UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

FRESENIUS KABI USA, LLC,
Petitioner

v.

CEPHALON, INC.,
Patent Owner

Case IPR2016-00098
Patent No. 8,791,270

DECLARATION OF BERNARD OLSEN, Ph.D., UNDER 37 C.F.R. § 1.68 IN SUPPORT OF PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 8,791,270

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I, Bernard Olsen, Ph.D. hereby declare as follows:

I. INTRODUCTION

1. I have been retained as an expert witness on behalf of Fresenius Kabi USA, LLC ("Fresenius") for the above-captioned Petition for *Inter Partes* Review ("IPR") of U.S. Patent No. 8,791,270 ("the '270 patent"). I am being compensated for my time in connection with this IPR at my standard consulting rate of $400 per hour. My compensation is in no way dependent on the outcome of this matter.

2. I have been asked to provide my opinions regarding whether claims 1-23 of the '270 patent are invalid, as anticipated by the prior art, or would have been obvious to a person having ordinary skill in the art at the time of the alleged invention.

3. The '270 patent issued on July 29, 2014, from U.S. Patent Application No. 13/969,724 ("the '724 Application"), filed on August 19, 2013. Exhibit 1001, the '270 patent. The face of the patent indicates Jason Edward Brittain and Joe Craig Franklin as the named inventors. The '270 patent is a continuation of U.S. Patent Application No. 13/719,409, filed December 19, 2012, which is a continuation of U.S. Patent Application No. 13/654,898, filed on October 18, 2012, which issued as U.S. Patent No. 8,461,350 ("the '350 patent"), which is a continuation of U.S. Patent Application No. 11/330,868, filed on January 12, 2006, which issued as U.S. Patent No. 8,436,190 ("the '190 patent").

4. In preparing this Declaration, I have reviewed the '270 patent, the file history of the '270 patent, and numerous prior art references from the time of the alleged invention.

5. I have been advised and it is my understanding that patent claims in an IPR are given their broadest reasonable construction in view of the patent specification, file history, and the understanding of one having ordinary skill in the relevant art at the time of the purported invention.

6. In forming the opinions expressed in this Declaration, I relied upon my education and experience in the relevant field of the art, and have considered the viewpoint of a person having ordinary skill in the relevant art, as of 2005. My opinions directed to the invalidity of claims 1-23 of the '270 patent are based, at least in part, on the following prior art publications:

Reference	Date of Public Availability
Maas, *Stability of Bendamustine Hydrochloride in Infusions*, 49 PHARMAZIE 775 (1994)	Maas was published in 1994, and the German language original and certified English translation are attached as Exhibit 1004 to the IPR.
Teagarden, *Practical aspects of lyophilization using non-aqueous co-solvent systems*, 15 EUR. J. PHARM. SCI. 115 (March 2002)	Teagarden was published in March 2002, and is attached as Exhibit 1005 to the IPR.
Gust, *Investigations on the Stability of Bendamustin, a*	Gust was published in 1997, and is

Cytostatic Agent of the Nitrogen Mustard Type, I. Synthesis, Isolation, and Characterization of Reference Substances, 128 MONATSHEFT FÜR CHEMIE 291 (1997)	attached as Exhibit 1006 to the IPR.
The Ribomustin® Product Monograph, 2002	The Ribomustin® Product Monograph was published in 2002, and is attached as Exhibit 1007 to the IPR.

II. BACKGROUND AND QUALIFICATIONS

7. I am currently an independent pharmaceutical consultant in Wake Forest, North Carolina. I received my Ph.D. in analytical chemistry from the University of Wisconsin-Madison. I also have an undergraduate degree in chemistry from Nebraska Wesleyan University.

8. After receiving my doctorate, I worked in the pharmaceutical industry for twenty-nine years at Eli Lilly and Company, where I achieved the rank of Senior Research Fellow. At Eli Lilly, I held a variety of senior research positions in the areas of analytical and bioanalytical development and chemistry.

9. I have supported the development and/or manufacture of more than twenty-five marketed products. I have extensive experience in the development and use of high-performance liquid chromatography (HPLC) methods. For over twenty years, on nearly a daily basis, I performed hands-on development and analysis using HPLC, employing seven different modes of HPLC. These analyses

included determination of purity and impurities in drug substances, drug products, intermediates, and starting materials to generate development information and for quality control purposes.

10. I have been involved in many activities within the scientific community. I am a member of the American Chemical Society (Analytical Division) and the American Association of Pharmaceutical Scientists (AAPS). In 2010, I was elected as a Fellow of the AAPS. For ten years, I have served on the United States Pharmacopeia as an expert committee member for monograph development and, in 2010 and 2015, was elected to chair an expert committee. I am a reviewer for the *Journal of Chromatography A* and the *Journal of Pharmaceutical and Biomedical Analysis*. I am also on the Editorial Advisory Board of the *Journal of Pharmaceutical and Biomedical Analysis*. From 2007 to 2010, I served as an adjunct professor in the Department of Industrial and Physical Pharmacy at Purdue University.

11. I have delivered over eighty-three external presentations, including many invited presentations at international venues. Many of my conference and workshop presentations have been on the development or use of high-performance liquid chromatography (HPLC) methods. I have also authored or co-authored fifty-one publications, including nine invited papers, eight book chapters, and an edited book. Many of these publications have directly focused on topics and

techniques in analytical chemistry, including over twenty papers on HPLC. The book I co-edited was on hydrophilic interaction chromatography, a form of HPLC.

12. A more detailed description of my background and qualifications is provided in my *curriculum vitae* (attached hereto as **Exhibit A**). A list of other cases in which I have testified as an expert at trial or by deposition during the previous four years is attached as **Exhibit B**.

III. MATERIALS CONSIDERED FOR THIS DECLARATION

13. In addition to my general knowledge, education, and experience, I considered the materials listed in **Exhibit C** in forming my opinions.

IV. BACKGROUND

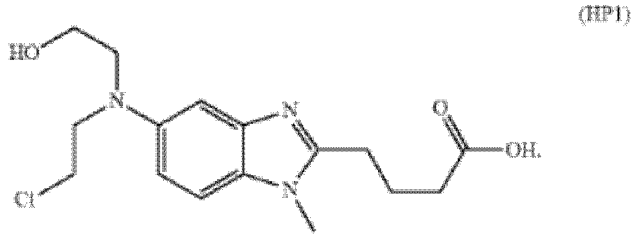
A. Overview of the '270 Patent

14. The '270 patent was filed on August 19, 2013, and issued on July 29, 2014. According to the Abstract, the '270 patent is directed generally to "pharmaceutical formulations of lyophilized bendamustine suitable for pharmaceutical use." Exhibit 1001 at Abstract.

15. The '270 patent acknowledges that pharmaceutical formulations of bendamustine hydrochloride were previously known and used in Germany. *Id.* at 2:1-10. In particular, formulations such as Cytostasan® and Ribomustin® had "been widely used in Germany to treat chronic lymphocytic leukemia, Hodgkin's disease, non-Hodgkin's lymphoma, multiple myeloma, and breast cancer." *Id.* at 2:5-10. The '270 patent also acknowledges that nitrogen mustards such as

bendamustine hydrochloride "are subject to degradation by hydrolysis." *Id.* at 1:45-50.

16. The '270 patent asserted that its improvement over this established prior art was a "better impurity profile than Ribomustin® with respect to certain impurities, in particular HP1 . . . and bendamustine ethylester . . . ." *Id.* at 12:31-38. The '270 patent, as issued, includes the following claims:

> 1. A pharmaceutical composition that has been reconstituted from a lyophilized preparation of bendamustine or bendamustine hydrochloride, said composition containing not more than about 0.9% (area percent of bendamustine) of HP1:
>
> 
>
>
> 2. The pharmaceutical composition of claim 1, wherein the amount of HP1 is measured at time zero after reconstitution of said lyophilized preparation.
>
> 3. The pharmaceutical composition of claim 1, wherein the amount of HP1 is not more than 0.5% (area percent of bendamustine).
>
> 4. The pharmaceutical composition of claim 2, wherein the amount of HP1 is not more than 0.5% (area percent of bendamustine).
>
> 5. The pharmaceutical composition of claim 1, wherein the amount of HP1 is not more than 0.4% (area percent of bendamustine).

6. The pharmaceutical composition of claim 2, wherein the amount of HP1 is not more than 0.4% (area percent of bendamustine).

7. A pharmaceutical composition of bendamustine hydrochloride, containing less than or equal to 4.0% (area percent of bendamustine) of bendamustine degradants.

8. The pharmaceutical composition of claim 7, containing between about 2.0% and 4.0% (area percent of bendamustine) of bendamustine degradants.

9. The pharmaceutical composition of claim 8, wherein the pharmaceutical composition has been reconstituted from a lyophilized preparation of bendamustine hydrochloride.

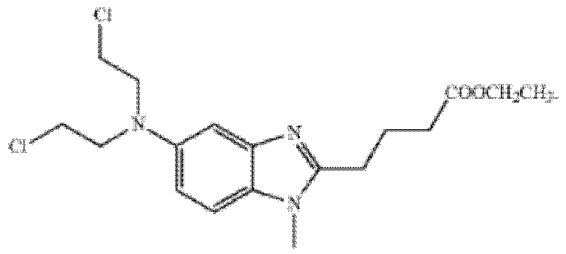
10. The pharmaceutical composition of claim 9, containing not more than about 0.9% (area percent of bendamustine) of HP1 at time zero after reconstitution.

11. The pharmaceutical composition of claim 9, containing not more than about 0.5% (area percent of bendamustine) of HP1 at time zero after reconstitution.

12. The pharmaceutical composition of claim 9, containing not more than about 0.4% (area percent of bendamustine) of HP1 at time zero after reconstitution.

13. The pharmaceutical composition of claim 10, containing not more than about 0.5% (area percent of bendamustine) of a compound of Formula IV at time zero after reconstitution:

Formula IV



14. The pharmaceutical composition of claim 7, wherein the pharmaceutical composition is a lyophilized composition.

15. The pharmaceutical composition of claim 8, wherein the pharmaceutical composition is a lyophilized composition.

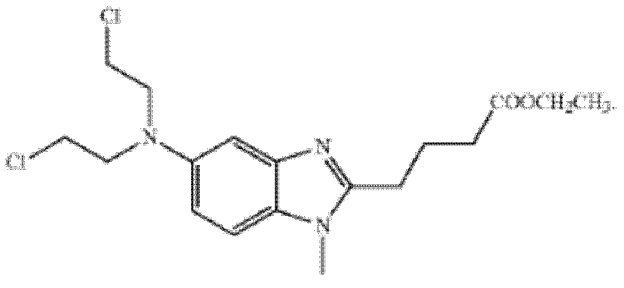
16. The pharmaceutical composition of claim 7, containing not more than about 0.9% (area percent of bendamustine) of HP1.

17. The pharmaceutical composition of claim 7, containing not more than about 0.5% (area percent of bendamustine) of HP1.

18. The pharmaceutical composition of claim 7, containing not more than about 0.4% (area percent of bendamustine) of HP1.

19. The pharmaceutical composition of claim 7, containing not more than about 0.5% (area percent of bendamustine) of a compound of Formula IV:

Formula IV



20. A method of treating cancer in a patient comprising administering to the patient a pharmaceutical composition of bendamustine hydrochloride according to claim 7.

21. The method according to claim 20, wherein the cancer is chronic lymphocytic leukemia, Hodgkin's disease, non-Hodgkin's lymphoma, multiple myeloma, or breast cancer.

22. The method according to claim 20, wherein the cancer is chronic lymphocytic leukemia.

23. The method according to claim 20, wherein the cancer is non-Hodgkin's lymphoma.

17. There appears to be some inconsistency between Cephalon's assertion with respect to alleged improved impurity levels and the specification of the '270 patent. In particular, Table 13 of the '270 specification includes the following impurity data for Ribomustin®:

TABLE 13

Ribomustine Impuirty Profile using HPLC Method 3
% Area

Batch	Bendamustine (HCl)	HP1	BM1EE	BM1 Dimer	BM1DCE
03H08	98.14	1.07	0.21	0.34	0.03
03H07	97.67	1.5	0.2	0.33	0.04
02K27	96.93	0.93	0.29	1.18	0.08
03C08	97.61	1.24	0.19	0.46	0.02

Exhibit 1001 at Table 13. As shown above, a number of the claims (*e.g.*, claims 7, 8, 13-15, and 19) appear to encompass the impurity profile for Ribomustin® rather

than "improve" the impurity level.

B. Overview of the Prosecution History of the '270 Patent

18. As noted above, the application that matured into the '270 patent was filed on August 19, 2013. Cephalon received Track One (accelerated) review from the Patent Office.

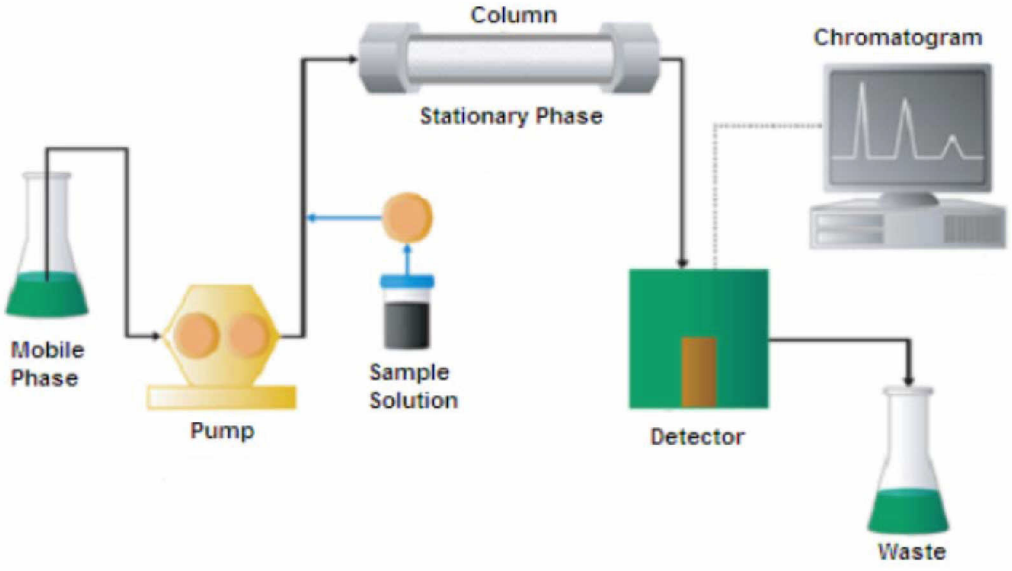
19. Claims 1-23 were issued without any substantive rejections over the prior art. Moreover, the Examiner's reasons for allowance appear to be inconsistent with the claims themselves:

> The prior art suggests using a combination of mannitol and tertiary-butyl alcohol with bendamustine to produce a formulation to be lyophilized. However, Applicant has unexpectedly found that the addition of a solvent stabilizes the formulation such that bendamustine degradation is negligible (no more than 0.5% formation of bendamustine ethyl ester).

Exhibit 1003 at 0300. In particular, these stated reasons for allowance appear to apply only to the claims reciting the bendamustine ethyl ester degradant (2 out of 23 claims). Moreover, the Examiner's reasons for allowance do not acknowledge that a number of the claims appear to encompass the Ribomustin® impurity profile that Cephalon sought to distinguish during prosecution.

V. OVERVIEW OF HIGH PERFORMANCE LIQUID CHROMATOGRAPHY (HPLC)

20. High-performance liquid chromatography (HPLC) is a technique used in the pharmaceutical, biomedical, and chemical sciences for the separation, identification, and quantitation of components in samples. The diagram below provides a generalized depiction of how HPLC works.[1]



21. HPLC is performed by passing a liquid called the "mobile phase" through a tube (or "column") that is packed with solid particles called the "stationary phase." A small volume of the sample to be analyzed is prepared in a solution and introduced into the flowing mobile phase. A high pressure pump moves the sample and mobile phase through the column containing the stationary phase particles. The liquid exiting the column (called the "eluate") is passed

[1] The diagrams in this declaration are modified graphics from the website of Waters Corporation, an analytical instrument company: http://www.waters.com/waters/nav.htm?cid=10049055.

through a detector. A "chromatogram" is generated based on the data from the detector. I discuss each of these steps in more detail below.

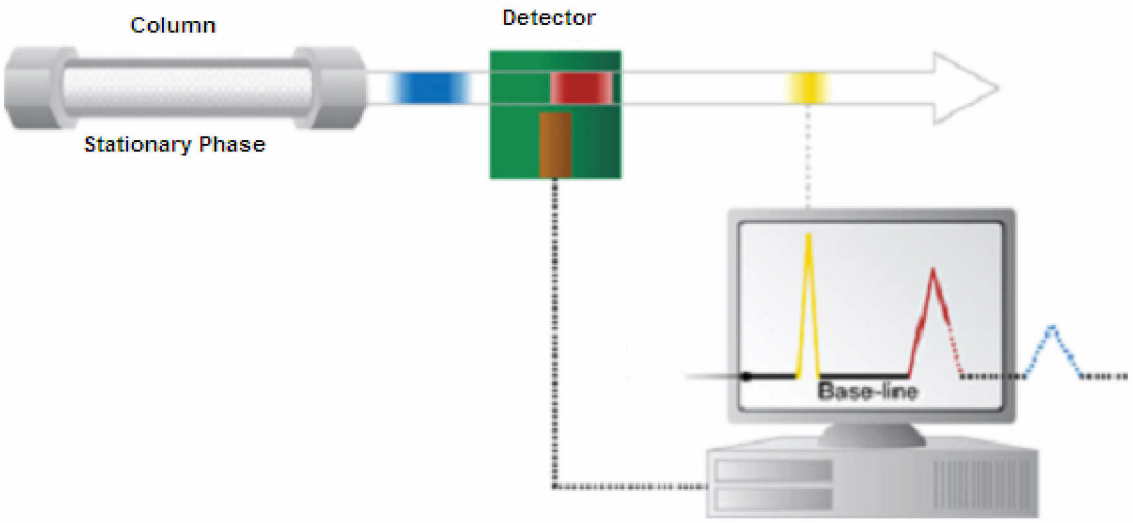
22. The components of the sample will interact differently with the stationary phase as they are carried through the column by the mobile phase. The interactions will differ because they depend on the chemical nature of each component, as well as the chemical nature of the stationary phase and mobile phase being used, among other variables. These different interactions provide the basis for separating the components in the sample.

23. In a given mobile phase, components that interact more strongly with the stationary phase will take longer to pass through the column than components that have weaker interactions. Some components may not emerge from the column at all. As the mobile phase flows through the column, the components of the sample travel at different speeds, and separate to different degrees depending on their chemical interactions with the column.

24. A detector analyzes the components of the sample that leave the other end of the column in the eluate. There are many types of HPLC detectors. For example, some detectors are based on measuring the absorption of ultraviolet light by the sample components in the eluate. Other types of detectors use refractive index, fluorescence, electrical conductivity, mass spectrometry, or evaporative light scattering. Depending on the detection method and the properties of the

sample components, some sample components in the eluate may not be detected. Components also will not be detected if they do not emerge from the column under the HPLC conditions used.

25. The detector provides a response as each component passes out of the end of the column. The level of detector response generally depends on the amount of material passing through it.



26. The detector is often connected to a computer that records the level of detector response (as compared to a baseline level) over time. The data output of HPLC is usually a chromatogram, which the computer generates by plotting the level of detector response over time as the components pass through the detector. In other words, the horizontal axis of the chromatogram corresponds to time. The vertical axis corresponds to the detector response level. The chromatogram often appears as a series of "peaks." As components pass through the detector, the

magnitude of the detector response typically rises and falls, forming peaks on the chromatogram.

VI. LEVEL OF ORDINARY SKILL IN THE PERTINENT ART

27. I have been advised that there are multiple factors relevant to determining the level of ordinary skill in the pertinent art, including the educational level of active workers in the field at the time of the invention, the sophistication of the technology, the type of problems encountered in the art, and the prior art solutions to those problems.

28. It is my opinion that a person having ordinary skill in the relevant art at the time of invention would have a Ph.D. in pharmaceutics, analytical chemistry, or a related field, with at least three years of practical experience in formulating and/or analyzing pharmaceutical formulations.

VII. BROADEST REASONABLE CONSTRUCTION

29. I have been advised that Fresenius has proposed the following constructions under the broadest reasonable interpretation:

Term	Broadest Reasonable Construction
"pharmaceutical composition"	"a composition that is made under conditions such that it is suitable for administration to humans"
"pharmaceutical composition that has been reconstituted"	"[pharmaceutical composition] (as construed above) that has been dissolved in a solvent or diluent"

"area percent of bendamustine"	"the amount of a specified degradant relative to the amount of bendamustine"
"bendamustine degradants"	"chemical compounds resulting from a change in chemical structure of bendamustine"
"time zero after reconstitution"	"soon after dissolution in a solvent or a diluent"

30. I have asked to apply several alternative constructions with respect to certain terms. For "pharmaceutical composition that has been reconstituted," I will also analyze that term under the alternative constructions of "pharmaceutical composition that has been dissolved in a solvent and that is suitable for medical administration" and "pharmaceutical composition that has been dissolved in a solvent."

31. With respect to "time zero after reconstitution," I understood that "soon after dissolution in a solvent or diluent" has been understood to refer to "the first measurement taken as soon as reasonably practicable" after reconstitution. I will analyze under the alternative construction of "30 minutes or less after reconstitution."

VIII. UNDERSTANDING OF THE LAW

32. I understand that prior art to the '270 patent includes patents and printed publications that predate the January 14, 2005 priority date.

33. I understand that a claim is invalid if it is anticipated or obvious.

Anticipation of a claim requires that every element of a claim be disclosed expressly or inherently in a single prior art reference, as claimed. I understand that a prior art reference need only have the same level of disclosure as the asserted patent to be anticipatory.

34. Obviousness requires that the claim be obvious from the perspective of a person having ordinary skill in the relevant art at the time the alleged invention was made. I understand that a claim may be obvious in light of one or more prior art references. I further understand that an obviousness analysis requires an understanding of the scope and content of the prior art, any differences between the alleged invention and the prior art, and the level of ordinary skill in evaluating the pertinent art. I understand that the concept of "inherency" can be used in an obviousness analysis.

35. I further understand that certain other factors should be considered to determine if they support or rebut the obviousness of a claim. I understand that such secondary considerations include, among other things, commercial success of the patented invention, skepticism of those having ordinary skill in the art at the time of invention, unexpected results of the invention, any long-felt but unsolved need in the art that was satisfied by the alleged invention, the failure of others to make the alleged invention, praise of the alleged invention by those having ordinary skill in the art, and copying of the alleged invention by others in the field.

I understand that there must be a nexus—a connection—between any such secondary considerations and the alleged invention.

IX. DETAILED INVALIDITY ANALYSIS

36. I have been asked to provide an opinion as to whether claims 1-23 of the '270 patent are invalid in view of the prior art. The discussion below provides a detailed invalidity analysis of how the prior art references identified in Section I anticipate and/or render obvious claims 1-23 of the '270 patent.

37. As part of my obviousness analysis, I have considered the scope and content of the prior art, and whether any differences between the alleged invention and the prior art are such that the subject matter, as a whole, would have been obvious to a person having ordinary skill in the art at the time of the alleged invention. I have also considered the level of ordinary skill in the pertinent art in performing my analyses.

38. I describe in detail below the scope and content of the prior art, as well as any differences between the alleged invention and the prior art, on an element-by-element basis for claims 1-23 of the '270 patent.

39. The prior art I describe below includes disclosure of all limitations recited in claims 1-23 of the '270 patent.

A. Summary of Opinions

40. In summary, it is my opinion that:

- The combination of Maas and Teagarden disclose all elements of claims 1-20 and therefore renders those claims obvious. Moreover, as I explain below, Maas and Teagarden are fully and logically combinable and one of skill in the art would have been motivated to combine them;
- The combination of Maas, Teagarden, and Gust disclose all elements of claims 13 and 19 and therefore renders those claims obvious. Moreover, as I explain below, Maas, Teagarden, and Gust are fully and logically combinable and one of skill in the art would have been motivated to combine them;
- The combination of Maas, Teagarden, and the Ribomustin® Product Monograph disclose all elements of claims 1-20 and therefore renders those claims obvious. Moreover, as I explain below, Maas, Teagarden, and the Ribomustin® Product Monograph are fully and logically combinable and one of skill in the art would have been motivated to combine them; and
- The combination of the admitted prior art in the '270 patent and Teagarden disclose all elements of claims 1-23 and therefore renders those claims obvious. As I explained above, the admitted Ribomustin® prior art and Teagarden are fully and logically combinable and one of skill in the art would have been motivated to combine them.

41. Below I describe in detail how each of the references or combinations of references anticipates and/or renders obvious the alleged invention of claims 1-23 of the '270 patent in view of the teachings of the prior art, as well as the knowledge of one having ordinary skill in the art at the time of the purported invention.

B. Ground 1: Claims 1-20 Are Obvious Over Maas In View of Teagarden.

1. Background on Maas

42. Maas published in 1994, and teaches an HPLC analysis of the Ribomustin® formulation. Maas recognizes that Ribomustin® was known to be "an effective chemotherapeutic drug in the treatment of malignant diseases," and that "[b]endamustine is very unstable in aqueous solution." Exhibit 1004 at 0004. Maas further recognized that "monohydroxy bendamustine" was formed upon hydrolysis of Ribomustin®, and specifically observes this "monohydroxy" product in her HPLC chromatogram. Exhibit 1004 at 0005.

43. Although certain data (such as data reflected in the tables) in Maas is "normalized," the HPLC chromatogram in Maas shows the total amount of detectable degradant present in Maas at the time the chromatogram was taken, including HP1. Exhibit 1004 at 0005. As I explain below, I believe the chromatogram in Maas is reflective of "time zero after reconstitution" regardless of which construction is applied.

2. Background on Teagarden

44. Teagarden published in the European Journal of Pharmaceutical Sciences in March 2002. Therefore, I have been advised that it qualifies as prior art with respect to the '270 patent.

45. Teagarden specifically identifies using tert-butyl alcohol ("TBA") in the pre-lyophilization solution for water-unstable drugs. Exhibit 1005 at 0003, 0004. Teagarden explains that the use of organic solvents such as TBA "'can have a profound effect on the chemical stability of the drug.'" *Id.* at 0003. Specifically, Teagarden teaches "use of tertiary butyl alcohol as a co-solvent [in the pre-lyophilization solution] slowed solution state degradation by a factor of approximately 4–5." *Id.* at 0004.

46. Teagarden further noted that this reduction in degradation rate enabled manufacturing at ambient conditions without a requirement for manufacturing in cooler conditions. *Id.* at 0003-0004. Teagarden observed that this type of effect "would be expected to be observed for many other drug products that are degraded in the presence of water." *Id.*

47. Teagarden further taught the specific benefits of utilizing TBA over other solvent systems. For example, Teagarden specifically disclosed that:

> The co-solvent system that has been most extensively evaluated was the tert-butanol/water combination. The tert-butanol

> possesses a high vapor pressure, freezes completely in most commercial freeze-dryers, readily sublimes during primary drying, can increase sublimation rates, and has low toxicity. This co-solvent system is being used in the manufacture of a marketed injectable pharmaceutical product . . . Other co-solvent systems which do not freeze completely in commercial freeze-dryers were more difficult to use and often resulted in unacceptable freeze-dried cakes.

Id. at 0017.

3. Motivation for Combining Maas and Teagarden

48. In my opinion, Maas and Teagarden are readily and logically combinable. In forming this opinion, I have also relied on the declaration of Dr. Michael Akers. In particular, Dr. Akers provides opinions concerning the motivation to combine these references from the perspective of a formulator. Declaration of Michael Akers ("Akers Decl.") ¶¶ 41-51.

49. Maas repeatedly emphasizes that bendamustine hydrochloride compositions are unstable. For example, Maas teaches that "[b]endamustine is very unstable in aqueous solution." Exhibit 1004 at 0004. Maas further taught that, "[d]ue to the rapid hydrolysis of aqueous bendamustine hydrochloride solutions, only freshly prepared solutions which must be injected immediately

following their preparation may be used in chromatographic determinations . . . ." *Id.* at 0005. Maas further teaches a t_{90} of 9 hours at room temperature. *Id.* at 0004.

50. The instability of bendamustine in aqueous solutions described by Maas means that the time for manufacturing steps where bendamustine is in aqueous solution must be limited. Lack of stability in solution places constraints on and reduces flexibility for manufacturing operations. Also, any degradation of bendamustine during manufacture of the lyophilized product exacerbates the limited storage time of reconstituted solution because the solutions would begin at a lower bendamustine concentration. This instability further constrains the flexibility for use of reconstituted bendamustine solutions in clinical practice.

51. Given these stability issues, one of ordinary skill in the art would have been motivated to further improve this stability. In particular, one of ordinary skill in the art would have been motivated to lower the HP1 levels to comply with FDA recommended guidelines concerning impurities, and to deliver the full dose of bendamustine hydrochloride to achieve maximum efficacy. *See generally* Exhibit 1011. I also note that Cephalon stated in the '190 prosecution history that "[t]he desirability of keeping the amount of impurities low in a pharmaceutical composition is well known in the art." Exhibit 1014 at 0297.

52. It is also my opinion that one of ordinary skill in the art would have looked to the teachings of Teagarden concerning TBA to improve these stability

issues. In particular, as noted by Cephalon, "[p]rior to the invention, bendamustine was historically lyophilized from a solution of ethanol, water, mannitol, and bendamustine." Exhibit 1014 at 0367. One of skill in the art would have been motivated to substitute TBA for ethanol in the pre-lyophilization solution to take advantage of the significant benefits of TBA described in Teagarden, such as the 4-5 fold reduction in degradation rate, formulation and filling over a 24 hour period, and a longer shelf-life for the lyophilized product. Exhibit 1005 at 0003, 0004. Teagarden further teaches that "[t]he co-solvent system that has been most extensively evaluated was the tert-butanol/water combination . . . Other co-solvent systems . . . were more difficult to use and often resulted in unacceptable freeze-dried cakes." *Id.* at 0017.

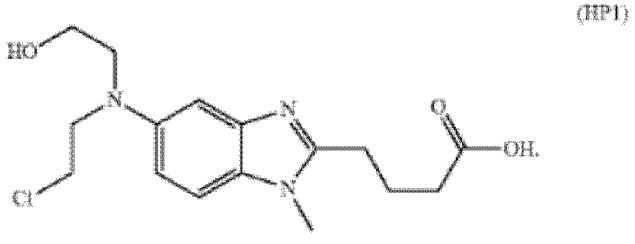
53. One of skill in the art would also have had a reasonable expectation of success in achieving lower degradant levels based on the substitution of TBA. *See also* Akers Decl. ¶¶ 52-58. In particular, Teagarden expressly teaches this expectation, explaining that reduced degradant levels "would be expected to be observed for many other drug products which are degraded in the presence of water." *Id.* at 0004. As noted by Maas, bendamustine hydrochloride is such a drug. Exhibit 1004 at 0004. Accordingly, it is my opinion that Maas and Teagarden are readily and logically combinable. I turn to the specific claim analysis below.

4. Maas and Teagarden Disclose All Elements of Claims 1-20.

54. Below is my analysis supporting my opinion that Maas and Teagarden render obvious claims 1-20. Additional evidence supporting my opinion is found in the claim charts for Ground 1 included in the body of the Petition.

(a) Claim 1

55. Claim 1 recites "[a] pharmaceutical composition that has been reconstituted from a lyophilized preparation of bendamustine or bendamustine hydrochloride, said composition containing not more than about 0.9% (area percent of bendamustine) of HP1":



56. In my opinion, Maas teaches a "pharmaceutical composition" under the broadest reasonable construction set forth above. In particular, Maas teaches that "[b]endamustine (Ribomustin®) is an effective chemotherapeutic drug in the treatment of malignant diseases," and that each vial of Ribomustin® contained "55 mg of dry substance [including] 25 mg of bendamustine hydrochloride (excipient: mannitol)." Exhibit 1004 at 0004, 0006.

57. Thus, Maas teaches that Ribomustin® was used in humans to treat

cancers, and that it contained pharmaceutically-acceptable excipients such as mannitol. *Id.* Accordingly, it is my opinion that Maas discloses "a composition that is made under conditions such that it is suitable for administration to humans."

58. Claim 1 further specifies that the "pharmaceutical composition" has been "reconstituted from a lyophilized preparation of bendamustine hydrochloride." Maas readily teaches these additional elements. In particular, Maas expressly teaches that Ribomustin® is a "lyophilized dry substance." Exhibit 1004 at 0004.

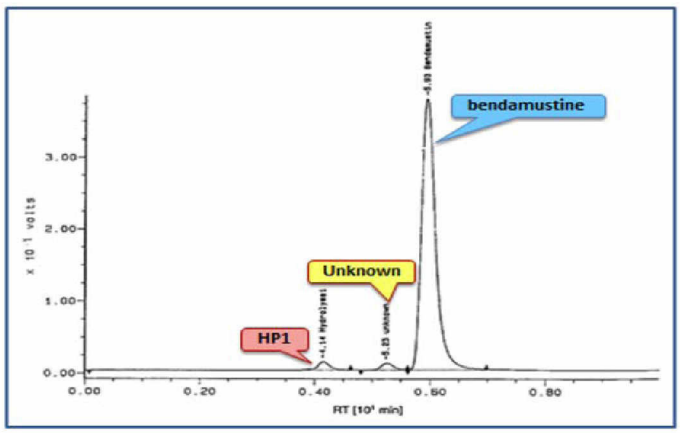
59. Second, I understand that Fresenius has proposed that the broadest reasonable construction of "pharmaceutical composition that has been reconstituted" is "[pharmaceutical composition] (as construed above) that has been dissolved in a solvent or diluent." I also understand that alternative constructions of "pharmaceutical composition that has been dissolved in a solvent and that is suitable for medical administration," and "pharmaceutical composition that has been dissolved in a solvent" have been proposed.

60. Maas meets any of these constructions. With respect to "[pharmaceutical composition] (as construed above) that has been dissolved in a solvent or diluent" and "pharmaceutical composition that has been dissolved in a solvent," Maas specifically teaches that Ribomustin® was "dissolved in 10 mL of water and then diluted with 0.9% sodium chloride solution to 100 mL." Exhibit

1004 at 0005. With respect to "pharmaceutical composition that has been dissolved in a solvent and that is suitable for medical administration," the Ribomustin® in Maas is clearly suitable for medical administration given its express disclosure that Ribomustin® "is an effective chemotherapeutic drug in the treatment of malignant diseases." Exhibit 1004 at 0004.

61. It is also my opinion that the combination of Maas and Teagarden teach the "composition contain[s] not more than about 0.9% (area percent of bendamustine) of HP1." As a threshold matter, one of skill would appreciate that the first peak in Maas corresponding to the "mono hydrolysis product" is HP1 ("hydrolysis product 1"). Exhibit 1004 at 0005. Indeed, the '270 patent itself refers to HP1 as "monohydroxy bendamustine." Exhibit 1001 at 21:4-5.

62. Moreover, one of skill in the art would have had different ways of estimating the peaks in Maas, which are included below:



63. In particular, a method that may be used is to digitize the

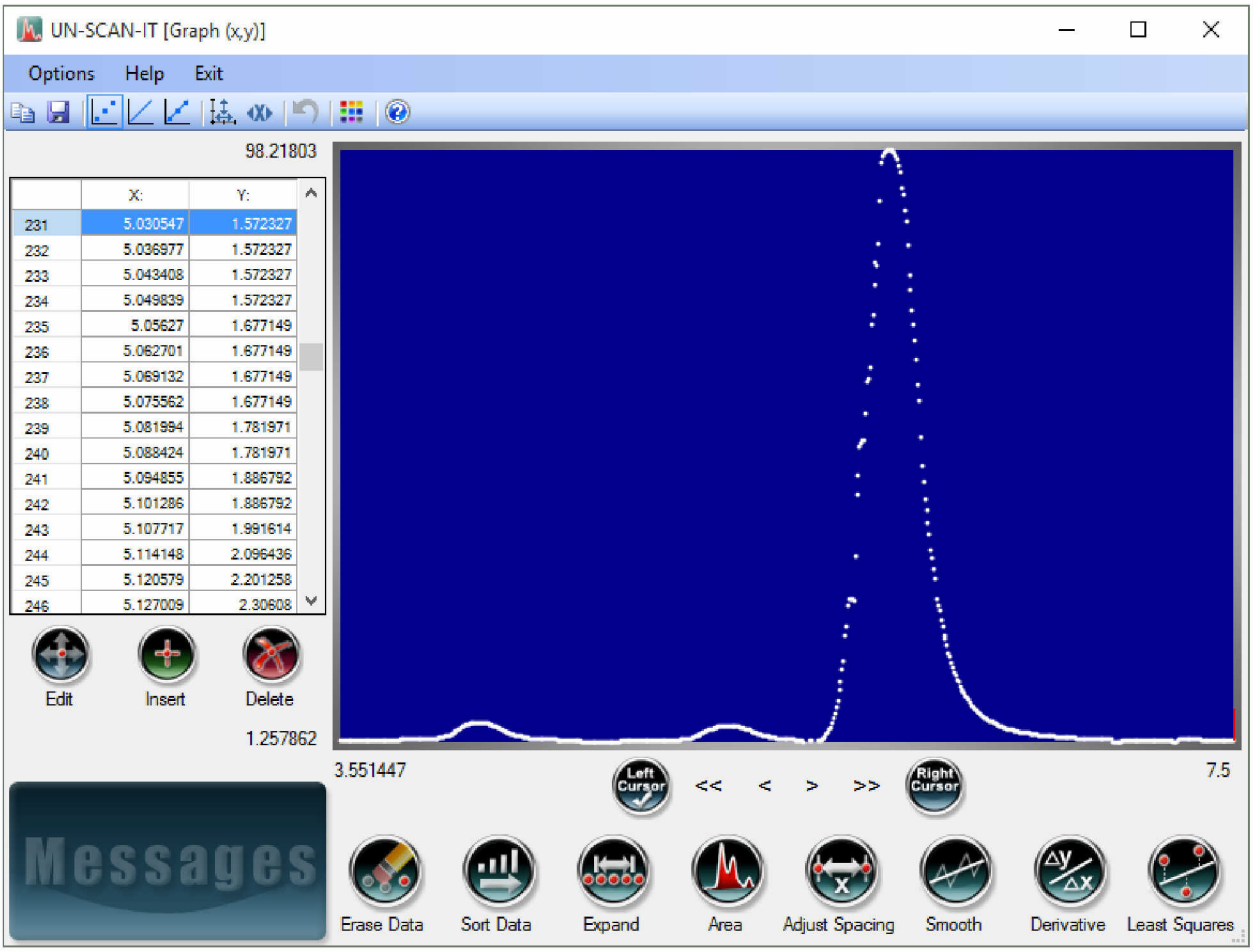
chromatogram and perform an integration of the peaks. *See, e.g.*, Exhibit 1023 at 0032 ("Digital and computing integrators give the fastest and most accurate measurement of peak areas"). Commercial software is available for this purpose. A similar method along these same lines is to use a digital image of the chromatogram and count the number of pixels under each peak.

64. I utilized these methods to attempt to determine peak area for the three peaks reported in the Maas HPLC chromatogram. Specifically, I personally digitized the HPLC chromatogram from an electronic image of the chromatogram using the UN-SCAN-IT Graph Digitizer software. Digitization produces a set of x-y data corresponding to the time (x) and detector response (y) values in the chromatogram. This software also has an integration tool with which peak areas for individual peaks can be measured.

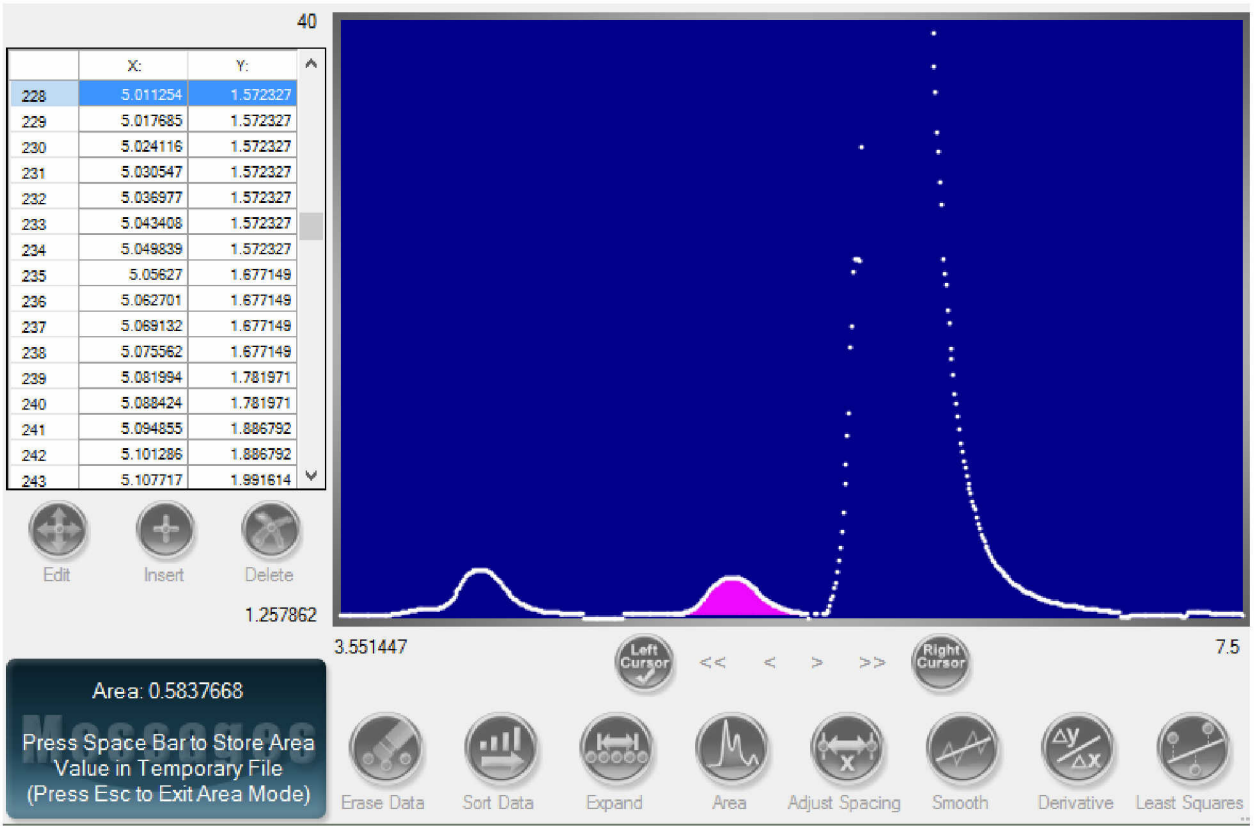
65. The peak areas for HP1, NP1, and bendamustine were measured and the area percent of the bendamustine peak area was calculated. As a check of this method, the digitized chromatographic data (time vs. response) were transferred to a Microsoft Excel spreadsheet. The peak areas were then calculated by summing the areas of small slices (time interval x response corrected for baseline) to give the total area across a peak. A summary of my results is attached as **Exhibit D** to this declaration, and the Excel spreadsheet that I utilized are attached as **Exhibit E** to this declaration. As noted above, I also counted the number of pixels under each

peak by utilizing a software program called GIMP 2, which has a histogram feature which allows for the counting of pixels in a selected area. Screenshots showing this process for each of the three major peaks are shown as **Exhibit F** to this declaration.

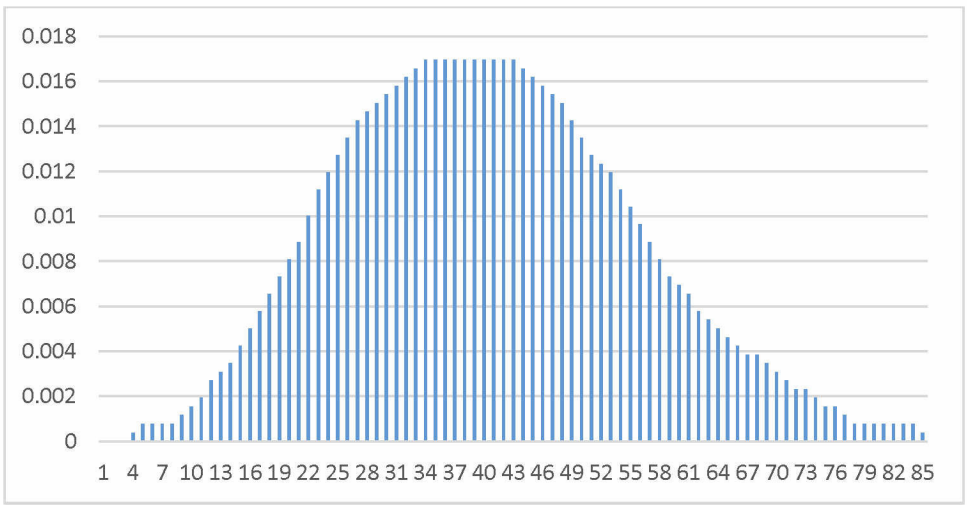
66. An illustration of the digitized chromatogram is given below.



67. An example peak integration with USCAN-IT-7.0 is shown below:



68. An example illustrating the integration from the Excel spreadsheet routine is as follows:



69. I summarize the results from both methods below. The figures in the table below are expressed as area percent of bendamustine:

Peak	Integration	Pixel
HP1	2.01 – 2.29	1.99 – 2.47
HP1 + HP2	2.34 – 2.72	2.33 – 2.67
NP1	1.95 – 2.09	1.81 – 2.08
Total Degradants[2]	4.43 – 4.81	4.14 – 4.63

70. As shown above, the amount of HP1 (calculated as area percent of bendamustine)[3] in Maas ranges from **1.99** to **2.47** under the specific methods described above. As I explain in further detail below with respect to the total degradant claims, Maas notes that the small shoulder peak at about 3.78 minutes corresponds to the dihydroxy derivative, HP2. Accordingly, I have excluded HP2 from my HP1 calculations, but have included it for "total degradants" to be conservative.

71. Applying the teachings of Teagarden concerning a 4-5 fold reduction in degradation rate (Exhibit 1005 at 0004), one of skill in the art would have the

[2] Includes HP1, NP1, and HP2.

[3] Calculated by dividing the response for the individual degradant by the response for bendamustine.

reasonable expectation that at least HP1 levels would be reduced to levels between as much as **0.398** and **0.494** (area percent of bendamustine). In particular, a 4-5 fold decrease in this degradation rate (as taught in Teagarden) would correspond to a 4-5 fold decrease in the level of degradation produced in the relevant range of about 10% degradation. A range of **0.398** to **0.494** (area percent of bendamustine) is within the claimed level of "not more than about 0.9% (area percent of bendamustine) of HP1." Accordingly, it is my opinion that the combination of Maas and Teagarden teach each and every limitation of claim 1 and therefore render it obvious.

(b) Claim 2

72. Claim 2 recites "[t]he pharmaceutical composition of claim 1, wherein the amount of HP1 is measured at time zero after reconstitution of said lyophilized preparation."

73. The teachings of Maas and Teagarden with respect to claim 1 are included above. Claim 2 additionally recites that the amount of HP1 is measured at "time zero after reconstitution."

74. As noted above, I understand that Fresenius has proposed a construction, solely for purposes of this IPR, of "soon after dissolution in a solvent or diluent," which is understood to refer to "the first measurement taken as soon as reasonably practicable" after reconstitution. Maas meets that construction, as

Maas specifically teaches that "the Maas chromatogram specifically indicates that it was taken "immediately after dilution." Exhibit 1004 at 0005. Maas further teaches that "only freshly prepared solutions which must be injected immediately following their preparation may be used in chromatographic determinations." *Id.* Accordingly, it is my opinion that Maas would meet the construction proposed by Fresenius for purposes of this petition.

75. I will analyze under the alternative construction of "30 minutes or less after reconstitution." I understand that Fresenius has proposed a construction of "reconstitution" above as "dissolution in a solvent or diluent. As noted in Maas, Ribomustin® is first dissolved in water, diluted in saline, and injected into the HPLC equipment "immediately after dilution." Exhibit 1004 at 0005. Applying the construction of "reconstitution" noted above, Maas would meet the construction "30 minutes or less after reconstitution." Even if "reconstitution" were construed in a more narrow manner to be limited to "dissolution in a solvent," Maas would still meet this construction because there is no indication from Maas that the dilution took anywhere near 30 minutes and Maas repeatedly emphasized that only "freshly prepared solutions" were used. *See, e.g., id.* at 0005.

76. As explained above, the Maas chromatogram (which meets the "time zero after reconstitution" described above) teaches HP1 levels ranging from **1.99** to **2.47**. Applying the teachings of Teagarden concerning a 4-5 fold reduction in

degradation level (Exhibit 1005 at 0004), one of skill in the art would have the reasonable expectation that at least HP1 levels would be reduced to levels between **0.398** to **0.494** (area percent of bendamustine).

77. This falls within the claimed level of "not more than about 0.9% (area percent of bendamustine) of HP1." Accordingly, it is my opinion that the combination of Maas and Teagarden teach each and every limitation of claim 2 and therefore render it obvious.

(c) Claim 3

78. Claim 3 recites "[t]he pharmaceutical composition of claim 1, wherein the amount of HP1 is not more than 0.5% (area percent of bendamustine)."

79. The teachings of Maas and Teagarden with respect to claim 1 are included above. Claim 3 additionally recites that the amount of HP1 is "not more than 0.5% (area percent of bendamustine)."

80. As explained above, the Maas chromatogram teaches HP1 levels ranging from **1.99** to **2.47**. Applying the teachings of Teagarden concerning a 4-5 fold reduction in degradation level (Exhibit 1005 at 0004), one of skill in the art would have the reasonable expectation that at least HP1 levels would be reduced to levels between **0.398** to **0.494** (area percent of bendamustine).

81. This falls within the claimed level of "not more than 0.5% (area percent of bendamustine) of HP1." Accordingly, it is my opinion that the

combination of Maas and Teagarden teach each and every limitation of claim 3 and therefore render it obvious.

(d) Claim 4

82. Claim 4 recites the "pharmaceutical composition of claim 2, wherein the amount of HP1 is not more than 0.5% (area percent of bendamustine)."

83. The teachings of Maas and Teagarden with respect to claim 2 are included above. Claim 4 additionally recites that the amount of HP1 is "not more than 0.5% (area percent of bendamustine)."

84. As explained above, the Maas chromatogram (which meets the "time zero after reconstitution" described above) teaches HP1 levels ranging from **1.99** to **2.47**. Applying the teachings of Teagarden concerning a 4-5 fold reduction in degradation level (Exhibit 1005 at 0004), one of skill in the art would have the reasonable expectation that at least HP1 levels would be reduced to levels between **0.398** to **0.494** (area percent of bendamustine).

85. This falls within the claimed level of "not more than 0.5% (area percent of bendamustine) of HP1." Accordingly, it is my opinion that the combination of Maas and Teagarden teach each and every limitation of claim 4 and therefore render it obvious.

(e) Claim 5

86. Claim 5 recites the "pharmaceutical composition of claim 1, wherein

the amount of HP1 is not more than 0.4% (area percent of bendamustine)."

87. The teachings of Maas and Teagarden with respect to claim 1 are included above. Claim 5 additionally recites that the amount of HP1 is "not more than 0.4% (area percent of bendamustine)."

88. As explained above, the Maas chromatogram teaches HP1 levels ranging from **1.99** to **2.47**. Applying the teachings of Teagarden concerning a 4-5 fold reduction in degradation level (Exhibit 1005 at 0004), one of skill in the art would have the reasonable expectation that at least HP1 levels would be reduced to levels between **0.398** to **0.494** (area percent of bendamustine).

89. This range overlaps with the claimed level of "not more than 0.4% (area percent of bendamustine) of HP1." I have been informed and advised that a prior art reference that discloses a range encompassing a somewhat narrower claimed range is sufficient to establish a *prima facie* case of obviousness. Accordingly, it is my opinion that the combination of Maas and Teagarden teach each and every limitation of claim 5 and therefore render it obvious.

(f) Claim 6

90. Claim 6 recites the "pharmaceutical composition of claim 2, wherein the amount of HP1 is not more than 0.4% (area percent of bendamustine)."

91. The teachings of Maas and Teagarden with respect to claim 2 are included above. Claim 6 additionally recites that the amount of HP1 is "not more

than 0.4% (area percent of bendamustine)."

92. As explained above, the Maas chromatogram (which meets the "time zero after reconstitution" described above) teaches HP1 levels ranging from **1.99** to **2.47**. Applying the teachings of Teagarden concerning a 4-5 fold reduction in degradation level (Exhibit 1005 at 0004), one of skill in the art would have the reasonable expectation that at least HP1 levels would be reduced to levels between **0.398** to **0.494** (area percent of bendamustine).

93. This range overlaps with the claimed level of "not more than 0.4% (area percent of bendamustine) of HP1." I have been informed and advised that a prior art reference that discloses a range encompassing a somewhat narrower claimed range is sufficient to establish a *prima facie* case of obviousness. Accordingly, it is my opinion that the combination of Maas and Teagarden teach each and every limitation of claim 6 and therefore render it obvious.

(g) Claim 7

94. Claim 7 recites "[a] pharmaceutical composition of bendamustine hydrochloride, containing less than or equal to 4.0% (area percent of bendamustine) of bendamustine degradants."

95. As noted above in claim 1, Maas teaches of a pharmaceutical composition of bendamustine hydrochloride. Moreover, as explained above, the Maas chromatogram teaches HP1 levels ranging from **1.99** to **2.47**, HP1+HP2

levels ranging from **2.33** to **2.72**, NP1 levels ranging from **1.81** to **2.09**, and total degradants (including the HP2 degradant) ranging from **4.14** to **4.81**.

96. Applying the teachings of Teagarden concerning a 4-5 fold reduction in degradation level (Exhibit 1005 at 0004), one of skill in the art would have the reasonable expectation that at least HP1 and HP2 levels would be reduced to levels **0.466%** to **0.544%** (area percent of bendamustine). I have limited my analysis to only HP1 and HP2 to be conservative because Teagarden specifically speaks in terms of reduction that is to be expected because of water instability, and HP1 and HP2 are the degradants produced as a result of that water instability. Exhibit 1005 at 0004. Thus, the total degradant levels based on HP1, NP1, and HP2 (after applying the teaching of Teagarden) would range between **2.28** to **2.63** as shown below:

Peak	**Range in Maas**	**Reduction Based on Teagarden**
HP1	1.99 – 2.47	Shown below
HP1 + HP2	2.33 – 2.72	0.466 – 0.544
NP1	1.81 – 2.09	1.81 – 2.09
Total Degradants[4]	4.14 – 4.81	2.28 – 2.63

[4] Includes HP1, NP1, and HP2.

97. This falls within the claimed level of "less than or equal to 4.0% (area percent of bendamustine) of bendamustine degradants." Accordingly, it is my opinion that the combination of Maas and Teagarden teach each and every limitation of claim 7 and therefore render it obvious.

(h) Claim 8

98. Claim 8 recites the "pharmaceutical composition of claim 7, containing between about 2.0% and 4.0% (area percent of bendamustine) of bendamustine degradants."

99. The teachings of Maas and Teagarden with respect to claim 7 are included above. As explained above, the total degradant levels based on HP1, NP1, and HP2 (after applying the teaching of Teagarden) would range between **2.28** to **2.63**. This overlaps with the claimed level of "between about 2.0% and 4.0% (area percent of bendamustine) of bendamustine degradants," which is obvious for the reasons discussed above with respect to overlapping ranges. Accordingly, it is my opinion that the combination of Maas and Teagarden teach each and every limitation of claim 8 and therefore render it obvious.

(i) Claim 9

100. Claim 9 recites the "pharmaceutical composition of claim 8, wherein the pharmaceutical composition has been reconstituted from a lyophilized preparation of bendamustine hydrochloride."

101. The teachings of Maas and Teagarden with respect to claim 8 are included above. Moreover, as explained above in the analysis relating to claim 1, Maas teaches "[a] pharmaceutical composition that has been reconstituted from a lyophilized preparation of bendamustine or bendamustine hydrochloride" under any of the proffered constructions. *See supra* ¶¶ 59-60. Accordingly, it is my opinion that the combination of Maas and Teagarden teach each and every limitation of claim 9 and therefore render it obvious.

(j) Claim 10

102. Claim 10 recites the "pharmaceutical composition of claim 9, containing not more than about 0.9% (area percent of bendamustine) of HP1 at time zero after reconstitution."

103. The teachings of Maas and Teagarden with respect to claim 9 are included above. Claim 10 additionally requires "not more than about 0.9% (area percent of bendamustine) of HP1 at time zero after reconstitution." The teachings of Maas and Teagarden with respect to this additional limitation are included, *inter alia*, in claim 2 above. *See supra* ¶¶ 74-77. Accordingly, it is my opinion that the combination of Maas and Teagarden teach each and every limitation of claim 10 and therefore render it obvious.

(k) Claim 11

104. Claim 11 recites the "pharmaceutical composition of claim 9,

containing not more than about 0.5% (area percent of bendamustine) of HP1 at time zero after reconstitution."

105. The teachings of Maas and Teagarden with respect to claim 9 are included above. Claim 11 additionally requires "not more than about 0.5% (area percent of bendamustine) of HP1 at time zero after reconstitution." The teachings of Maas and Teagarden with respect to this additional limitation are included, *inter alia*, in claim 4 above. *See supra* ¶¶ 83-84. Accordingly, it is my opinion that the combination of Maas and Teagarden teach each and every limitation of claim 11 and therefore render it obvious.

(l) Claim 12

106. Claim 12 recites the "pharmaceutical composition of claim 9, containing not more than about 0.4% (area percent of bendamustine) of HP1 at time zero after reconstitution."

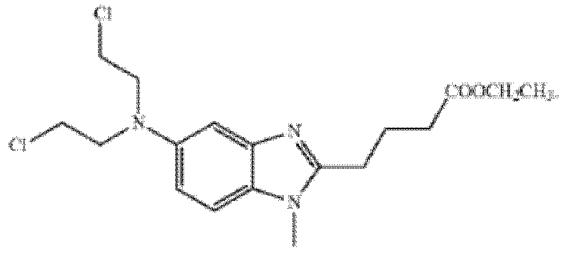
107. The teachings of Maas and Teagarden with respect to claim 9 are included above. Claim 12 additionally requires "not more than about 0.4% (area percent of bendamustine) of HP1 at time zero after reconstitution." The teachings of Maas and Teagarden with respect to this additional limitation are included, *inter alia*, in claim 6 above. *See supra* ¶¶ 91-93. Additionally, I note that claim 12 specifically recites the term "about" and uses one significant figure. Based on this number of significant figures, scientists would understand "about 0.4%" to

encompass figures up to 0.44% because 0.4% is understood to mean "four tenths, rounded to the nearest tenth." Exhibit 1033 at 0005. This reinforces my conclusion that the range taught by the combination of Maas and Teagarden overlaps with the claimed range. Accordingly, it is my opinion that the combination of Maas and Teagarden teach each and every limitation of claim 12 and therefore render it obvious.

(m) Claim 13

108. Claim 13 recites "[t]he pharmaceutical composition of claim 10, containing not more than about 0.5% (area percent of bendamustine) of a compound of Formula IV at time zero after reconstitution:

Formula IV



109. The teachings of Maas and Teagarden with respect to claim 10 are included above. Claim 13 additionally requires "not more than about 0.5% (area percent of bendamustine)" of BM1EE. Maas does not report BM1EE in her chromatogram, so Maas would meet this limitation by itself (and is measured at time zero after reconstitution under either construction). In particular, with the mobile phase that Maas used (Exhibit 1004 at 0006), I believe that Maas would

have likely seen BM1EE had it been there.

110. As I explained above, one of skill in the art would have a reasonable expectation of reducing BM1EE levels of Ribomustin® by replacing ethanol with TBA (assuming the same general drug synthesis). As noted above, Cephalon noted that Ribomustin® "was historically lyophilized from a solution of ethanol, water, mannitol, and bendamustine." Exhibit 1014 at 0367. It is known that ethyl esters are formed based on an esterification of the compound by ethanol (*see, e.g.*, Exhibit 1009 at 0003), so a person of ordinary skill in the art would reasonably expect that replacing ethanol with TBA would further reduce BM1EE levels beyond what is reported in Maas (which does not report BM1EE).

111. Accordingly, it is my opinion that the combination of Maas and Teagarden teach each and every limitation of claim 13 and therefore render it obvious.

(n) Claim 14

112. Claim 14 recites the "pharmaceutical composition of claim 7, wherein the pharmaceutical composition is a lyophilized composition." The teachings of Maas and Teagarden with respect to claim 7 are included above. Claim 14 additionally recites the pharmaceutical composition is "a lyophilized composition." As noted above, Maas teaches such a lyophilized composition. Exhibit 1004 at 0004 ("lyophilized dry substance").

113. Accordingly, it is my opinion that the combination of Maas and Teagarden teach each and every limitation of claim 13 and therefore render it obvious.

(o) Claim 15

114. Claim 15 recites the "pharmaceutical composition of claim 8, wherein the pharmaceutical composition is a lyophilized composition."

115. The teachings of Maas and Teagarden with respect to claim 8 are included above. Claim 15 additionally recites the pharmaceutical composition is "a lyophilized composition." As noted above, Maas teaches such a lyophilized composition. Exhibit 1004 at 0004 ("lyophilized dry substance").

116. Accordingly, it is my opinion that the combination of Maas and Teagarden teach each and every limitation of claim 15 and therefore render it obvious.

(p) Claim 16

117. Claim 16 recites the "pharmaceutical composition of claim 7, containing not more than about 0.9% (area percent of bendamustine) of HP1."

118. The teachings of Maas and Teagarden with respect to claim 7 are included above. Claim 16 additionally requires "not more than about 0.9% (area percent of bendamustine) of HP1." The teachings of Maas and Teagarden with respect to this additional limitation are included, *inter alia*, in claim 1 above. *See*

supra ¶¶ 56-71. Accordingly, it is my opinion that the combination of Maas and Teagarden teach each and every limitation of claim 16 and therefore render it obvious.

(q) Claim 17

119. Claim 17 recites "the pharmaceutical composition of claim 7, containing not more than about 0.5% (area percent of bendamustine) of HP1."

120. The teachings of Maas and Teagarden with respect to claim 7 are included above. Claim 17 additionally requires "not more than about 0.5% (area percent of bendamustine) of HP1." The teachings of Maas and Teagarden with respect to this additional limitation are included, *inter alia*, in claim 3 above. *See supra* ¶¶ 79-81. Accordingly, it is my opinion that the combination of Maas and Teagarden teach each and every limitation of claim 17 and therefore render it obvious.

(r) Claim 18

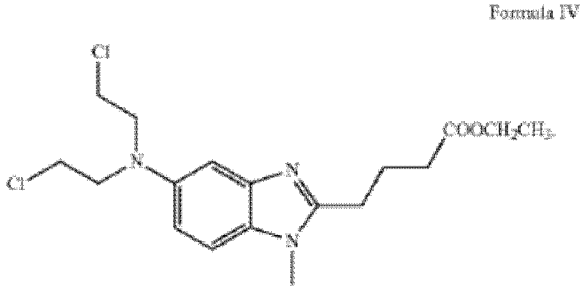
121. Claim 18 recites "the pharmaceutical composition of claim 7, containing not more than about 0.4% (area percent of bendamustine) of HP1."

122. The teachings of Maas and Teagarden with respect to claim 7 are included above. Claim 18 additionally requires "not more than about 0.4% (area percent of bendamustine) of HP1." The teachings of Maas and Teagarden with respect to this additional limitation are included, *inter alia*, in claim 5 above. *See*

supra ¶¶ 87-89. Additionally, I note that claim 18 specifically recites the term "about" and uses one significant figure. Based on this number of significant figures, scientists would understand "about 0.4%" to encompass figures up to 0.44% because 0.4% is understood to mean "four tenths, rounded to the nearest tenth." Exhibit 1033 at 0005. This reinforces my conclusion that the range taught by the combination of Maas and Teagarden overlaps with the claimed range. Accordingly, it is my opinion that the combination of Maas and Teagarden teach each and every limitation of claim 18 and therefore render it obvious.

(r) Claim 19

123. Claim 19 recites "[t]he pharmaceutical composition of claim 7, containing not more than about 0.5% (area percent of bendamustine) of a compound of Formula IV:



124. The teachings of Maas and Teagarden with respect to claim 7 are included above. Claim 19 additionally requires "not more than about 0.5% (area percent of bendamustine)" of BM1EE. The teachings of Maas and Teagarden with respect to this additional limitation are included, *inter alia*, in claim 13 above. *See*

supra ¶¶ 109-111. Accordingly, it is my opinion that the combination of Maas and Teagarden teach each and every limitation of claim 19 and therefore render it obvious.

(s) Claim 20

125. Claim 20 recites "[a] method of treating cancer in a patient comprising administering to the patient a pharmaceutical composition of bendamustine hydrochloride according to claim 7."

126. The teachings of Maas and Teagarden with respect to claim 7 are included above. Claim 20 additionally requires "a method of treating cancer in a patient" comprising administering the pharmaceutical composition recited in claim 7. With respect to this additional limitation, Maas expressly teaches that Ribomustin® is "an effective chemotherapeutic drug in the treatment of malignant diseases." Exhibit 1004 at 0004.

127. It is my opinion that it would have been obvious for a person of skill in the art to utilize the composition prepared based on the teachings of Maas and Teagarden for the same indications for which Ribomustin® was previously used. Accordingly, it is my opinion that the combination of Maas and Teagarden teach each and every limitation of claim 20 and therefore render it obvious.

3. Maas and Teagarden Disclose All Elements of Claims 1-20 Under An Inherency Theory.

128. I understand that Fresenius has alternatively asserted that Table 13 of

the ‘270 patent provides additional information concerning the inherent properties of Ribomustin® as reported in Maas, and that the combination of Maas (in view of these inherent properties) and Teagarden render claims 1-20 obvious. Although I do not intend to opine on legal concepts, I have been advised that inherency may supply a missing element in an obviousness analysis.

129. The area percent of bendamustine that I have calculated for each of the lots of Ribomustin® reported in Table 13 is included below. I have calculated these values to be conservative—it may be that the values are reported in Table 13 area already calculated as area percent of bendamustine:

Batch	Bendamustine HCl	HP1	BM1EE	BM1 Dimer	BM1DCE	Total Degradants
03H08	98.14	1.09	0.21	0.35	0.03	1.86
03H07	97.67	1.54	0.20	0.34	0.04	2.33
02K27	96.93	0.96	0.30	1.22	0.08	3.07
03C08	97.61	1.27	0.19	0.47	0.02	2.39

130. The degradant profile in Table 13 may be somewhat lower than Maas because the Ribomustin® analyzed for Table 13 was dissolved in methanol and not water, which would lead to a lower formation of degradants because less hydrolysis would occur. In my view of the claims of the ‘270 patent, none of the claims appeared to require dissolution in a specific solvent, so the results of Table 13 are relevant here.

131. Additionally, dissolution in methanol does not change the fact that

Ribomustin® is a "pharmaceutical composition" and/or a "pharmaceutical composition that has been reconstituted" under the broadest reasonable construction set forth above in my opinion.

132. In particular, Ribomustin® is a pharmaceutical composition that was administered to humans for years (Exhibit 1001 at 2:5-8), and the fact that methanol was used in the testing assay does not change the fact that Ribomustin® was and is a pharmaceutical composition. Moreover, I note that, in the specification, Cephalon characterized a number of compositions with high levels alcohols as "pharmaceutical compositions." Exhibit 1001 at 11:5-15

133. With respect to "pharmaceutical composition that has been reconstituted," I understand that, even if a construction is adopted of this term that requires suitability for medical administration, Table 13 meets this limitation because Ribomustin® is suitable for medical administration for the reasons discussed above. The fact that alcohol is used as the testing assay does not change that. If the broader construction of "dissolved in a solvent" is adopted, Table 13 meets that construction because the construction does not require dissolution in any particular solvent.

134. The analysis in Table 13 would also meet "time zero after reconstitution" regardless of the construction. In particular, the HPLC analysis in Table 13 was performed approximately 6 minutes after dissolution in methanol and

sonication. Exhibit 1001 at 9:29-31. This would meet "soon after dissolution in a solvent" as well as "30 minutes after reconstitution."

135. Below is my analysis supporting my opinion that the inherent properties of Ribomustin® in Maas in combination with Teagarden render obvious claims 1-20. Additional evidence supporting my opinion is found in the claim charts for Ground 2 included in the body of the Petition.

136. Claims 1, 3, and 5 require "[a] pharmaceutical composition that has been reconstituted from a lyophilized preparation of bendamustine or bendamustine hydrochloride, said composition containing not more than about 0.9%[0.5%/0.4%] (area percent of bendamustine) of HP1." As explained above, the Ribomustin® analyzed in Table 13 meets the "pharmaceutical composition that has been reconstituted from a lyophilized preparation of bendamustine or bendamustine hydrochloride."

137. The inherent properties of Ribomustin® in view of Teagarden also meets the additional limitation of "not more than about 0.9%[0.5%/0.4%] (area percent of bendamustine) of HP1." Applying the teachings of Teagarden concerning a 4-5 fold reduction in degradation level (Exhibit 1005 at 0004) to the HP1 figures reported in Table 13, one of skill in the art would have the reasonable expectation that at least HP1 levels would be reduced to levels between **0.192** and **0.308** (area percent of bendamustine) of HP1.

138. This falls within the claimed level of "not more than about 0.9%[0.5%/0.4%] (area percent of bendamustine) of HP1." Accordingly, it is my opinion that the combination of inherent properties of Ribomustin® in Maas and Teagarden teach each and every limitation of claims 1, 3, and 5 and therefore render them obvious.

139. Claims 2, 4, and 6 require "[a] pharmaceutical composition that has been reconstituted from a lyophilized preparation of bendamustine or bendamustine hydrochloride, said composition containing not more than about 0.9%[0.5%/0.4%] (area percent of bendamustine) of HP1," wherein those HP1 levels are measured at time zero after reconstitution. As explained above, the Ribomustin® analyzed in Table 13 meets the "pharmaceutical composition that has been reconstituted from a lyophilized preparation of bendamustine or bendamustine hydrochloride." As also explained above, the analysis in Table 13 meets time zero after reconstitution under either construction.

140. The inherent properties of Ribomustin® in view of Teagarden also meets the additional limitation of "not more than about 0.9%[0.5%/0.4%] (area percent of bendamustine) of HP1" at time zero after reconstitution. Applying the teachings of Teagarden concerning a 4-5 fold reduction in degradation level (Exhibit 1005 at 0004) to the HP1 figures reported in Table 13, one of skill in the art would have the reasonable expectation that at least HP1 levels would be

reduced to levels between **0.192** and **0.308** (area percent of bendamustine) of HP1.

141. This falls within the claimed level of "not more than about 0.9%[0.5%/0.4%] (area percent of bendamustine) of HP1" at time zero after reconstitution. Accordingly, it is my opinion that the combination of inherent properties of Ribomustin® in Maas and Teagarden teach each and every limitation of claims 2, 4, and 6 and therefore render them obvious.

142. Claims 7-8 respectively require "less than or equal to 4.0% (area percent of bendamustine)" range recited in claim 7, and the "between about 2.0% and 4.0% (area percent of bendamustine)." As shown above the Ribomustin® values reported in Table 13 are already within those ranges (1.86% - 3.07%) and therefore meet the limitations of those claims.

143. Claim 9 depends from claim 7 and additionally requires that the "pharmaceutical composition has been reconstituted from a lyophilized preparation of bendamustine hydrochloride." As noted above, Table 13 teaches a "pharmaceutical composition that has been reconstituted" regardless of which construction is adopted. Moreover, the '270 patent and Maas make clear that Ribomustin is lyophilized. Exhibit 1004 at 0004; Exhibit 1001 at 2:1-10. Accordingly, it is my opinion that the combination of inherent properties of Ribomustin® in Maas and Teagarden teach each and every limitation of claim 9 and therefore render it obvious.

144. Claims 10-12 depend from claim 9 and further require "not more than about 0.9%[0.5%/0.4%] (area percent of bendamustine) of HP1 at time zero after reconstitution." The relevant teachings concerning the inherent properties of Ribomustin® and Teagarden with respect to these additional limitations are included, *inter alia*, in claims 2, 4, and 6 above. *See supra* ¶¶ 139-141. Accordingly, it is my opinion that the combination of Maas and Teagarden teach each and every limitation of claims 10-12 and therefore render them obvious.

145. Claim 13 depends from claim 10 and requires "not more than about 0.5%" BM1EE at time zero after reconstitution. As shown above, the levels of BM1EE in Table 13 (which is at time zero after reconstitution under either construction) are already below that claimed level. As I explained above, one of skill in the art would understand that substituting TBA for ethanol would lower those levels even further given that BM1EE is formed by esterification from ethanol. *See supra* ¶ 110. Accordingly, it is my opinion that the combination of inherent properties of Ribomustin® in Maas and Teagarden teach each and every limitation of claim 13 and therefore render it obvious.

146. Claims 14 and 15 depend from claim 7 and require that the "pharmaceutical composition is a lyophilized composition." This additional limitation is met for the same reasons I discussed above with respect to claim 9. Accordingly, it is my opinion that the combination of inherent properties of

Ribomustin® in Maas and Teagarden teach each and every limitation of claims 14 and 15 and therefore render them obvious.

147. Claims 16-18 depend from claim 7 and further require "not more than about 0.9%[0.5%/0.4%] (area percent of bendamustine) of HP1." The relevant teachings concerning the inherent properties of Ribomustin® and Teagarden with respect to these additional limitations are included, *inter alia*, in claims 1, 3, and 5 above. *See supra* ¶¶ 136-138. Accordingly, it is my opinion that the combination of Maas and Teagarden teach each and every limitation of claims 16-18 and therefore render them obvious.

148. Claim 19 depends from claim 7 and additionally requires "not more than about 0.5% (area percent of bendamustine) of a compound." As discussed above in claim 13, the levels of BM1EE in Table 13 are already below that claimed level. As I explained above, one of skill in the art would understand that substituting TBA for ethanol would lower those levels even further given that BM1EE is formed by esterification from ethanol. *See supra* ¶ 110. Accordingly, it is my opinion that the combination of inherent properties of Ribomustin® in Maas and Teagarden teach each and every limitation of claim 19 and therefore render it obvious.

149. Claim 20 depends from claim 7 and additionally requires "a method of treating cancer in a patient" comprising administering the pharmaceutical

composition recited in claim 7. With respect to this additional limitation, Maas expressly teaches that Ribomustin® is "an effective chemotherapeutic drug in the treatment of malignant diseases." Exhibit 1004 at 0004.

150. For all these reasons, it is my opinion that Maas and Teagarden expressly or inherently disclose all limitations of claims 1-20, and therefore render those claims obvious.

C. Ground 2: Claims 13 and 19 Are Obvious Over Maas in View of Gust and Teagarden.

1. Background on Gust

151. Gust was published in 1997 in Monatshefte für Chemie Chemical Monthly. Exhibit 1006 at 0001. Therefore, I have been informed that it qualifies as prior art with respect to the '270 patent.

152. Gust taught the synthesis, isolation, and characterization of reference substances of bendamustin. Exhibit 1006 at 0002. In particular, Gust taught that bendamustine ethyl ester (BM1EE) is present in crude bendamustine. *Id.* at 0008. Gust further taught that BM1EE was synthesized by esterification of bendamustine hydrochloride in ethanolic HCl. *Id.* at 0003.

153. Maas, Teagarden, and Gust are readily and logically combinable. Maas and Gust both relate to bendamustine hydrochloride, including pharmaceutical formulations of bendamustine hydrochloride such as Ribomustin®. Exhibit 1004 at 1004; Exhibit 1006 at 0002. Both Maas and Gust teach

information concerning the stability of Ribomustin® (Exhibit 1004 at 0005; Exhibit 1006 at 0002), and Gust cross-references the teachings of Maas. Exhibit 1006 at 0002. Thus, it is my opinion that one of skill in the art would have been motivated to combine the teachings of Maas and Gust.

154. As explained above and in the Akers Declaration, one of skill in the art would have been motivated to improve the stability of Ribomustin® as described in Maas and Gust, and would have consulted the teachings of Teagarden concerning the use of TBA in the pre-lyophilization solution of Ribomustin®. *See supra* ¶¶ 48-53. Accordingly, it is my opinion that Maas, Gust, and Teagarden are readily and logically combinable. I turn to the specific claim analysis below.

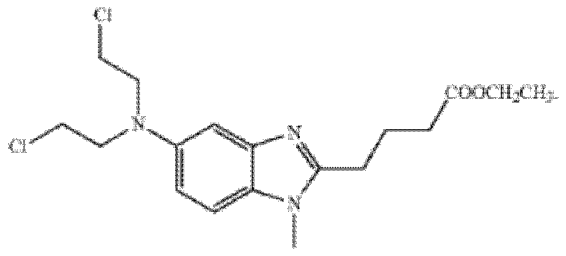
2. Maas, Teagarden, and Gust Disclose All Elements of Claims 13 and 19.

155. Below is my analysis supporting my opinion that Maas, Teagarden, and Gust render obvious claims 13 and 19. Additional evidence supporting my opinion is found in the claim charts for Ground 3 included in the body of the Petition.

(a) Claim 13

156. Claim 13 recites "[t]he pharmaceutical composition of claim 10, containing not more than about 0.5% (area percent of bendamustine) of a compound of Formula IV at time zero after reconstitution:

Formula IV



157. Formula IV is the bendamustine ethyl ester referred to *supra* as BM1EE.

158. The teachings of Maas and Teagarden with respect to claim 10 are included above.

159. As explained above in Grounds 1 and 2, Maas alone and/or Maas in combination with Teagarden teach the "pharmaceutical composition" recited in claim 10, and Maas teaches analysis at "time zero after reconstitution."

160. Gust teaches that the dichloroester was produced by esterification in ethanolic HCl. Exhibit 1006 at 0003 and 0008-0009.

161. As noted above, it is my opinion that a person of ordinary skill in the art would have looked to Teagarden's teachings concerning the benefits of TBA over other organic solvents to improve the stability of Ribomustin®. *See supra* ¶¶ 48-53.

162. A person of ordinary skill in the art also would have understood from Gust that BM1EE forms as an impurity via esterification of bendamustine with ethanol. Exhibit 1006 at 0003 and 0008-0009. Accordingly, it is my opinion that

by lyophilizing from TBA as taught by Teagarden, a person of ordinary skill in the art would have had a reasonable expectation of success in producing a composition with less BM1EE than was in Ribomustin®, which was lyophilized in ethanol as discussed in the '190 prosecution history. Exhibit 1014 at 0367.

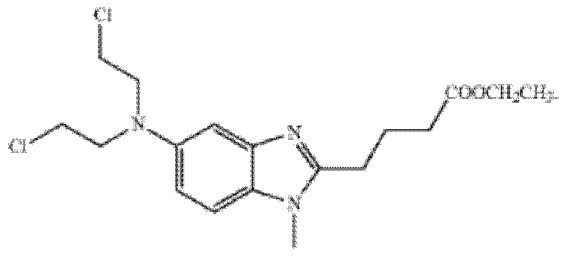
163. I also understand that the Patent Trial and Appeal Board has concluded that "Ribomustin® inherently contains less than 0.5% bendamustine ethylester" based on the data in Table 13 in the '270 specification. Exhibit 1012 at 0025. Based on the substitution of TBA for ethanol, one of skill in the art would have expected an even lower level of BM1EE than is reported in Table 13 given that BM1EE is formed by an esterification of bendamustine with ethanol as discussed above.

164. It is thus my opinion that the combination of Maas, Teagarden, and Gust teach each and every limitation of claim 13.

(b) Claim 19

165. Claim 19 recites "[t]he pharmaceutical composition of claim 7, containing not more than about 0.5% (area percent of bendamustine) of a compound of Formula IV:

Formula IV



166. Formula IV is the bendamustine ethyl ester referred to *supra* as BM1EE.

167. The teachings of Maas and Teagarden with respect to claim 7 are included above.

168. As explained above in Grounds 1 and 2, Maas alone and/or Maas in combination with Teagarden teach the "pharmaceutical composition" recited in claim 10, and Maas teaches analysis at "time zero after reconstitution."

169. Gust teaches isolation of dichloroester from crude bendamustine. Exhibit 1006 at 0003 and 0008-0009. Gust further teaches that the dichloroester was produced by esterification in ethanolic HCl. *Id.*

170. As noted above, it is my opinion that a person of ordinary skill in the art would have looked to Teagarden's teachings concerning the benefits of TBA over other organic solvents to improve the stability of Ribomustin®. *See supra* ¶¶ 48-53.

171. A person of ordinary skill in the art also would have understood from Gust that BM1EE forms as an impurity via esterification of bendamustine with

ethanol. Exhibit 1006 at 0003 and 0008-0009. Accordingly, it is my opinion that by lyophilizing from TBA as taught by Teagarden, a person of ordinary skill in the art would have had a reasonable expectation of success in producing a composition with less BM1EE than was in Ribomustin®, which was lyophilized in ethanol as discussed in the '190 prosecution history. Exhibit 1014 at 0367.

172. I also understand that the Patent Trial and Appeal Board has concluded that "Ribomustin® inherently contains less than 0.5% bendamustine ethylester" based on the data in Table 13 in the '270 specification. Exhibit 1012 at 0025. Based on the substitution of TBA for ethanol, one of skill in the art would have expected an even lower level of BM1EE than is reported in Table 13 given that BM1EE is formed by an esterification of bendamustine with ethanol as discussed above.

173. It is thus my opinion that the combination of Maas, Teagarden, and Gust teach each and every limitation of claim 19.

D. Ground 3: Claims 20-23 Are Obvious Over Maas in View of Teagarden and the Ribomustin® Product Monograph.

1. Background on the Ribomustin® Product Monograph

174. The Ribomustin® Product Monograph was published by Ribosepharm in 2002. Exhibit 1007 at 0001. Therefore, I understand that it qualifies as prior art with respect to the '270 patent.

175. The Ribomustin® Product Monograph defined the safety,

effectiveness, and labeling of Ribomustin®, which included its indications and clinical uses. *See, e.g.*, Exhibit 1007 at 0008. For example, the Ribomustin® Product Monograph taught that Ribomustin® could be used to treat various cancers, including CLL and NHL. *Id.* at 0008.

176. In particular, the Ribomustin® Product Monograph taught that "Ribomustin® is indicated as single-agent therapy or in combination with other antineoplastic drugs for the treatment of the following malignancies:

- Hodgkin's disease (stages II-IV)
- Non-Hodgkin's lymphoma
- Plasmocytoma
- Chronic lymphocytic leukemia
- Breast cancer."

Id. at 0008.

177. In my opinion, Maas, Teagarden, and the Ribomustin® Product Monograph are readily and logically combinable. As noted above, it is my opinion that a person of ordinary skill in the art would have looked to Teagarden's teachings concerning the benefits of TBA to improve the stability of Ribomustin®. *See supra* ¶¶ 48-53. Given Ribomustin®'s established efficacy against certain malignancies, a person of ordinary skill in the art would have been motivated to use this pharmaceutical indication for the same indications that Ribomustin® was

previously administered.

2. Maas, Teagarden, and the Ribomustin Product Monograph® Disclose All Elements of Claims 20-23.

178. Below is my analysis supporting my opinion that Maas, Teagarden, and the Ribomustin® Product Monograph disclose all elements of claims 20-23. Additional evidence supporting my opinion is found in the claim charts for Ground 4 included in the body of the Petition.

(b) Claim 20

179. Claim 20 recites "[a] method of treating cancer in a patient comprising administering to the patient a pharmaceutical composition of bendamustine hydrochloride according to claim 7."

180. As explained above in Grounds 1 and 2, Maas alone and/or Maas in combination with Teagarden teach the "pharmaceutical composition of bendamustine hydrochloride" recited in claim 7.

181. Both Maas and the Ribomustin® Product Monograph teach the remaining limitations of claim 20. In particular, both references teach that Ribomustin® is used to treat cancer in a patient. *See, e.g.*, Exhibit 1004 at 0004 ("Bendamustine (Ribomustin® . . .) is an effective chemotherapeutic drug in the treatment of malignant diseases. The stability of the lyophilized dry substance is already known"); Exhibit 1007 at 0008. Accordingly, it is my opinion that the combination of Maas, Teagarden, and the Ribomustin® Product Monograph teach

each and every limitation of claim 20.

(b) Claim 21

182. Claim 21 recites "[t]he method according to claim 20, wherein the cancer is chronic lymphocytic leukemia, Hodgkin's disease, non-Hodgkin's lymphoma, multiple myeloma, or breast cancer."

183. The disclosures of Maas, Teagarden, and the Ribomustin® Product Monograph with respect to claim 20 are included above.

184. As shown above, the Ribomustin® Product Monograph specifically taught that Ribomustin was indicated for various cancers, including "Hodgkin's disease (stages II-IV)[,] Non-Hodgkin's lymphoma[,] Plasmocytoma[,] chronic lymphocytic leukemia[,] [and] breast cancer." Exhibit 1007 at 0008.

185. As I explained in detail above, one of skill in the art would have been motivated to utilize the bendamustine hydrochloride pharmaceutical composition taught by Maas and Teagarden for the same indications for which Ribomustin® had been previously administered given the extensive history with Ribomustin®. Accordingly, it is my opinion that the combination of Maas, Teagarden, and the Ribomustin® Product Monograph teach each and every limitation of claim 21.

(c) Claim 22

186. Claim 22 recites "[t]he method according to claim 20, wherein the cancer is chronic lymphocytic leukemia."

187. The disclosures of Maas, Teagarden, and the Ribomustin® Product Monograph with respect to claim 20 are included above.

188. As shown above, the Ribomustin® Product Monograph specifically taught that Ribomustin® was indicated for chronic lymphocytic leukemia. Exhibit 1008 at 0008 (indicated cancers include "Hodgkin's disease (stages II-IV)[,] Non-Hodgkin's lymphoma[,] Plasmocytoma[,] chronic lymphocytic leukemia[,] [and] breast cancer") (emphasis added).

189. As I explained in detail above, one of skill in the art would have been motivated to utilize the bendamustine hydrochloride pharmaceutical composition taught by Maas and Teagarden for the same indications for which Ribomustin® had been previously administered given the extensive history with Ribomustin®. Accordingly, it is my opinion that the combination of Maas, Teagarden, and the Ribomustin® Product Monograph teach each and every limitation of claim 22.

(d) Claim 23

190. Claim 23 recites "[t]he method according to claim 20, wherein the cancer is non-Hodgkin's lymphoma."

191. The disclosures of Maas, Teagarden, and the Ribomustin® Product Monograph with respect to claim 20 are included above.

192. As shown above, the Ribomustin® Product Monograph specifically taught that Ribomustin® was indicated for non-Hodgkin's lymphoma. *Id.* at 0008

(indicated cancers include "Hodgkin's disease (stages II-IV)[,] Non-Hodgkin's lymphoma[,] Plasmocytoma[,] chronic lymphocytic leukemia[,] [and] breast cancer") (emphasis added).

193. As I explained in detail above, one of skill in the art would have been motivated to utilize the bendamustine hydrochloride pharmaceutical composition taught by Maas and Teagarden for the same indications for which Ribomustin® had been previously administered given the extensive history with Ribomustin®. Accordingly, it is my opinion that the combination of Maas, Teagarden, and the Ribomustin® Product Monograph teach each and every limitation of claim 23.

E. Ground 4: Claims 1-23 Are Obvious Over the Admitted Prior Art in the '270 Patent in View of Teagarden.

194. I have been advised that Fresenius also contends that the admitted prior art in the '270 patent with respect to Ribomustin® in view of Teagarden renders all claims obvious. I do not intend to opine on any legal conclusions with respect to admitted prior art, but merely apply the claims against Table 13 and its associated disclosure, which I understand Fresenius contends represents admitted prior art that can be utilized in an IPR proceeding.

195. My opinions with respect to the disclosure of Table 13 in view of Teagarden, and how those disclosures meet the elements of claims 1-20, are included above. *See supra* ¶¶ B.129B.149.

196. I understand that claims 21-23 respectively recite the method of claim 20, wherein "the cancer is chronic lymphocytic leukemia, Hodgkin's disease, non-Hodgkin's lymphoma, multiple myeloma, or breast cancer," "chronic lymphocytic leukemia," and/or "non-Hodgkin's lymphoma." The '270 patent clearly teaches that, with respect to Ribomustin®, it had been widely used in Germany to treat both chronic lymphocytic leukemia and non-Hodgkin's lymphoma. Exhibit 1001 at 2:1-10.

197. Accordingly, it is my opinion that the admitted prior art in the '270 patent (described here and in connection with the disclosures regarding Table 13 in Ground 2) in combination with Teagarden teach each and every limitation of claims 1-23, and therefore render those claims obvious.

X. SUPPLEMENTATION

198. I may utilize the documents cited and/or listed herein, or portions of those documents, as exhibits at any hearing or trial in this litigation. I may further prepare and use exhibits that summarize portions of my testimony or key terms or concepts presented therein, or other demonstrative exhibits, at any hearing or trial in this litigation.

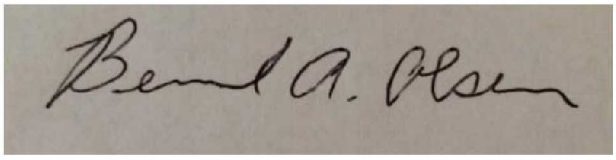
199. I reserve the right to supplement my testimony and this report in response to any judicial determinations, in response to the opinions expressed by the Cephalon's experts in this proceeding, and/or in light of additional evidence or

testimony brought forth at trial or otherwise brought to my attention after the date of my signature below.

XI. CONCLUSION

200. I hereby declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct, and that all statements made of my own knowledge are true and that all statements made on information and belief are believed to be true. I understand that willful false statements are punishable by fine or imprisonment or both. *See* 18 U.S.C. § 1004.

Dated: October 28, 2015



Bernard Olsen, Ph.D.

Exhibit A

BERNARD A. OLSEN, Ph.D.
curriculum vitae

Contact Information

520 Kings Glen Way
Wake Forest, NC
Phone: 765-414-4459
Email: olsen.bernard@gmail.com

Education

Ph.D. (Analytical Chemistry), University of Wisconsin, Madison, 1979

B. S. (Chemistry, with highest distinction), Nebraska Wesleyan University, Lincoln, Nebraska, 1975.

Employment

Olsen Pharmaceutical Consulting, LLC, January 2010-present

- Independent consultant

Independent pharmaceutical consultant, July 2009-December 2009

Aptuit and Aptuit Consulting

- Managing Director, January 2009-July 2009

Eli Lilly and Company, retired December 2008

- Senior Research Fellow, October 2007
- Research Fellow, January, 2002
- Senior Research Scientist, January, 1993
- Research Scientist, March, 1990
- Head, Bioanalytical Development, January, 1989
- Head, Analytical Development, October, 1987
- Research Scientist, January, 1986
- Senior Analytical Chemist, October, 1979

Eastman Kodak

- Summer Professional Program, May-July, 1975

Aptuit Responsibilites

- Manage consulting efforts and develop new opportunities for 5-person patent litigation support group
- Direct contract research organization efforts with management team of SSCI – an Aptuit Company

Lilly Responsibilities – Senior Research Fellow, Analytical Sciences R&D

- Global analytical technical advisor for all small-molecule development projects in Lilly portfolio and technology advancement projects

- Regulatory submission preparation and review of chemistry, manufacturing, and control sections - INDs, CTDs, briefing documents for end-of-phase 2 meetings, pre-NDA meetings, responses to regulatory questions from agencies world-wide, pharmacopeial monographs
- Specification development, member Lilly Specification Committee
- Analytical method development and validation including methods for impurities, trace impurities, and solid state characterization
- Transfer of analytical methods to production sites
- Problem-solving related to marketed product issues such as quality and production problems, counterfeiting, patent infringement
- Contribute to pan-development (analytical, chemical, and formulation development) strategies, coordination, and technical review of projects
- Technical and career mentoring for senior scientists, new managers
- Identification and recruitment of technical talent for analytical sciences
- Due diligence assessment for CMC aspects of in-license opportunities

Job Accomplishments

- Analytical method development, API process development problem-solving, and global product registration related to synthetic and semi-synthetic drug substances as well as intermediates and raw materials. Contributed to the development and support of over 25 commercial drugs and numerous developmental drugs, including cephalosporin and macrolide antibiotics and several central nervous system drugs. Commercial drugs include Ceclor, Dynabac, Prozac, Gemzar, Zyprexa, Evista, Cialis, Alimta, Strattera, Cymbalta, Effient.
- Mentoring and development of many Lilly scientists at all levels and in several functions (analytical, chemical process, formulation process, regulatory, quality, technical services, discovery).
- Developed successful project partnerships with staff at multiple Lilly sites and third-party companies.
- Contributed to stewardship of Lilly products including pharmacopeial monograph development and defense, patent infringement investigations (including $110MM settlement to Lilly for cefaclor patent infringement)

Skills and Areas of Expertise

- Strategic decision-making for drug development especially related to chemistry, manufacturing, and control issues
- HPLC, GC, chiral chromatography, LC-MS
- Analytical method development, including chromatographic and other separation techniques, spectroscopic methods, chiral analysis, trace analysis, chemometric methods
- Method validation
- Impurity investigations including related substances, degradation products, catalysts, residual solvents
- Genotoxic impurity strategies
- Physical property and solid state characterization and development strategy

- Technology transfer
- Drug substance and drug product stability
- Specification setting
- Preparation of worldwide clinical (IND) and marketing authorization (CTD) regulatory submissions
- Responding to regulatory questions
- Patent litigation support as a non-testifying expert or expert witness (deposition and trial experience)
- Suspect counterfeit drug analysis and authentication
- Pharmacopeial monograph development and public standard-setting
- Collaboration, co-development with third parties
- Training and staff development
- GMP quality audits for analytical laboratories

Professional Affiliations and Activities

- American Chemical Society (Analytical Division)
- American Association of Pharmaceutical Scientists
- Reviewer: Journal of Chromatography, Journal of Pharmaceutical and Biomedical Analysis
- Editorial Advisory Board: Journal of Pharmaceutical and Biomedical Analysis, 2007-present
- United States Pharmacopeia, Expert Committees (2000-present), Vice chair of Committee for Monograph Development - Ophthalmology, Oncology, and Dermatology (2005-2010)
- United States Pharmacopeia, Council of Experts – Chair, Monograph Development Committee for Small Molecules-3, July 2010-June 2015
- United States Pharmacopeia, Council of Experts – Chair, Monograph Development Committee for Chemical Medicines-3, July 2015-present
- Product Quality Research Institute, working group on Drug Substance Specifications, 2001-2004
- Purdue University, Adjunct Professor, Department of Industrial and Physical Pharmacy, 2007-2010
- Co-moderator, APQ open forum on QbD for Analytical Methods, AAPS National Meeting, November 2008

Professional Awards and Recognition

- Fellow, American Association of Pharmaceutical Scientists, Nov. 2010
- Journal of Pharmaceutical and Biomedical Analysis – Top Referee recognition, 2007
- Eli Lilly Research Technologies, Product Development and Project Management – Change the World Award, 2001
- Lilly Research Laboratories President's Award, 1998

Publications and Presentations

- 51 publications, including 9 invited papers, 8 book chapters, and an edited book.

- >83 external presentations, including many invited presentations at international venues

Publications

1. B. A. Olsen and D. H. Evans*, "Electron-Transfer Reactions and Conformational Changes Associated with the Reduction of Bianthrone", *Journal of the American Chemical Society*, *103*, 839 (1981).

2. B. A. Olsen, D. H. Evans*, and I. Agranat, "Electron-Transfer Reactions and Conformational Changes Associated with the Reduction of Substituted Bianthrones", *Journal of Electronanalytical Chemistry*, *136*, 139 (1982).

3. J. H. Kennedy* and B. A. Olsen, "Investigation of Perchlorate, Phosphate, and Ion-Pairing Eluent Modifiers for the Separation of Cephalosporin Epimers", J. Chromatogr., 389, 369 (1987).

4. S. V. Snorek*, B. A. Olsen, and D. A. Pierson, "Liquid Chromatographic Determination of Low-molecular-weight Amides in Pharmaceutical Matrices", J. Chromatogr., 458, 287 (1989).

5. E. L. Inman*, R. L. Clemens, and B. A. Olsen, "Determination of EDTA in Vancomycin by HPLC", J. Pharm. Biomed. Anal., 8, 513 (1990).

6. B. A. Olsen*, J. D. Stafford, and D. E. Reed, "Determination of dirithromycin purity and related substances by high-performance liquid chromatography", J. Chromatogr., 594, 203 (1992).

7. L. J. Lorenz, F. N. Bashore, and B. A. Olsen*, "Determination of Process-Related Impurities and Degradation Products in Cefaclor by High-Performance Liquid Chromatography, J. Chromatogr. Sci. , 30, 211 (1992).

8. Olsen, B.A.*; Baertschi, S.W.; Riggin, R.M. "Multidimensional Evaluation of Impurity Profiles for Generic Cephalexin and Cefaclor Antibiotics", J. Chromatogr., 1993, 648, 165-173.

9. Olsen, B.A.*; Sullivan, G.R., "Chemometric Categorization of Octadecylsilyl Bonded-Phase Silica Columns Using Test Mixtures and Confirmation of Results with Pharmaceutical Compound Separations", J. Chromatogr., 1995, 692, 147-159.

10. Larew, L.A.*; Olsen, B.A.; Stafford, J.D.; Wilhelm, M.V., "Comparison of Theory-Based and Empirical Modeling for the Prediction of Chromatographic Behavior in the Ion-Pairing Separation of Benzodiazepine Derived Pharmaceutical Compounds", J. Chromatogr., 1995, 692, 183-193.

11. Olsen, B.A.*; Argentine, M.D., "HPLC Method Development for Duloxetine Hydrochloride Using a Combination of Computer-based Solvent Strength Optimization and Solvent Selectivity Mixture Design", J. Liq. Chromatogr. & Rel. Technol., 1996, 19, 1993-2007.

12. Perry, F.M.*; Wirth, D.D.; Olsen, B.A., "Drug substitution and assumptions of equivalence", Aus. J. Pharm., 1997, 78, 105.

13. Olsen, B.A.*; Argentine, M.D., "Investigation of response factor ruggedness for the determination of drug impurities using high-performance liquid chromatography with ultraviolet detection", J. Chromatogr. A, 1997, 762, 227-234.

14. Olsen, B.A.*; Tsang, P.K.S., "Considerations for the development of separation methods for pharmaceutical process control", Process Control and Quality, 1997, 10, 25-39. invited review

15. Olsen, B.A.*; Perry, F.M.; Snorek, S.V.; Lewellen, P.L., "Accelerated Conditions for Stability Assessment of Bulk and Formulated Cefaclor Monohydrate", Pharm. Dev. and Tech., 1997, 2, 303-312.

16. Wirth, D.D.; Olsen, B.A.*; Hallenbeck, D.K.; Lake, M.E.; Gregg, S.M.; Perry, F.M., "Screening Methods for Impurities in Multi-sourced Fluoxetine Hydrochloride Drug Substances and Formulations", Chromatographia, 1997, 46, 511-523.

17. Olsen, B.A.*; Wirth, D.D.; Larew, J.S., "Determination of Fluoxetine Hydrochloride Enantiomeric Excess Using High Performance Liquid Chromatography with Chiral Stationary Phases", J. Pharm. Biomed. Anal., 1998, 17, 623-630.

18. B. A. Olsen* and M. D. Argentine, "Wavelength system suitability for HPLC with UV dectection", American Laboratory, November 1998. invited paper

19. B. A. Olsen* and J. L. Shimek, "Chromatographic System Suitability Using Peak Valley-Height Measurements", Pharmacopeial Forum, 26 (2000) 1170-1176.

20. L. Yang*, L. Liu, B. A. Olsen and M. A. Nussbaum, "The determination of oxalic acid, oxamic acid, and oxamide in a drug substance by ion-exclusion chromatography", J. Pharm. Biomed. Anal., 22 (2000) 487-493.

21. B. A. Olsen, "Hydrophilic Interaction Chromatography Using Amino and Silica Columns for the Determination of Polar Pharmaceuticals and Impurities", J. Chromatogr. A, 913 (2001) 113-122.

22. B. A. Olsen*, M. W. Borer, F. M. Perry and R. A. Forbes, "Screening for Counterfeit Drugs by Near-Infrared Spectroscopy", Pharm. Tech., 26 (2002) 62, 64, 66, 68, 70, 71, 95.

23. B. A. Olsen and S. W. Baertschi, "Strategies for Investigation and Control of Process and Degradation-Related Impurities", in Handbook of Isolation and Characterization of Impurities in Pharmaceuticals, S. Ahuja and K. M. Alsante, Eds., Academic Press, San Diego, 2003, pp.89-117, invited chapter.

24. B.A. Olsen "Developing and Using Analytical Methods to Achieve Quality by Design and Efficiency in Drug Development", Pharm. Tech., supplement on Scaling up Manufacturing Processes, 2005, S14, S16-S18, S20-S22, S24-S25. invited article.

25. Baertschi, S.W.; Olsen, B.A., Alsante, K.M. "Stress Testing: Relation to the Development Timeline", in Pharmaceutical Stress Testing, Baertschi, S.W., Ed., Taylor and Franics, Boca Raton, 2005, pp. 173-179, invited chapter.

26. Olsen, B.A.*, Larew, L.A. "Comparative Stress Stability Studies for Rapid Evaluation of Manufacturing Changes or Materials from Multiple Sources", in Pharmaceutical Stress Testing, Baertschi, S.W., Ed., Taylor and Francis, Boca Raton, 2005, pp. 235-259, invited chapter.

27. Olsen, B.A.*; Kiehl, D.E.; "Authentication and Fingerprinting of Suspect Counterfeit Drugs" Am. Pharm. Rev. 9 (2006) 115-118. invited article.

28. Sellers, J.A., Olsen, B.A.*, Owens, P.K., Gavin, P.F.; "Determination of the enantiomer and positional isomer impurities in atomoxetine hydrochloride with liquid chromatography using polysaccharide chiral stationary phases", J. Pharm. Biomed. Anal., 41 (2006) 1088-1094.

29. Gavin, P.F.*, Olsen, B.A., Wirth, D.A., Lorenz, K.T.; "A quality evaluation strategy for multi-sourced active pharmaceutical ingredient (API) starting materials", J. Pharm. Biomed. Anal., 41 (2006) 1251-1259.

30. Olsen, B.A.*, Castle, B.C., Myers, D.P. "Advances in HPLC technology for the determination of drug impurities" Trends Anal. Chem. 25 (2006) 796-805. invited article.

31. Argentine, M.D.; Owens, P.K.; Olsen, B.A.*, "Strategies for investigation and control of process-related impurities in drug substances", Adv. Drug Del. Rev. 59 (2007) 12-28, invited article.

32. Hofer, J.D., Olsen, B.A.*, Rickard, E.C., "Is Drug Substance HPLC Assay a Useful Quality Control Attribute", J. Pharm. Biomed. Anal. 44 (2007) 906-913.

33. Olsen, B.A.*; Gavin, P.F.; Wozniak, T.J., "Quality by Design Considerations for Analytical Methods", AAPS Newsmagazine, 10, Dec. 2007, 16-23.

34. Gavin, P.F.*; Olsen, B.A., "A quality by design approach to impurity method development for atomoxetine hydrochloride (LY139603)", J. Pharm. Biomed. Anal. 46 (2008) 431-441.

35. Pierson, D.A.*; Olsen, B.A.; Robbins, D.K.; DeVries, K.M; Varie, D.L.; "Approaches to assessment, testing decisions, and analytical determination of genotoxic impurities in drug substances", Org. Process Res. Dev. 13 (2009) 285-291.

36. Biswas, K.M.; Castle, B.C.*; Olsen, B.A.; Risley, D.S.; Skibic, M.J.; Wright, P.B.; "A simple and efficient approach to reversed-phase HPLC method screening", J. Pharm. Biomed. Anal. 49 (2009) 692-701.

37. Debrus, B.*; Lebrun, P.; Ceccato, A.; Caliaro, G.; Govaerts, B.; Olsen, B.; Rozet, E.; Boulanger, B.; Hubert, P.; "A new statistical method for the automated detection of peaks in UV-DAD chromatograms of a sample mixture", Talanta 79 (2009) 77-85.

38. Chi, H.-M.; Moskowitz, H, Ersoy, O.K.; Altinkemer , K.; Gavin, P.F; Huff, B.E.; Olsen, B.A.; "Machine learning and genetic algorithms in pharmaceutical development and manufacturing processes", Decision Support Systems 48 (2009) 69–80.

39. B.A. Olsen, "Genotoxic Impurity Issues in Drug Development", *Pharma Focus Asia*, 12 (2009) 20-22.

40. Baertschi, S.W.; Olsen, B.A.; Alsante, K.M; Reed, R.A. "Relation to the Development Timeline" in Pharmaceutical Stress Testing: Predicting Drug Degradation, Second Edition, S.W. Baertschi, K.M. Alsante, R.A. Reed, Eds., Informa Healthcare, London, 2011.

41. Nussbaum, M.A.; Jansen, P.J; Baertschi, S.W.; Kaerner, A.; Olsen, B.A. "Role of "Mass Balance" in Pharmaceutical Stress Testing" in Pharmaceutical Stress Testing: Predicting Drug Degradation, Second Edition, S.W. Baertschi, K.M. Alsante, R.A. Reed, Eds., Informa Healthcare, London, 2011.

42. Olsen, B.A.; Larew, L.A.; Watkins, M.A.; "Comparative Stress Stability Studies for Rapid Evaluation of Manufacturing Changes or Materials from Multiple Sources" in Pharmaceutical Stress Testing: Predicting Drug Degradation, Second Edition, S.W. Baertschi, K.M. Alsante, R.A. Reed, Eds., Informa Healthcare, London, 2011.

43. Olsen, B.A., "Quality by Design (QbD) and Analytical Method Development" invited chapter in Encyclopedia of Pharmaceutical Science and Technology, 4th Ed., in press.

44. USP Council of Experts, USP Reference Standards Committee, Hauck W.W., "Primary and Secondary Reference Materials for Procedures to Test the Quality of Medicines and Foods", Pharm. Res. 29 (2012) 922–931.

45. Olsen, B.A; Risley, D.S.; Sharp, V.S.; Pack, B.W.; Lytle, M.L.; "Pharmaceutical Applications of Hydrophilic Interaction Chromatograpy" in Hydrophilic Interaction Chromatography – A Guide for Practitioners, B.A. Olsen and B.W. Pack, Eds., Wiley, Hoboken, NJ USA, 2013, 111-168.

46. Rabel, F; Olsen, B.A.; "Advances in Hydrophilic Interaction Chromatography (HILIC) for Biochemical Applications, in Hydrophilic Interaction Chromatography – A Guide for Practitioners, B.A. Olsen and B.W. Pack, Eds., Wiley, Hoboken, NJ USA, 2013, 195-218.

47. B.A. Olsen and B.W. Pack, Eds.; Hydrophilic Interaction Chromatography – A Guide for Practitioners, Wiley, Hoboken, NJ USA, 2013.

48. K.A. Russo, S.S. DeMars, M. Van Hook, A.J DeStefano, M. Cutera, B.A. Olsen, E. Parente, G. Van Buskirk, R.L. Williams; "USP's Monographs in Support of FDA's OTC Monograph System: Modernization Opportunities", Pharm. Forum., 39(1), 2013.

49. B. Olsen, E. Parente, J. Daniels, E. McGonigle, T. Engel, D. Tuck, M. Cutera, G. Van Buskirk; "System Suitability for USP Chromatographic Procedures – Small Molecules", Pharm. Forum, 39(5), 2013.

50. K.M. Alsante, K.C. Huynh-Ba, S.W. Baertschi, R.A. Reed, M.S. Landis, S. Furness, B. Olsen, M. Mowery, K. Russo, R. Iser, G.A. Stephenson, P. Jansen; "Recent Trends in Product Development and Regulatory Issues on Impurities in Active Pharmaceutical Ingredient (API) and Drug Products. Part 2: Safety Considerations of Impurities in Pharmaceutical Products and Surveying the Impurity Landscape", AAPS PharmSciTech, 15 (2014) 237-251.

51. N.Lewen, A.C. Bevilacqua, B.A. Olsen, A. Warner, M. Adamson, G. Carr, P. Chen, J. DeVries, M. Dmitriieva, M. Hornig, J. Rohrer, A. Hernandez-Cardoso; Modernization of Identification Tests in *USP–NF*, Pharm. Forum, 41(2), 2015.

External Presentations/Posters

1. T.L. Hassinger* and B.A. Olsen, "Analysis of Fermentation Broths and Raw Materials Utilizing Ion Chromatographic Techniques", Rocky Mountain Conference, Denver, Colorado, August, 1982, oral presentation.

2. B.A. Olsen*, T.L. Hassinger, and M.P. Fogarty, "Determination of Ionic Impurities in Pharmaceutical Raw Materials by Ion Chromatography", Pittsburgh Conference on Analytical Chemistry and Applied Spectroscopy, Atlantic City, New Jersey, March, 1984, oral presentation.

3. J.H. Kennedy* and B.A. Olsen, "Investigation of Perchlorate, Phosphate, and Ion-Pairing Eluent Modifiers for the Separation of Cephalosporin Epimers", Pittsburgh Conference on Analytical Chemistry and Applied Spectroscopy, New Orleans, Louisana, March, 1985, oral presentation.

4. C.S. Bryant* and B.A. Olsen, "Industrial Applications of Ion Chromatography", Great Lakes Regional American Chemical Society Meeting, West Lafayette, Indiana, June, 1985, oral presentation.

5. S.V. Snorek*, R.A. Dunham, and B.A. Olsen, "Investigation of Headspace Methods for the Determination of Residual Organic Solvents in Bulk Pharmaceuticals", Pittsburgh Conference on Analytical Chemistry and Applied Spectroscopy, Atlantic City, New Jersey, March, 1986, oral presentation.

6. S.V. Snorek, B.A. Olsen, and D.A. Pierson, "Liquid Chromatographic Determination of Low Molecular Weight Amides in Pharmaceutical Matrices", Twelfth International Symposium on Column Liquid Chromatography, Washington, D. C., June, 1988, poster.

7. B.A. Olsen, "Undergraduate Education in Analytical Chemistry - A Perspective from Industry", 196th American Chemical Society National Meeting, Los Angeles, California, September, 1988. Invited lecture.

8. B.A. Olsen, "Analytical Problem Solving in Pharmaceutical Process Development", Uni. of Wisconsin-Madison, April 18, 1991, Analytical Sciences Division seminar.

9. P. K. Tsang*, B. A. Olsen, T. J. Wozniak, and S. L. Vogtman, "Peak Homogeneity Determination - Is Photodiode Array Detection the Answer?", Sixteenth International Symposium on Column Liquid Chromatography, Baltimore, Maryland, June, 1992, poster.

10. B. A. Olsen*, S. W. Baertschi, and R. M. Riggin, "Multidimensional Evaluation of Impurity Profiles for Generic Cephalexin and Cefaclor Antibiotics", 204th American Chemical Society National Meeting, Washington, D. C., August, 1992, poster.

11. Olsen, B.A., "From High School to the Pharmaceutical Industry - A Path Starting with Project SEED", American Chemical Society National Meeting, Chicago, Illinois, August 22-26, 1993. Invited lecture.

12. Olsen, B.A., "Chemical Clues to Patent Infringement - The Ceclodan Case", University of Illinois at Urbana-Champaign, March 9, 1994. Invited lecture.

13. Olsen, B.A.*; Sullivan, G.R., "Chemometric Categorization of Octadecylsilyl Bonded-Phase Silica Columns Using Test Mixtures and Confirmation of Results with Pharmaceutical Compound Separations", Eighteenth International Symposium

on Column Liquid Chromatography, Minneapolis, MN, May 9-13, 1994, oral and poster presentations.

14. Larew, L.A.*; Olsen, B.A.; Stafford, J.D.; Wilhelm, M.V., "Comparison of Theory-Based and Empirical Modeling for the Prediction of Chromatographic Behavior in the Ion-Pairing Separation of Benzodiazepine Derived Pharmaceutical Compounds", Eighteenth International Symposium on Column Liquid Chromatography, Minneapolis, MN, May 9-13, 1994, poster.

15. Berglund, R.A.; Olsen, B.A., "Process and Analytical Development at Tippecanoe Laboratories", DePauw Uni., Oct. 6, 1994; Valparaiso Uni., Nov. 29, 1994; Uni. of Dayton, Dec. 5, 1994, Indiana State Uni., Jan. 24, 1995; Butler Uni., Feb. 9, 1995; IUPU-Ft. Wayne, Oct. 25, 1995; Oberlin College, Jan. 17,1996; College of Wooster, Jan. 18, 1996; Denison Uni., Jan. 19, 1996; Earlham College, May 8, 1996; Chicago State Uni., Oct. 7, 1996; Bradley Uni., Oct. 22, 1996; Eastern Kentucky Uni., Apr. 24, 1997; Centre College, Apr. 24, 1997; Berea College, Apr. 25, 1997; Beloit College, Sep. 23, 1997; Rockford College, Sep. 23, 1997; Northern Kentucky Uni., Oct. 20, 1997; Western Michigan Uni./Kalamazoo College, Nov. 24, 1997; Albion College, April 16, 1998; DePauw Uni., Nov. 5, 1998; Indiana State Uni., Nov. 17, 1998; Uni. of Toledo, Feb. 1, 1999; Ohio Northern Uni., Feb. 2, 1999; Denison Uni., Oct. 26, 1999; Ohio Wesleyan Uni., Oct. 27, 1999; Kenyon College, Oct. 28, 1999; Purdue Uni. Dec. 6, 1999; Calvin College, Apr. 6, 2000; Hope College, Apr. 7, 2000; Kent State Uni., Sep. 14, 2000; Youngstown State Uni., Sep. 15, 2000; Uni. of Cincinnati, Oct. 26, 2000; Xavier Uni., Oct. 27, 2000; Illinois State Uni., Mar. 1, 2001; DePaul Uni., May 11, 2001.

16. Olsen, B.A.*; Argentine, M.D., "HPLC Method Development Using a Combination Approach -- DryLab® and Solvent Selectivity Mixture Design", Sixth International Symposium on Pharmaceutical and Biomedical Analysis, April 23-26, 1995, poster.

17. Olsen, B.A.*; Argentine, M.D., "Investigation of Response Factor Ruggedness for the Determination of Drug Impurities by HPLC with UV Detection", 20th International Symposium on High Performance Liquid Phase Separations and Related Techniques (HPLC '96), San Francisco, CA, June 1996, poster

18. Olsen, B.A.*; Perry, F.M., "Rapid Stability Assessment of Bulk and Formulated Cefaclor Monohydrate", 1996 American Association of Pharmaceutical Scientists National meeting, Seattle, WA, Oct. 28-31, 1996, poster.

19. Olsen, B.A. "Strategies for Investigation and Control of Impurities in Pharmaceutical Development I: Process-Related Impurities", American Association of Pharmaceutical Scientists Midwest Regional Meeting, May 19, 1997, Chicago, IL. Invited lecture.

20. Olsen, B.A., "Considerations in the Development of Chiral Assays for Quality Control Use", 31st American Chemical Society Middle Atlantic Regional Meeting, May 30, 1997, Pleasantville, NY. Invited lecture.

21. Wirth, D.D; Olsen, B.A., "Appropriate Techniques for Investigating Drug Impurities from Multiple Manufacturing Sources", FDA seminar program, Rockville, MD, September 26, 1997. Invited lecture.

22. Olsen, B.A., "HPLC Method Development for Investigation of Drug Substance Impurities", 24th Annual Conference of the Federation of Analytical Chemistry and Spectroscopy Societies, Providence, RI, October 27, 1997. Invited lecture.

23. Argentine, M.D.*; Olsen, B.A., "Investigation of Capillary Electrochromatography (CEC) in Relation to HPLC for Drugs and Related Compounds", 1998 International Symposium on Column Chromatography and Related Techniques - HPLC-98, St. Louis, MO, MAY 3-8, 1998, poster.

24. Yang,L.*; Liu,L.; Olsen, B.A.; Nussbaum, M.A., "The Determination of Oxalic Acid, Oxamic Acid, and Oxamide in a Drug Substance by Ion-Exclusion Chromatography", Tenth International Symposium on Pharmaceutical and Biomedical Analysis, May 9-12, 1999, Washington DC, poster.

25. Olsen, B.A.*; Yang, L., "Hydrophilic Interaction Chromatography for the Determination of Polar Pharmaceutical Compounds and Impurities", Tenth International Symposium on Pharmaceutical and Biomedical Analysis, May 9-12, 1999, Washington DC, oral and poster presentation.

26. B.A. Olsen, "Analytical Problem-Solving in Pharmaceutical Development", Florida A&M University, March 1, 2000. Invited lecture.

27. B.A. Olsen, "Analytical Problem-Solving in Pharmaceutical Development", Florida State University, March 2, 2000. Invited lecture.

28. B.A. Olsen, "Hydrophilic Interaction Chromatography Using Amino and Silica Columns for the Determination of Polar Pharmaceuticals and Impurities", 24th International Symposium on High Performance Liquid Phase Separations and Related Techniques, June 24-30, 2000, Seattle, WA, poster.

29. P.F. Gavin* and B.A. Olsen, "HPLC Analysis of Tomoxetine Hydrochloride Using Correlated-Peak System Suitability", Pittsburgh Conference, New Orleans, LA, March 1-6, 2001, poster.

30. B.A. Olsen, "Strategies for Investigation and Control of Process-Related Impurities", Institute for International Research conference on Detecting, Identifying and Quantitating Impurities, Philadephia, PA, March 26-28, 2001. Invited lecture.

31. B.A. Olsen, "Analytical Method Development for Impurities in Pharmaceuticals", Florida State University, April 19, 2001. Invited lecture.

32. B.A. Olsen*, M. W. Borer, F. M. Perry and R. A. Forbes, "Screening for Counterfeit Drugs by Near-Infrared Spectroscopy", Pittsburgh Conference, New Orleans, LA, March 2002, oral presentation.

33. B.A. Olsen, "Screening for Counterfeit Drugs by Near-Infrared Spectroscopy" Seminar presentation at FDA Forensic Chemistry Center, Cincinnati, OH, Nov. 29, 2001.

34. N.P. Toltl*, R.P Grant, W. Lau, C. Cameron, M. Angod, Y.C. Lee, T.J. Wozniak, N.E. McDonald, B.A. Olsen, P.F. Gavin, "Investigating the Use of Monolithic Columns for HPLC Method Development and High-Throughput Analysis, Federation of Analytical Chemistry and Spectroscopy Societies Annual Meeting, Providence, RI, October 13-17, 2002. Oral presentation

35. B.A. Olsen*, M.W. Borer, F.M. Perry, R.A. Forbes, "Screening for Counterfeit Drugs by Near-Infrared Spectroscopy" Pittsburgh Conference, New Orleans, LA, March 18-21, 2002. Oral presentation.

36. P.F. Gavin*, K.T. Lorenz, B.A. Olsen, D.D. Wirth, "Strategies for Quality Evaluation of Multi-Sourced Starting Materials", American Association of Pharmaceutical Scientists, Annual Meeting, Toronto, Canada, Nov. 10-14, 2002. Poster presentation

37. B.A. Olsen, "Strategies for Investigation and Control of Process-Related Impurities", FDA Workshop on Pharmaceutical Impurities, Gaithersburg, MD, March 22, 2004. Invited lecture.

38. B.A. Olsen, "HPLC Methods for Investigation of Process-Related Impurities", HPLC 2004, Philadelphia, PA, June 15, 2004. Invited lecture.

39. B.A. Olsen* and S.V. Snorek, "API Physical Property Characterization and Issues During Drug Development", Calibration Validation Group/Therapeutic Product Directorate joint meeting, Toronto, Canada, September 27, 2004. Invited lecture.

40. B.A. Olsen, "Design and Utilization of Analytical Methodologies and Appropriate Specifications to Enhance Product Quality and Achieve Accelerated Drug Development", American Association of Pharmaceutical Scientists, Annual Meeting, November 11, 2004, Baltimore, MD. Invited lecture.

41. B.A. Olsen, Invited participant in Hot Topic panel discussion on counterfeit drugs and technologies for authentication, American Association of Pharmaceutical Scientists, Annual Meeting, November 10, 2004, Baltimore, MD.

42. B.A. Olsen*, D. E. Reed, D. E. Kiehl, "Quality Measures to Prevent Counterfeit Medicines: Industry's Measures", Quality International-FIP Conference, Royal Pharmaceutical Society, London, England, November 21-23, 2005. Invited lecture.

43. N. Toltl, S. W. Baertschi, T. J. Wozniak, B. A. Olsen*, "Artifact Peaks in HPLC Impurity Analysis Caused by Trace Levels of Copper", HPLC 2006, San Francisco, CA, June 19-22, 2006, poster.

44. Olsen, B.A., "New Analytical Technologies and Monograph Impact", USP Annual Scientific Meeting, Denver, CO, Sept 27-29, 2006. Invited lecture.

45. Olsen, B.A., "Genotoxic Impurities Strategies", USP Annual Scientific Meeting, Denver, CO, Sept 27-29, 2006. Invited lecture.

46. Hofer, J.D., Olsen, B.A.*, Rickard, E.C., "Is Drug Substance HPLC Assay a Useful Quality Control Attribute", American Association of Pharmaceutical Scientists National meeting, San Antonio, TX, Oct. 29-Nov. 2, 2006. poster

47. Olsen, B.A*., Castle, B.C., "Application of Fast HPLC Techniques to Pharmaceutical Analysis", Canadian Society of Chemistry 2007 Conference, Winnipeg, Canada, May 27, 2007. Invited lecture.

48. Olsen, B.A*., Castle, B.C, "Application of Fast HPLC Techniques to Pharmaceutical Analysis", Dalian International Symposium and Exhibition on Chromatography, Dalian, China, June 5, 2007. Invited lecture.

49. B.C. Castle, J.M. Cintrón, T.D. Maloney, B.A. Olsen, J.D. Stafford*, "High Efficiency Fast-Liquid Chromatography Utilizing 2.5 μm Particle Columns", HPLC 2008, Baltimore, MD, May 12-15, 2008, oral presentation.

50. B.A. Olsen, "Chemical process and analytical approaches for addressing genotoxic impurities throughout development", Genotoxic Impurities, Informa Life Sciences, Brussels, Belgium, June 17-18, 2008. Invited lecture.

51. B.A. Olsen, "Degradation products and synthetic process impurities in API and drug products", Pharmaceutical Impurities, International Pharmaceutical Academy, Somerset, NJ, March 30-31, 2009. Invited lecture.

52. B.A. Olsen, "Impurity investigation and quality control: Specification strategies", Pharmaceutical Impurities, International Pharmaceutical Academy, Somerset, NJ, March 30-31, 2009. Invited lecture.

53. B.A. Olsen, "Investigation of process-related impurities", Sindusfarma-USP Workshop on Impurities and Forced Degradation Studies, São Paulo, Brazil, June 22-23, 2009. Invited lecture.

54. B.A. Olsen, "Analytical methods for impurities", Sindusfarma-USP Workshop on Impurities and Forced Degradation Studies, São Paulo, Brazil, June 22-23, 2009. Invited lecture.

55. B.A. Olsen, "Addressing Genotoxic Impurities in Drug Development", Land o' Lakes Conference – 49th Annual Conference on Pharmaceutical Analysis, Merrimac, WI, July 27-31, 2009, Invited lecture.

56. B.A. Olsen, "HPLC-UV Quantitation and Relative Response Factors", Sindusfarma-USP Workshop on Liquid Chromatography, São Paulo, Brazil, September 21-22, 2009. Invited lecture.

57. B.A. Olsen, "Chromatographic System Suitability", Sindusfarma-USP Workshop on Liquid Chromatography, São Paulo, Brazil, September 21-22, 2009. Invited lecture.

58. B.A. Olsen, "Chiral HPLC Separations", Sindusfarma-USP Workshop on Liquid Chromatography, São Paulo, Brazil, September 21-22, 2009. Invited lecture.

59. B.A. Olsen, "Spectroscopic Tools and Approaches for Investigating Suspect Counterfeit Medicines", Analysis and Pharmaceutical Quality Open Forum, American Association of Pharmaceutical Scientists Annual Meeting, Los Angeles, CA, November 8-12, 2009. Invited lecture.

60. B.A. Olsen, "Quality by Design in Analytical Methods", USP and Middle East/North Africa Stakeholders, 5th Annual Science Meeting, Amman, Jordan, November 15-16, 2009. Invited lecture.

61. B.A. Olsen, "Impurities: ICH Perspective", USP and Middle East/North Africa Stakeholders, 5th Annual Science Meeting, Amman, Jordan, November 15-16, 2009. Invited lecture.

62. B.A. Olsen, "ICH Q8, Q9, and Q10", USP and Middle East/North Africa Stakeholders, 3rd Compendial Science Meeting, Cairo, Egypt, November 18-19, 2009. Invited lecture.

63. B.A. Olsen, "Supply Chain Security and Counterfeit Drug Analysis", USP and Middle East/North Africa Stakeholders, 3rd Compendial Science Meeting, Cairo, Egypt, November 18-19, 2009. Invited lecture.

64. B.A. Olsen, "Supply Chain Security and Counterfeit Drug Analysis", USP and Ekin Kimya, 3rd Annual Science Meeting, Istanbul, Turkey, November 20, 2009. Invited lecture.

65. B.A. Olsen, "Strategies to Address Genotoxic Impurities in Process Development", Organic Process Research and Development, San Diego, CA, January 20-22, 2010, Invited lecture.

66. B.A. Olsen, "Making Decisions Regarding Stress Degradation Studies and Genotoxic Impurities", Institute for International Research 6th Annual Forced Degradation Forum, Philadelphia, PA, March 15-16, 2010.

67. B.A. Olsen, Invited presenter for Hot Topic panel discussion on "Development and Regulatory Considerations for Preparing New Formulations Based on Established Active Pharmaceutical Ingredients", American Association of Pharmaceutical Scientists, Annual Meeting, November 17, 2010, New Orleans, LA.

68. B.A. Olsen, "Current Issues and Concerns for Impurities in Pharmaceuticals" USP Western Compendial Discussion Group & AOAC-Southern California Section, April 15, 2011, Irvine, CA. Invited lecture.

69. B.A. Olsen, "Investigation and Control Strategies for Process-Related Impurities", USP Workshop on Impurities and Forced Degradation, May 19-20, 2011, São Paulo, Brazil. Invited lecture.

70. B.A. Olsen, "Analytical Methods for Impurity Investigations", USP Workshop on Impurities and Forced Degradation, May 19-20, 2011, São Paulo, Brazil. Invited lecture.

71. B.A. Olsen, "Genotoxic Impurities – An Overview of Current Status and Issues", Webinar sponsored by American Association of Pharmaceutical Scientists, September 22, 2011.

72. B.A. Olsen, "Impurities in Pharmaceuticals – A Survey Course", one-day short course, Eastern Analytical Symposium, Somerset, NJ, November 13, 2011.

73. B.A. Olsen, "Impurities in Pharmaceuticals – A Survey Course", one-day short course, PittCon, Orlando, FL, March 13, 2012.

74. B.A. Olsen, "Genotoxic Impurities in Drug Substances and Products – A Regulatory Update", Telecon presentation sponsored by FX Conferences, July 9, 2013.

75. B.A. Olsen, "Chemical Medicines: Impurities", USP Science and Standards Symposium, São Paulo, Brazil, July 25, 2013. Invited lecture.

76. B.A. Olsen, "Chemical Medicines: Impurities", Workshop em Controle de Qualidade de Medicamentos e Cosméticos: Atualização e Tendênicas", University of São Paulo, July 29, 2013. Invited lecture.

77. B.A. Olsen, "USP modernization through a reference procedure", USP Science and Standards Symposium, Baltimore, MD, September 19, 2013. Invited lecture.

78. B.A. Olsen, "Impurities in Pharmaceuticals – A Survey Course", one-day short course, PittCon, Chicago, IL, March 6, 2014

79. B.A. Olsen, "Chemical Medicines: Impurities", 4th ASEAN-USP Scientific Symposium, Da Nang, Vietnam, June 16-17, 2014, Invited lecture.

80. B.A. Olsen, "Impurities in Drug Substances and Drug Products – A USP Approach", one-day short course, USP Global Education and Training, Da Nang, Vietnam, June 18, 2014.

81. B.A. Olsen, "Chemical Medicines: Impurities", Ministry of Food and Drug Safety-USP Joint Scientific Symposium, Seoul, Korea, June 19, 2014. Invited lecture.

82. B.A. Olsen, "Impurities in Drug Substances and Drug Products – A USP Approach", one-day short course, USP Global Education and Training, Seoul, Korea, June 20, 2014.

83. B.A. Olsen, "GMPs for Finished Pharmaceuticals", two-day short course, USP Global Education and Training, Mumbai, India March 23-24, 2015; Hyderabad, India, March 26-27, 2015.

*Presenter(s)

Exhibit B

Exhibit B: Depositions and Testimony

Of

Bernard A. Olsen, PhD

In Last 4 Years

1. Cephalon, Inc. and Cima Labs, Inc. v. Mylan Pharmaceuticals, Inc. and Mylan Inc., Case No. 11-164 (SLR) (D. Del.)

Exhibit C

Materials Considered by Bernard Olsen

- U.S. Patent No. 8,791,270
- Prosecution History of '270 patent
- Prosecution History of '190 patent
- Maas, *Stability of Bendamustine Hydrochloride in Infusions*, 49 PHARMAZIE 775 (1994)
- The Ribomustin® Product Monograph, 2002
- Teagarden, *Practical Aspects of Lyophilization Using Non-Aqueous Co-Solvent Systems*, 15 EUR. J. PHARM. SCI. 115 (March 2002)
- Gust, *Investigations on the Stability of Bendamustin, a Cytostatic Agent of the Nitrogen Mustard Type, I. Synthesis, Isolation, and Characterization of Reference Substances,* 128 MONATSHEFT FÜR CHEMIE 291 (1997)
- http://www.waters.com/waters/nav.htm?cid=10049055
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Exhibit D

Peak Integration Summary Results

Integration	Peak Area %			
	HP1	HP1 +HP2	NP1	Total
Pixel 1	2.37	2.65	1.95	4.60
Pixel 2	2.18	2.38	2.08	4.46
Pixel 3	2.39	2.67	1.96	4.63
Pixel 4	1.99	2.33	1.81	4.14
Pixel 5	2.21	2.51	1.83	4.34
Pixel 6	2.47	2.66	1.93	4.59
USCAN-IT 1	2.05	2.52	2.05	4.57
USCAN-IT 2	2.09	2.67	2.03	4.70
USCAN-IT 3	2.04	2.51	1.95	4.46
USCAN-IT 4	2.03	2.53	2.04	4.57
Excel 1	2.29	2.72	2.09	4.81
Excel 2	2.01	2.34	2.09	4.43

Exhibit E

3.493548	1.058201		Column 1 = Time points			
3.5	1.058201		Column 2 = Response			
3.506452	1.058201					
3.512903	1.058201					
3.519355	1.058201					
3.525806	0.952381					
3.532258	0.952381					
3.53871	1.375661		baseline slope for HP1 =	-0.39523123		
3.545161	1.375661		baseline slope for NP1=	0.170855164		
3.551613	1.375661		baseline slope for BM1=	0.079237939		
3.558064	1.375661					
3.564516	1.375661		baseline slope for HP1 + HP2=	0.169095534		
3.570968	1.375661					
3.577419	1.375661					
3.583871	1.375661					
3.590322	1.375661					
3.596774	1.375661					
3.603226	1.375661					
3.609677	1.375661					
3.616129	1.375661					
3.622581	1.375661					
3.629032	1.375661					
3.635484	1.375661					
3.641936	1.375661					
3.648387	1.375661					
3.654839	1.375661					
3.66129	1.375661					
3.667742	1.269841					
3.674194	1.269841					
3.680645	1.269841					
3.687097	1.269841					
3.693548	1.375661					
3.7	1.375661					
3.706452	1.375661					
3.712903	1.375661					
3.719355	1.375661					
3.725806	1.375661					
3.732258	1.375661					
3.73871	1.375661					

3.745161	1.375661					
3.751613	1.375661					
3.758065	1.375661					
3.764516	1.375661					
3.770968	1.375661					
3.777419	1.375661					
3.783871	1.481481					
3.790323	1.481481					
3.796774	1.481481					
3.803226	1.481481					
3.809677	1.481481			Baseline response for HP1+HP2	Area slice for HP1+HP2	
3.816129	1.587302			1.48366284		
3.822581	1.587302			1.484753844	0.00066516	
3.829032	1.587302			1.485844679	0.00065802	
3.835484	1.587302			1.486935684	0.000651083	
3.841935	1.587302			1.488026519	0.000643945	
3.848387	1.587302			1.489117523	0.000637006	
3.854839	1.693122			1.490208528	0.000971342	
3.86129	1.693122			1.491299363	0.001305476	
3.867742	1.693122			1.492390367	0.00129864	
3.874193	1.693122			1.493481203	0.001291401	
3.880645	1.693122			1.494572207	0.001284563	
3.887097	1.798942			1.495663212	0.001618899	
3.893548	1.798942			1.496754047	0.001952933	
3.9	1.798942	Baseline Response for HP1	Area slice for HP1	1.497845051	0.001946197	
3.906452	1.798942	1.793841936		1.498936056	0.001939158	
3.912903	1.798942	1.7912923	4.11244E-05	1.500026891	0.00193182	
3.919355	1.798942	1.788742268	5.75823E-05	1.501117895	0.001925081	
3.925807	1.798942	1.786192236	7.40351E-05	1.5022089	0.001918042	
3.932258	1.798942	1.783642599	9.04726E-05	1.503299735	0.001910707	
3.93871	1.798942	1.781092567	0.000106938	1.504390739	0.001903964	
3.945161	1.798942	1.778542931	0.000123371	1.505481575	0.001896632	
3.951613	1.798942	1.775992899	0.000139841	1.506572579	0.001889887	
3.958065	1.798942	1.773442867	0.000156294	1.507663583	0.001882848	
3.964516	1.798942	1.77089323	0.000172719	1.508754419	0.001875519	
3.970968	1.798942	1.768343198	0.000189197	1.509845423	0.001868771	
3.977419	1.798942	1.765793562	0.000205617	1.510936258	0.001861444	
3.983871	1.904762	1.76324353	0.000563475	1.512027263	0.002196069	
3.990323	1.904762	1.760693498	0.000921304	1.513118267	0.002530405	
3.996774	1.904762	1.758143861	0.00093761	1.514209102	0.002522975	
4.003226	2.010582	1.755593829	0.001295582	1.515300107	0.002857703	
4.009677	2.116402	1.753044192	0.001994475	1.516390942	0.003532867	
4.016129	2.222222	1.750494161	0.002693986	1.517481947	0.004209127	

4.022581	2.328042	1.747944129	0.00339319	1.518572951	0.004884839	
4.029032	2.433862	1.745394492	0.004091758	1.519663786	0.005559689	
4.035484	2.539682	1.74284446	0.004791594	1.520754791	0.006236263	
4.041935	2.645503	1.740294823	0.005489948	1.521845626	0.006910907	
4.048387	2.857143	1.737744792	0.00653138	1.52293663	0.007929068	
4.054839	3.068783	1.73519476	0.007913334	1.524027635	0.009287531	
4.06129	3.174603	1.732645123	0.008952524	1.52511847	0.010303021	
4.067742	3.280423	1.730095091	0.009653114	1.526209474	0.01098033	
4.074193	3.492064	1.727545454	0.010692037	1.52730031	0.011995561	
4.080645	3.703704	1.724995423	0.012075651	1.528391314	0.013355886	
4.087097	3.809524	1.722445391	0.013116229	1.529482318	0.014372973	
4.093548	3.915344	1.719895754	0.01381329	1.530573154	0.015046353	
4.1	4.021164	1.717345722	0.014514634	1.531664158	0.015724397	
4.106452	4.126984	1.71479569	0.015213837	1.532755163	0.016400109	
4.112903	4.232804	1.712246054	0.015910573	1.533845998	0.017073174	
4.119355	4.232804	1.709696022	0.016270866	1.534937002	0.017410157	
4.125806	4.232804	1.707146385	0.016284793	1.536027837	0.017400422	
4.132258	4.338624	1.704596353	0.016645145	1.537118842	0.017737456	
4.13871	4.338624	1.702046321	0.017002973	1.538209846	0.018071792	
4.145161	4.338624	1.699496685	0.017016786	1.539300682	0.018061953	
4.151613	4.338624	1.696946653	0.017035876	1.540391686	0.018057714	
4.158064	4.338624	1.694397016	0.017049684	1.541482521	0.018047878	
4.164516	4.338624	1.691846984	0.017068779	1.542573526	0.018043637	
4.170968	4.338624	1.689296952	0.017085232	1.54366453	0.018036598	
4.177419	4.232804	1.686747315	0.01675771	1.544755365	0.017685443	
4.183871	4.232804	1.684197284	0.016435384	1.54584637	0.01733977	
4.190322	4.126984	1.681647647	0.016107963	1.546937205	0.016988723	
4.196774	4.126984	1.679097615	0.015785537	1.548028209	0.016642942	
4.203226	4.021164	1.676547583	0.015460614	1.549119214	0.016294528	
4.209677	3.915344	1.673997946	0.014792022	1.550210049	0.01560232	
4.216129	3.809524	1.671447915	0.014128016	1.551301053	0.014914949	
4.22258	3.703704	1.668898278	0.01345963	1.552391889	0.014222955	
4.229032	3.597883	1.666348246	0.012795414	1.553482893	0.013535368	
4.235484	3.492064	1.663798214	0.012129117	1.554573898	0.012845578	
4.241935	3.386243	1.661248577	0.011461041	1.555664733	0.012153905	
4.248387	3.280423	1.658698546	0.010796515	1.556755737	0.011465996	
4.254838	3.068783	1.656148909	0.009787323	1.557846572	0.010433214	
4.26129	2.962963	1.653598877	0.008781166	1.558937577	0.009403667	
4.267742	2.857143	1.651048845	0.008114868	1.560028581	0.008713877	
4.274194	2.857143	1.648498813	0.007789946	1.561119586	0.008365463	
4.280645	2.751323	1.645949177	0.007463865	1.562210421	0.008015806	
4.287097	2.645503	1.643399145	0.006798723	1.563301425	0.007327259	
4.293549	2.539682	1.640849113	0.006132422	1.56439243	0.006637466	
4.3	2.433862	1.638299476	0.005465272	1.565483265	0.005946752	
4.306452	2.328042	1.635749444	0.00479982	1.566574269	0.005257885	
4.312903	2.222222	1.633199808	0.004132881	1.567665105	0.004567387	
4.319355	2.116402	1.630649776	0.003467222	1.568756109	0.003878306	

4.325807	2.116402	1.628099744	0.0031423	1.569847113	0.003529892	
4.332258	2.116402	1.625550107	0.003158262	1.570937949	0.003522307	
4.33871	2.010582	1.623000075	0.002833827	1.572028953	0.003174439	
4.345161	2.010582	1.620450438	0.002508515	1.573119788	0.002825587	
4.351613	1.904762	1.617900407	0.00218398	1.574210793	0.002477611	
4.358065	1.904762	1.615350375	0.001859057	1.575301797	0.002129197	
4.364516	1.904762	1.612800738	0.001875218	1.576392633	0.002121829	
4.370968	1.798942	1.610250706	0.001550585	1.577483637	0.001773744	
4.377419	1.798942	1.607701069	0.001225471	1.578574472	0.001425109	
4.383871	1.798942	1.605151038	0.001242113	1.579665477	0.001418292	
4.390323	1.798942	1.602601006	0.001258566	1.580756481	0.001411253	
4.396774	1.693122	1.600051369	0.000933497	1.581847316	0.001062674	
4.403226	1.693122	1.597501337	0.000608718	1.582938321	0.000714425	
4.409678	1.587302	1.594951305	0.000283796	1.584029325	0.00036601	
4.416129	1.587302	1.592401669	-4.1122E-05	1.58512016	1.75935E-05	
4.422581	1.587302	1.589851637				
4.429032	1.587302	1.587302		Peak Area HP1=	0.574842108	
4.435484	1.587302			Area % HP1=	2.010315167	
4.441936	1.587302			Peak Area HP1+HP2=	0.668714912	
4.448387	1.587302			Area% HP1+HP2=	2.338603438	
4.454839	1.587302					
4.46129	1.587302					
4.467742	1.587302					
4.474194	1.481481					
4.480645	1.481481					
4.487097	1.481481					
4.493548	1.481481					
4.5	1.481481					
4.506452	1.481481					
4.512903	1.481481					
4.519355	1.481481					
4.525806	1.481481					
4.532258	1.481481					
4.53871	1.481481					
4.545161	1.481481					
4.551613	1.481481					
4.558064	1.481481					
4.564516	1.481481					
4.570968	1.481481					
4.577419	1.481481					
4.583871	1.481481					
4.590322	1.481481					
4.596774	1.481481					
4.603226	1.481481					
4.609677	1.164021					

4.616129	1.164021					
4.622581	1.164021					
4.629032	1.164021					
4.635484	1.164021					
4.641935	1.164021					
4.648387	1.164021					
4.654839	1.164021					
4.66129	1.164021					
4.667742	1.164021					
4.674193	1.164021					
4.680645	1.375661					
4.687097	1.375661					
4.693548	1.375661					
4.7	1.375661					
4.706451	1.375661					
4.712903	1.375661					
4.719355	1.375661					
4.725806	1.375661					
4.732258	1.375661					
4.738709	1.375661					
4.745161	1.481481					
4.751613	1.481481					
4.758064	1.375661					
4.764516	1.375661					
4.770968	1.375661					
4.77742	1.375661					
4.783871	1.375661					
4.790323	1.375661					
4.796774	1.375661					
4.803226	1.375661					
4.809678	1.375661					
4.816129	1.375661					
4.822581	1.375661					
4.829032	1.375661					
4.835484	1.375661					
4.841936	1.375661					
4.848387	1.375661					
4.854839	1.375661					
4.86129	1.375661					
4.867742	1.375661					
4.874194	1.375661					
4.880645	1.375661					
4.887097	1.375661					
4.893548	1.375661					
4.9	1.375661					
4.906452	1.375661					
4.912903	1.375661					

4.919355	1.375661					
4.925807	1.375661					
4.932258	1.375661					
4.93871	1.375661					
4.945161	1.481481					
4.951613	1.481481					
4.958065	1.481481					
4.964516	1.481481					
4.970968	1.481481					
4.977419	1.481481					
4.983871	1.481481					
4.990323	1.481481					
4.996774	1.375661					
5.003226	1.375661	Baseline Response for NP1	Area slice for NP1			
5.009677	1.481481	1.377865544				
5.016129	1.481481	1.378967902	0.000664971		Peak Area NP1=	0.59798
5.022581	1.481481	1.380070259	0.000657858		Area% NP1=	2.091233
5.029032	1.481481	1.381172446	0.000650646			
5.035484	1.481481	1.382274803	0.000643635			
5.041935	1.481481	1.38337699	0.000636424			
5.048387	1.481481	1.384479348	0.000629411			
5.054839	1.481481	1.385581705	0.000622298			
5.06129	1.587302	1.386683892	0.000956417			
5.067742	1.587302	1.387786249	0.001290832			
5.074193	1.587302	1.388888436	0.001283521			
5.080645	1.693122	1.389990793	0.001617983			
5.087097	1.798942	1.391093151	0.002293622			
5.093548	1.798942	1.392195338	0.002627478			
5.1	1.904762	1.393297695	0.002962149			
5.106452	1.904762	1.394400053	0.003296411			
5.112903	2.010582	1.395502239	0.003630112			
5.119355	2.116402	1.396604597	0.004306314			
5.125806	2.222222	1.397706784	0.00498118			
5.132258	2.328042	1.398809141	0.005657591			
5.13871	2.433862	1.399911499	0.00633323			
5.145161	2.539682	1.401013685	0.007007782			
5.151613	2.751323	1.402116043	0.008025886			
5.158064	2.857143	1.403218229	0.009041501			
5.164516	2.962963	1.404320587	0.009718542			
5.170968	3.068783	1.405422944	0.01039418			
5.177419	3.174603	1.406525131	0.011068103			
5.183871	3.280423	1.407627489	0.011745458			
5.190322	3.386243	1.408729675	0.012419171			
5.196774	3.492064	1.409832033	0.013096738			
5.203226	3.597883	1.41093439	0.013772377			

5.209677	3.597883	1.412036577	0.01410445			
5.216129	3.597883	1.413138934	0.014099525			
5.22258	3.703704	1.414241121	0.014431554			
5.229032	3.703704	1.415343479	0.014768058			
5.235484	3.809524	1.416445836	0.015102321			
5.241935	3.809524	1.417548023	0.015434192			
5.248387	3.809524	1.41865038	0.015429473			
5.254838	3.809524	1.419752567	0.015419971			
5.26129	3.809524	1.420854925	0.015415249			
5.267742	3.809524	1.421957282	0.015408137			
5.274193	3.809524	1.423059469	0.015398638			
5.280645	3.809524	1.424161826	0.015393913			
5.287097	3.809524	1.425264184	0.015386801			
5.293549	3.703704	1.426366541	0.015038313			
5.3	3.703704	1.427468728	0.014687549			
5.306452	3.597883	1.428571085	0.014341335			
5.312903	3.597883	1.429673272	0.013990676			
5.319355	3.492064	1.43077563	0.013644361			
5.325807	3.386243	1.431877987	0.012954498			
5.332258	3.280423	1.432980174	0.012262731			
5.33871	3.174603	1.434082531	0.01157477			
5.345161	3.174603	1.435184718	0.011224542			
5.351613	3.068783	1.436287075	0.010877795			
5.358065	3.068783	1.437389433	0.010529307			
5.364516	2.962963	1.43849162	0.010179242			
5.370968	2.751323	1.439593977	0.009149583			
5.377419	2.645503	1.440696164	0.008117086			
5.383871	2.539682	1.441798521	0.007428479			
5.390323	2.433862	1.442900879	0.006738613			
5.396774	2.433862	1.444003066	0.006389135			
5.403226	2.328042	1.445105423	0.006041638			
5.409678	2.328042	1.446207781	0.005693151			
5.416129	2.222222	1.447309967	0.005343835			
5.422581	2.116402	1.448412325	0.004654801			
5.429032	2.116402	1.449514511	0.004305646			
5.435484	2.010582	1.450616869	0.003957827			
5.441936	2.010582	1.451719226	0.003609339			
5.448387	2.010582	1.452821413	0.003601669			
5.454839	1.904762	1.453923771	0.00325374			
5.46129	1.904762	1.455025957	0.002904802			
5.467742	1.798942	1.456128315	0.002556765			
5.474194	1.798942	1.457230672	0.002208278			
5.480645	1.798942	1.458332859	0.002200825			
5.487097	1.693122	1.459435216	0.001852679			
5.493548	1.693122	1.460537403	0.001503958			
5.5	1.693122	1.461639761	0.00149708			
5.506452	1.587302	1.462742118	0.001148592			

5.512903	1.587302	1.463844305	0.000799981			
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5.558064	1.481481	1.471560295	6.75536E-05			
5.564516	1.481481	1.472662652	6.04522E-05			
5.570968	1.481481	1.47376501	5.33398E-05			
5.577419	1.481481	1.474867197	4.62207E-05			
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5.590322	1.481481					
5.616129	1.481481					
5.622581	1.481481	Baseline Response for BM1	Area slice for BM1			
5.629032	1.481481	1.482503407				
5.635484	1.481481	1.48301465	-8.2458E-06		Peak area BM1=	28.59463
5.648387	1.481481	1.484037057	-2.6385E-05			
5.654839	1.481481	1.484548301	-1.8141E-05			
5.66129	1.481481	1.485059465	-2.1436E-05			
5.667742	1.481481	1.485570708	-2.4738E-05			
5.674193	1.481481	1.486081872	-2.8031E-05			
5.680645	1.587302	1.486593115	0.000310044			
5.687097	1.798942	1.487104358	0.001330875			
5.693548	2.328042	1.487615522	0.003716628			
5.7	2.539682	1.488126765	0.006103533			
5.706451	2.962963	1.488637929	0.008147227			
5.712903	3.280423	1.489149172	0.010534822			
5.719355	4.021164	1.489660416	0.01394528			
5.725806	4.444444	1.490171579	0.017694371			
5.732258	5.714286	1.490682823	0.023155827			
5.738709	6.243386	1.491193987	0.028951427			
5.745161	7.407407	1.49170523	0.034414625			
5.751613	9.73545	1.492216473	0.045676725			
5.758064	10.68783	1.492727637	0.056247352			
5.764516	12.38095	1.49323888	0.064787156			
5.770967	13.22751	1.493750044	0.072965555			
5.777419	15.7672	1.494261287	0.08389761			
5.783871	20	1.49477253	0.105742364			
5.790323	20.31746	1.495283774	0.120418204			
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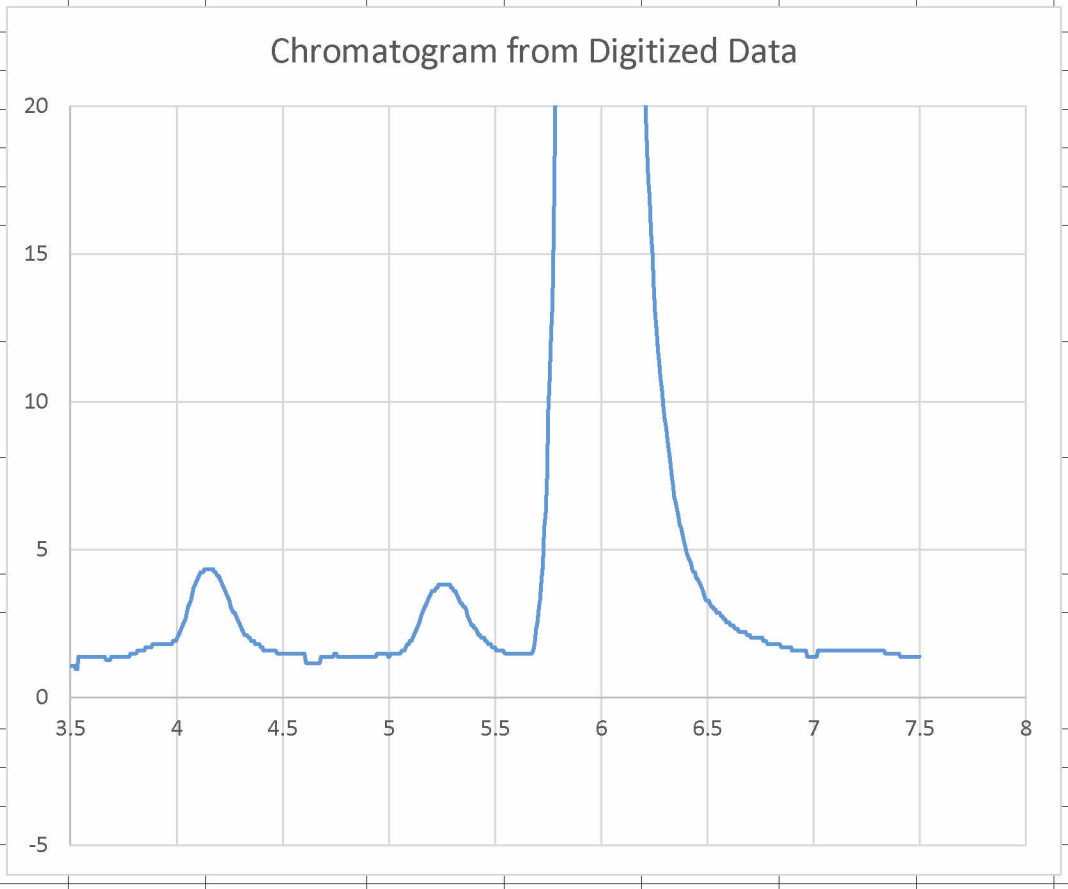
Chromatogram from Digitized Data
20
15
10
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4
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5
5.5
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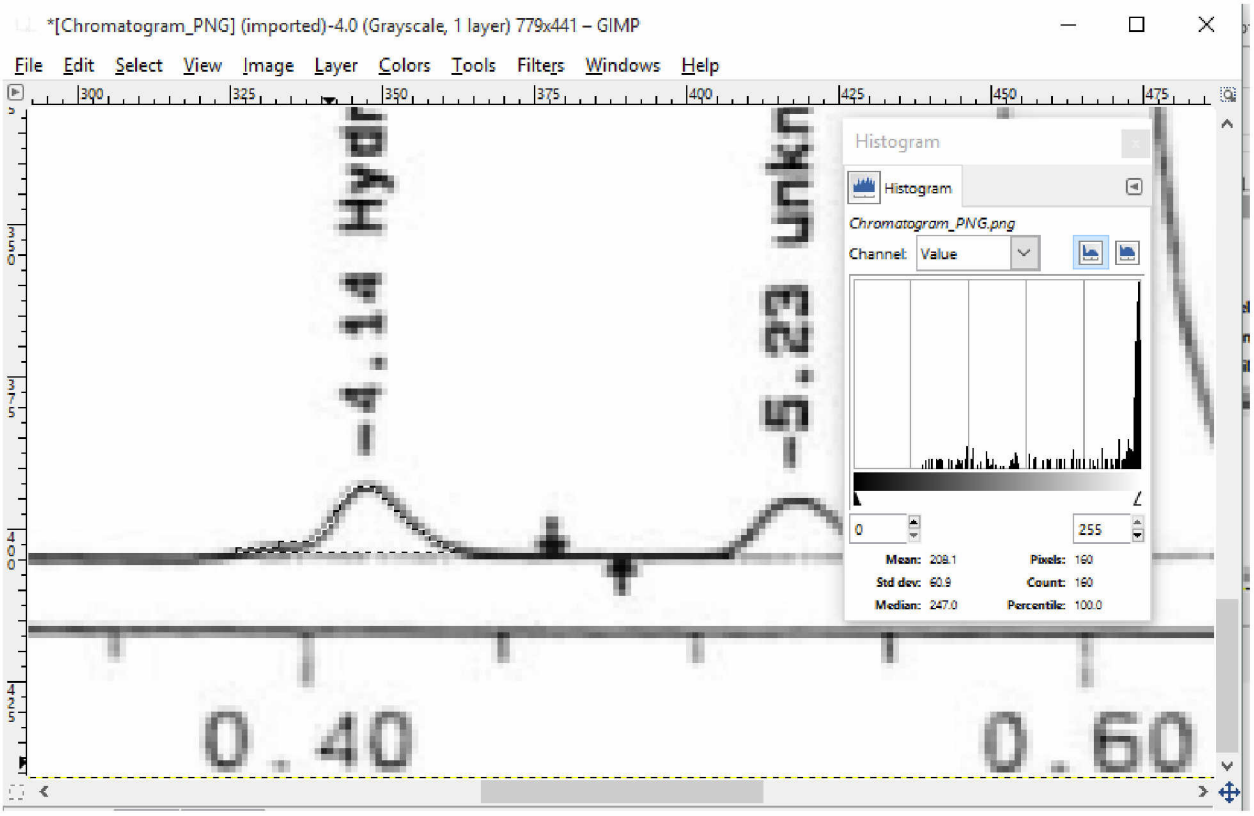
6.5
7
7.5
8

Exhibit F

HP1 +HP2, pixel count = 160



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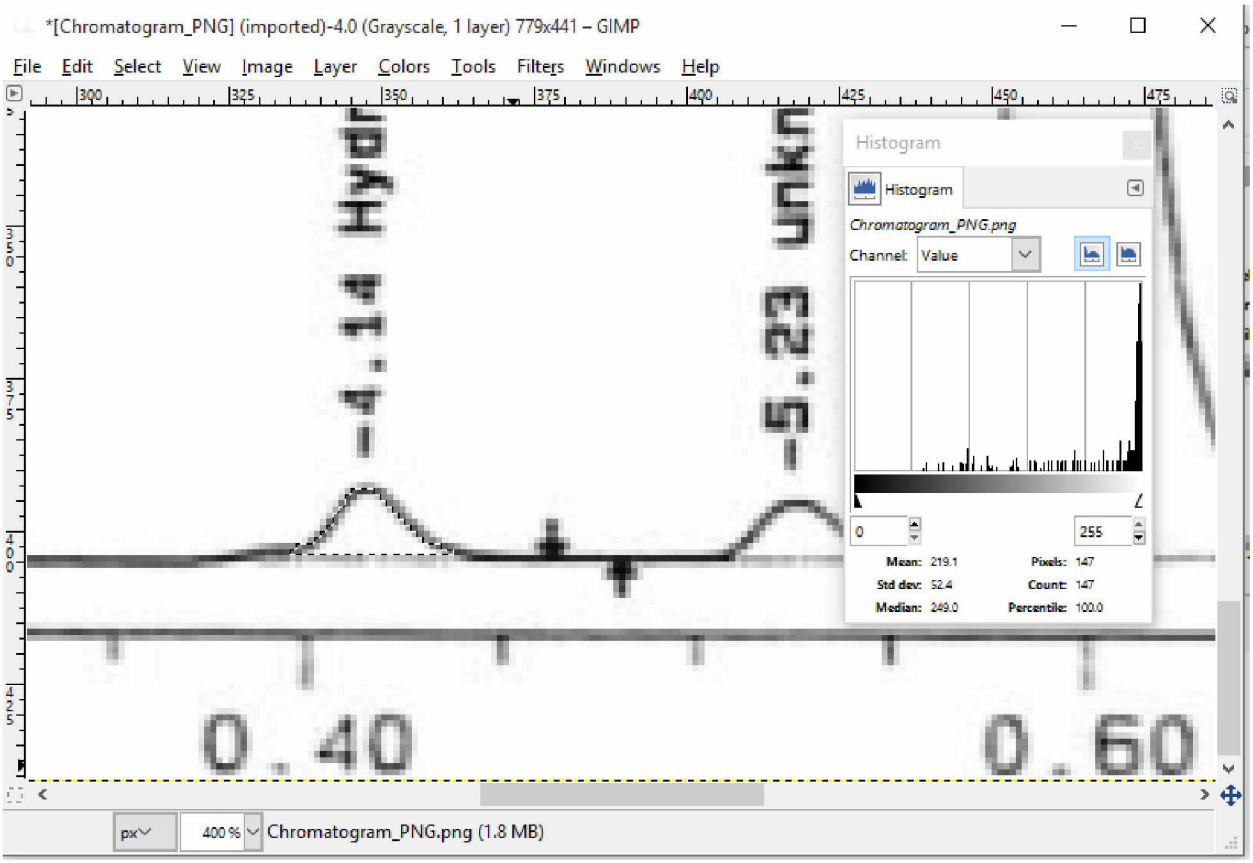

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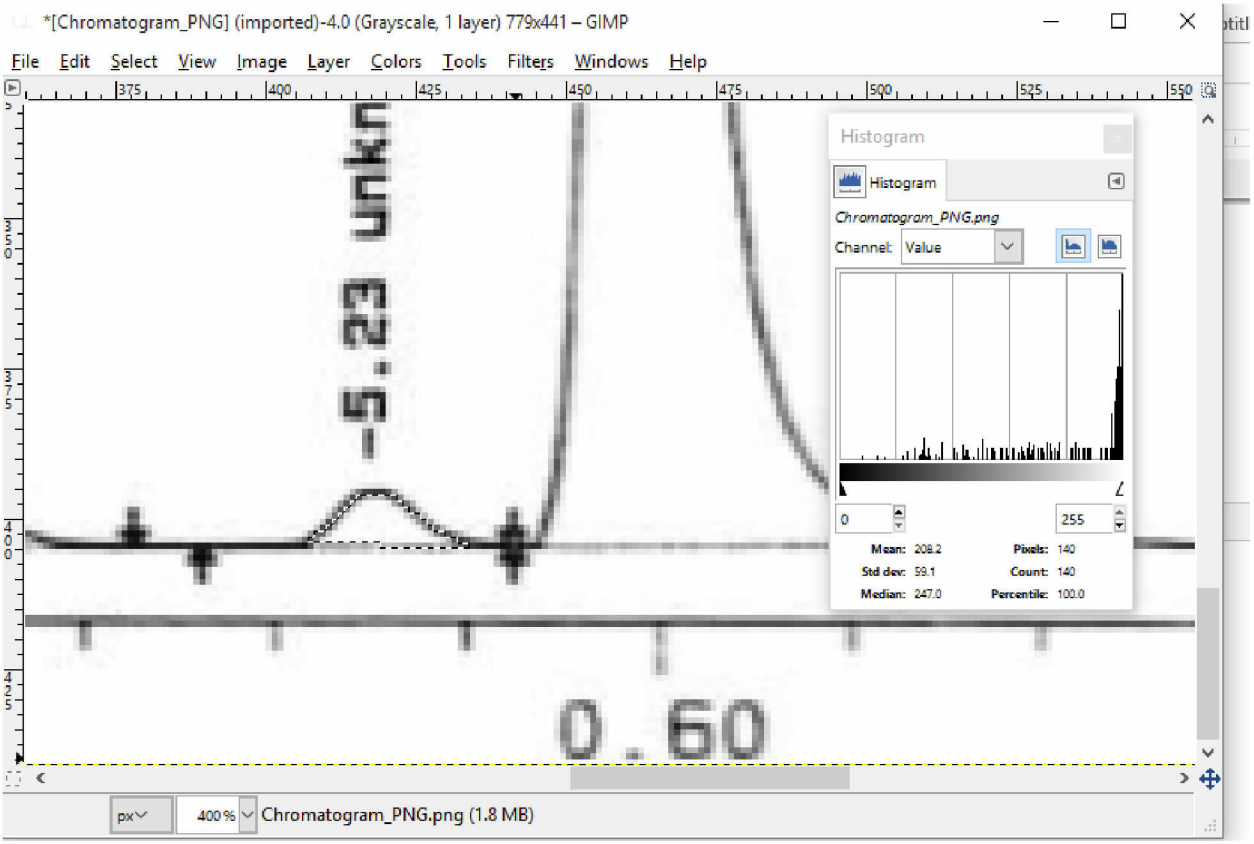

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