfungen für Qualitätskontrolle II. Produkte mit modifizierter Freisetzung
APV Basics - Dissolution (Darmstadt, November 2011)

Poorly soluble drugs: Developability, formulation selection and prediction of *in vivo* performance
One Day pRED Formulation Research Mini-Symposium
F. Hoffmann LaRoche (Basel, November 2011)

2012

**Verwendung *in vitro-in silico-in vivo* Modellen zur Vorhersage der peroralen Resorption
DPhG, Univeristy of Braunschweig (Braunschweig, January 2012)

Predicting Plasma Profiles from *in vitro* dissolution tests coupled with PBPK Models
Stada (Bad Vilbel, February 2012)

*Integrating dissolution data in PBPK models: Case example Dantrolene sodium
European Drug Absorption Network (Leuven, March 2012)

** The Why and How of Bioequivalence Testing
AAPS/FIP International Symposium on bioequivalence testing
(Bangkok, Thailand August 2012)

**Product approval using the Biowaiver in the WHO Guideline
AAPS/FIP International Symposium on bioequivalence testing
(Bangkok, Thailand August 2012)

**IVIVC – alternative methods using PBPK modeling and role of IVIVC in Quality by Design
AAPS/FIP International Symposium on bioequivalence testing

(Bangkok, Thailand August 2012)

**Review of GI physiology and use of biorelevant media
PQRI Workshop on Application of IVIVC in Formulation Development
(Bethesda, USA September 2012)

**What does the future hold for biowaiver-based drug approval?
Symposium on Biowaiver Monographs, FIP Centennial Meeting
(Amsterdam, October 2012)

***Linking the lab to the patient:* Predicting Plasma Profiles from biorelevant dissolution tests coupled with PBPK Models
Workshop on Oral Bioperformance and 21st Century Testing
AAPS Annual Meeting (Chicago, October 2012)

**The BCS Concept and its Application in Pharmaceutical Development
Drug development and registration: «Pharma-2020» strategy realization
I.M. Sechenov First Moscow State Medical University (Moscow, October 2012)

***Linking the lab to the patient:* Predicting food effects from biorelevant dissolution tests coupled with PBPK Models
APV Workshop on Use of DissolutionTesting to Predict *in vivo* Performance of Oral Dosage forms (Berlin, November 2012)

**Preclinical in vitro testing: bridging the testing of formulations in preclinical development to the clinic using biorelevant media
APV Seminar Successful early stage development of pharmacueticals (Darmstadt March, 2013)

** Gastrointestinal physiology and biorelevant in vitro performance testing of orally administered drug products: what and why?
AAPS Workshop Biorelevant in vitro performance testing of orally administered dosage forms
(Washington DC March, 2013)

*Dissolution media simulating the proximal canine gastrointestinal tract in the fasted state and its application to in vitro studies and in silico modeling
FDA Veterinary Medicine Section (Bethesda Maryland, March 2013)

*IVISIV for lipid based formulations of fenofibrate
European Drug Absorption Network (Leuven, March 2013)

*Unlocking the value of drug candidates using physicochemical data to predict plasma profiles
SCINOVA conference (Stevenage April 2013)

**In vitro - in silico - in vivo* relationships: a way forward to optimizing oral drug performance?
Ludwig Maximilian University (München June 2013)

*Proposed revisions to the WHO Guidance on Approval of multisource drug products
48th Meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations (Geneva, October 2013)

**Scenario 3: APIs requiring a targeted window of release or consideration of chronotherapeutics
AAPS Workshop on developing a Biopharmaceutics Risk Assessment Roadmap
AAPS Annual Meeting (San Antonio, November 2013)

*Conditions under which drugs are exposed in the gastrointestinal tract
European Medicines Agency Invited Training on predicting in vivo performance of oral drugs
products (London, December 2013)

Surface Activity Profiling: *prediction of biological membrane penetration?*
Boehringer Ingelheim, (Biberach an der Riss, January 2014)

**Medicines eligible for biowaivers, examples of justification of biowaivers. What does the future hold for biowaiver-based medicine approval?
**Physiology of GI Tract and biorelevant dissolution media
Pharmaceutical Science, Medicine Registration and Control: "A scientific approach"
Southern African Regional and International Symposium (March 2014)

*Mesoporous silica as a carrier for drugs: the Merck Experience
Merck Millipore, (Darmstadt, March 2014)

**The Role of Biopharmaceutics Tools in Quality by Design
FIP Pharmaceutical Sciences World Congress, (Melbourne, April 2014)

**Combining Biorelevant Dissolution Testing with PBPK Modeling to Forecast Oral Drug Absorption
Third Galenus Workshop: Predictive Dissolution Testing – News and Views
(Greifswald, July 2014)

**Improving formulations to improve patient access to medicines
Annual Meeting of the FIP, (Bangkok, September 2014)

*Simulating food effects by dissolution methodology
OrBiTo Workshop on Predictive Biopharmaceutic Methods in Drug Discovery and Oral Product Development (Mainz, September 2014)

**Connecting oral formulation performance to therapeutic effect: ibuprofen as an example
DPhG Annual Meeting, (Frankfurt, September 2014)

**Challenges and benefits of using PBPK to evaluate an IVIVC for drugs with non-ideal solubility and/or permeability
PKUK, (Bath, November 2014)

**International workshop on implementation of biowaivers based on the biopharmaceutics classification system (BCS), Sponsored by FIP and AAPS,
(Buenos Aires March 2015)

1. Coupling dissolution with PBPK modelling for predicting in vivo behaviour
2. The Biowaiver monographs
3. Solubility data and requirements for biowaiving
4. Comparison of EMA WHO and FDA Biowaiver guidances

*Merck Millipore Workshop (Darmstadt, March 2015)
Mesoporous silica as a carrier for poorly soluble drugs

** Navigating the Biopharmaceutics Risk Assessment Road Map (BioRAM): Therapy-Driven QTPP Strategies for Clinically Relevant-Specification Setting
Sponsored by FDA and AAPS (Washington DC, April 2015)
Impact of BioRAM for enhancing patient benefit according to therapy-driven drug delivery scenarios, and learn and confirm studies for feasibility assessments

** Gordon Conference on Preclinical Form & Formulation for Drug Discovery
Plenary Speaker (Waterville NH, June 2015)
Linking the Lab to the Patient: Strategies for Combining *In Vitro* and *In Silico* Tools to Predict Performance of Orally Administered Drugs

** ACHEMA German-Japanese Symposium (Frankfurt am Main, June 2015)
Coupling biorelevant dissolution with physiologically based pharmacokinetic modelling to predict *in vivo* drug performance after oral administration

**FIP Annual Meeting (Bangkok, November 2015)
A Tale of Two Weak Bases: Influence of precipitation characteristics on in vivo behaviour

* conference/meeting with invited participation
** open conferences, meetings sponsored by scientific organizations

SHORT COURSES AND WORKSHOPS (ORGANIZER AND/OR SPEAKER)

University of Michigan,1987 (co-organizer, speaker)
Short course: Strategies for drug delivery

Center for Professional Advancement (main speaker)
Short course: Chemical degradation in pharmaceuticals

Merck, 1993 (organized and main speaker)
Short course: Role of gastrointestinal physiology in oral drug absorption

University of Michigan, 1993 (co-organizer, speaker)
Short course: Gastrointestinal drug absorption

University of Uppsala, Sweden, 1994 (speaker)
Short course: Biopharmaceutics and pharmacokinetics strategies for oral drug delivery

Athens, 1996 (co-organizer)
Satellite to Sixth European Congress on Biopharmaceutics and Pharmacokinetics
Workshop: Methods for assessing oral drug absorption

Ascona, 1996 (speaker)
sponsored by ETH, Zurich
Short course: Biopharmaceutics and pharmacokinetics strategies for oral drug delivery

Eschborn, 1996 (co-organizer, speaker)
sponsored by ZL
Workshop: Dissolution Workshop

Boston, 1997 (speaker)
sponsored by AAPS
Symposium: Models for oral drug absorption

APV/AAPS/CRS/EUFEPS/FDA, Frankfurt am Main, 1998 (organizer, speaker)
Symposium: Biopharmaceutics classification system and in vitro/in vivo correlations

GlaxoWellcome, Verona 1998 (organizer, main speaker)
Short course: Oral Drug Absorption

- •Factors affecting drug absorption
- •Introduction to the BCS
- •Design of physiologically based dissolution tests

Bad Soden, 1999 (April and November) (co-organizer, speaker)
Dissolution Workshop sponsored by APV 'Dissolution für Praktiker'
Praxisrelevanten Methodenentwicklung unter Maßgabe physiologischer Bedingungen

APV/AAPS/CRS/EUFEPS/FDA, Frankfurt am Main, 1999 (organizer)
Workshop: Challenges in the design and evaluation of bioequivalence studies

Dissolution '99 workshop (co-organizer)
Short course sponsored by FIP, Melbourne, Australia

University of Frankfurt, Frankfurt 2000 (co-organizer, speaker)
APV University Short Course
Gastrointestinal physiology and drug absorption

APV/AAPS, Berlin, 2000 (co-organizer)
Workshop: Bioequivalence of special dosage forms

Universität Saarland, Saarbrücken 2000 (speaker)
Short course „Cell culture and other alternative methods for drug delivery research“
Physiological dissolution tests

West Point, PA and Rahway, NJ 2001 (main speaker)
Short course sponsored by Merck & Co.
Oral Drug Absorption

FIP, India 2001 (co-organizer, speaker)
“Hands-On” Dissolution Workshop

APV Dissolution Workshop für Fortgeschrittene
Nürnberg, 10/11.12.2002 (co-organizer, speaker)

AAPS, Washington DC 2002 (co-organizer, speaker)
Workshop: Dissolution from Special Dosage Forms (with FIP)

FIP, Thailand and Vietnam 2003 (co-organizer, speaker)
“Hands-On” Dissolution and Bioequivalence Workshop

EDAN, Frankfurt am Main 2003 (co-organizer)
Conference: European Drug Absorption Network (with Lilly Belgium and U-Leuven)

EDAN, Leuven 2004 (co-organizer, speaker)
Conference: European Drug Absorption Network (with Lilly Belgium and U-Leuven)

CRS, Honolulu, USA 2004 (co-organizer)
Workshop on Dissolution of Oral Dosage Forms

APV “Dissolution Workshop für Praktiker” (Co-organizer and speaker)
Nürnberg, December 2004

Drug Delivery Foundation, Garmisch-Patenkirchen 2005 (speaker)
Workshop: Strategies in oral drug delivery

EDAN, Leuven 2005 (co-organizer)
Conference: European Drug Absorption Network (with Lilly Belgium and U-Leuven)

CRS, Miami USA 2005 (Organizer and Speaker)
“Colon Targeting for Systemic and Local Delivery”

APV “Dissolution Workshop für Praktiker” (Co-organizer and speaker)
Nürnberg, December 2005

EUFEPS Verona, Italy 2006 (speaker)
Conference on “When poor solubility becomes an issue: from early stage
to proof of principle”,

CRS Vienna, Austria 2006 (speaker)
Workshop on “Role of intestinal and hepatic transporters on oral bioavailability”

University of Tübingen (speaker)
Blockseminar “Biopharmazie”
Tübingen 2006

APV “Dissolution Workshop für Fortgeschrittene” (co-organizer and speaker)
Dresden, December 2006

APV "Dissolution Workshop für Praktiker" (Co-organizer and speaker)
Dresden, December 2007

AAPS Symposium: Application of biorelevant USP dissolution methods in pharmaceutical development. (Co-organizer and Speaker)
AAPS Annual Meeting, Atlanta USA 2008

Nycomed
Dissolution Workshop (Organizer and Speaker)
Constance, April 2009

**FDA/AAPS/U-Wisconsin Workshop "Applied Biopharmaceutics and QbD for dissolution/release specification setting (Co-Organizer and Speaker)
Rockville, MD (USA), June 2009

Pfizer, Inc
Dissolution workshop (Organizer and speaker)
Sandwich, June 2009

**APV "Workshop on dissolution" (Organizer and Speaker)
Wiesbaden, December 2009

2010

**Application of biorelevant dissolution testing to predicting plasma profiles
Mahidol University, Thailand, March 2010

*Poorly soluble compounds in oral formulations - proven and new solutions for pharmaceutical development
R.P.Scherer Symposium
Frankfurt am Main, June 2010

**The Challenge of Poorly Soluble Drugs: Formulation options
Drug Transport and Delivery Symposium
Swedish Academy of Pharmaceutical Sciences
Gothenburg June2010

Freigabeprüfung oraler Darreichungsformen 2010
BfARM, Bonn July, 2010

**Product approval using the Biowaiver in the EMA Guideline
APV workshop on the European Medicines Agency Guideline on Bioequivalence of Immediate release dosage forms, Titisee, June 2010

**WHY IS DISSOLUTION TESTING STILL NEEDED?: Biorelevant dissolution testing"
FIP Annual Meeting Lisbon August 2010

**APPROVING GENERICS WITHOUT HUMAN BIOEQUIVALENCE STUDIES - HOW FAR ARE WE? – *In which cases can human studies be waived? The ground rules*
FIP Annual Meeting Lisbon August 2010

Poorly soluble compounds in oral formulations - proven and new solutions for pharmaceutical development
Grünenthal GmbH Aachen, September 2010

Biorelevant dissolution testing:an Update

Grünenthal GmbH Aachen, September 2010

Biorelevant *in vitro* methods for prediction of the *in vivo* performance of poorly soluble and weakly basic drugs
Novartis AG Basel, September 2010

**Standards for Essential Drugs: Biowaivers based on the BCS
PSWC 2010 New Orleans November 2010

**Advances in Dissolution Methodology and Application of IVIVC to biowaivers
PSWC 2010 New Orleans November 2010

2011

**Predicting food effects form dissolution tests
PK-PD Expertentreffen 2011 (Heppenheim, April 2011)
Arbeitsgemeinschaft für Angewandte Humanpharmakologie e.V.

**Predicting bioequivalence from in vitro dissolution tests
International Symposium on BA/BE of oral drug products
FIP and Japanese Pharmaceutical Society (Kobe, Japan, June 2011)

Predicting bioequivalence from in vitro dissolution tests combined with PBPK modelling
Bayer Pharma AG (Wuppertal, September 2011)

**1) Freisetzungsprüfungen für Qualitätskontrolle. I. Schnellfreisetzende Produkte
2) Freisetzungsprüfungen für Qualitätskontrolle II. Produkte mit modifizierter Freisetzung
APV Basics - Dissolution (Darmstadt, November 2011)

Poorly soluble drugs: Developability, formulation selection and prediction of in vivo performance
One Day pRED Formulation Research Mini-Symposium
F. Hoffmann LaRoche (Basel, November 2011)

2012

** International Symposium on bioequivalence testing (co-organizer and speaker)
AAPS/FIP (Bangkok, Thailand August 2012)

**PQRI Workshop on Application of IVIVC in Formulation Development
(co-organizer and speaker)
Co-sponsored with FDA, USP, and FIP (Bethesda, USA September 2012)

**FIP Symposium on Biowaiver Monographs (Organizer and speaker)
FIP Centennial Meeting (Amsterdam, October 2012)

**APV Workshop on Use of DissolutionTesting to Predict *in vivo* Performance of Oral Dosage forms (Organizer and Speaker)
(Berlin, November 2012)

2013

**AAPS Workshop on Developing a Biopharmaceutics Risk Assessment Road Map
(Organizer and Speaker)
AAPS Annual Meeting (San Antonio, November 2013)

2014

**FIP Symposium on Technological approaches to improving patient access to medicines
Annual Meeting of FIP (Organizer and Speaker)
(Bangkok, September 2014)

**DPhG Annual Meeting
Symposium on Optimizing oral drug performance (Organizer and Speaker)
(Frankfurt am Main, September 2014)

2015

**International workshop on implementation of biowaivers based on the biopharmaceutics classification system (BCS), Buenos Aires March 2015
(Co-Organizer)

** Navigating the Biopharmaceutics Risk Assessment Road Map (BioRAM): Therapy-Driven QTPP Strategies for Clinically Relevant-Specification Setting Sponsored by FDA and AAPS (Washington DC, April 2015)
(Co-Organizer)

Current Teaching Responsibilities

7th Semester Pharmaceutics course in "Biopharmaceutics and dosage form driven pharmacokinetics". I taught this course in its entirety, two lectures per week and two seminar hours per week from 2002 till 2017 and will resume the course in Fall 2018.

Ring lectures (3 semesters in the 5th, 6th and 7th semesters of the Pharmacy degree) on "Pharmaceutical technology". I teach this course in its entirety, 2-3 lectures a week over three semesters.

8th Semester Pharmacy Seminars on "Utilization of drugs in pharmacy practice". Team taught course (ten professors, each serves as a mentor for a group of students preparing a presentation on a themed topic. Recent examples have included hormone therapy and blockbuster drugs).

8th Semester Pharmacy elective courses. I offer electives in "Good Manufacturing Practice" and in "Waiver of *in vivo* bioequivalence studies".

Institute seminar series for graduate students in Pharmaceutical Technology
Special topics in pharmaceutics, I initiated and organize this seminar series, which occurs once a week during semester.

State examinations: registered examiner for the 2nd (Pharmacy degree) oral examinations in Pharmaceutical Technology and the 3rd (Pharmacy registration) oral examinations.

Appendix B. List of Material Considered

1. IPR2017-01648 Paper 08, Corrected Petition for IPR of US 6,866,866.
2. IPR2017-01648 Paper 11, Patent Owner Preliminary Response.
3. IPR2017-01648 Paper 12, Decision on Institution.
4. IPR2017-01648 Paper 22, Joint Motion to Limit the Petition.
5. IPR2017-01648 Paper 23, Order Granting Joint Motion to Limit the Petition.
6. IPR2017-01648, Exhibits 1001-1020.
7. IPR2017-01648, Exhibits 2001-2002.
8. IPR2017-01648, Exhibit 2004, Basson *et al.*, Pharmaceutical Research, Vol. 15, No. 2, 1998, 276-279.
9. IPR2017-01648, Exhibit 2005, FDA Guidance for Industry: Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs — General Considerations.
10. IPR2017-01648, Exhibit 2006 (https://www.certara.com/2013/02/11/why-cmax-is-a-continuous-variable-and-tmax-is-a-categorical-variable/?).
11. IPR2017-01648, Exhibit 2007, Basson *et al.*, Pharmaceutical Research, Vol. 13, No. 2, 1996, 324-328.

12. IPR2017-01648, Exhibit 2008, Keraliya, *et al.*, ISRN Pharmaceutics, Volume 2012, 2012, 1-9.

13. IPR2017-01648, Exhibit 2009, Vidon, *et al.*, *Diabetes Research and Clinical Practice*, 4, 1988, 223-229.

14. IPR2017-01648, Exhibit 2011, Deposition Transcript of Dr. Akhlaghi.