UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN PHARMACEUTICALS INC.,
Petitioner

v.

POZEN INC. and HORIZON PHARMA USA, INC.,
Patent Owners

U.S. Patent No. 9,393,208

Inter Partes Review IPR2018-00272

DECLARATION OF MICHAEL MAYERSOHN, PH.D. IN SUPPORT OF PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 9,393,208

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I, Michael Mayersohn, Ph.D., do hereby declare:

I. Introduction

1. My name is Michael Mayersohn. I have been retained by Mylan Pharmaceuticals Inc. ("Mylan") in the matter set forth in the caption above. I understand that Mylan is petitioning for *inter partes* review ("IPR") of claims 1-7 of U.S. Patent No. 9,393,208 to Ault *et al.* ("the '208 patent") [Ex. 1001]. I submit this expert declaration in support of Mylan's IPR petition for the '208 patent.

II. Qualifications and Background

A. Education and Experience

2. I am Professor Emeritus of Pharmaceutical Sciences (since June 2016) in the College of Pharmacy at the University of Arizona, in Tucson, Arizona.

3. I earned my Bachelor of Science degree in Pharmacy from the College of Pharmaceutical Sciences at Columbia University, in New York, in 1966. I earned a Ph.D. in Pharmaceutics/Pharmacokinetics from the State University of New York at Buffalo, in 1970. From 1971 until 1976, I was an assistant and then an associate professor in the Faculty of Pharmacy at the University of Toronto (Canada). In 1976, I joined the faculty of the University of Arizona, as an associate professor in the College of Pharmacy. In 1983, I became a professor in the University of Arizona College of Pharmacy, and am currently a Professor Emeritus there.

4. My research, training, and experience are all in the area of pharmaceutical sciences generally, and specifically in the areas of pharmacokinetics, pharmaceutics, biopharmaceutics, and pharmacodynamics. My research has involved pharmaceutical formulation development and evaluation, including examining the relationship between the physical-chemical characteristics of a drug and its dosage form; the fate and performance of that drug in the body; and the design of rational drug dosing regimens based upon analytical, mathematical, and clinical data. My extensive research in these areas includes *in vitro* experimentation and *in situ* and *in vivo* studies in animals and humans, including evaluating and analyzing immediate-release and extended-release solid oral dosage forms. I have also conducted theoretical, or *in silico*, analyses and simulations of drug behavior in the body.

5. I am the author of numerous book chapters related to drug absorption and pharmacokinetics, and over 160 original scientific peer-reviewed articles in the pharmaceutical sciences, many relating to biopharmaceutics and pharmacokinetics, and about 15 professional and educational publications. I have published over 160 abstracts of research studies that were presented at international and national scientific or professional meetings.

6. I have received several professional awards for my research, and I have been elected a fellow of several professional organizations, including the

Academy of Pharmaceutical Sciences (American Pharmaceutical Association), the American Association of Pharmaceutical Scientists, and the American College of Clinical Pharmacology. Fellowship elections are recognition by my scientific peers of my valuable contributions to my field.

7. Between 1995 and 1998, I was a member of the U.S. Food and Drug Administration's ("FDA") Generic Drug Advisory Committee (currently the Pharmaceutical Sciences Advisory Committee). This Committee reviews, comments on, and provides direction to FDA on issues of drug bioavailability and bioequivalence; this work then forms the regulatory standards for the pharmaceutical industry through, for example, issuance of FDA Guidances.

8. I was a member of the Dissolution and Bioavailability Expert Committee of the United States Pharmacopeia for a 5-year term. I also served as Vice Chair of the same expert committee, renamed the Biopharmaceutics Expert Committee of the United States Pharmacopeia, for an additional 5-year term. The Committee sets the official standards for dissolution and bioavailability metrics that are applied throughout the pharmaceutical industry.

9. I have been the director and principal instructor of a one-week course, "Principles of Pharmacokinetics and Toxicokinetics for the Industrial Scientist," which has been given in Tucson, Arizona, for 15 years, with over 750 scientists having attended. In the past, I gave a version of this course on-site to many

companies in the pharmaceutical industry as "Selected Topics in Pharmacokinetics," and over the years about 1,000 scientists attended. I also gave a short course on the same topic sponsored by the American Chemical Society at their annual meetings.

10. A copy of my *curriculum vitae*, which lists my publications and describes my qualifications in detail, is attached as Attachment A.

B. Bases for Opinions

11. In forming my opinions set forth in this declaration, I have considered and relied upon my education, background, and decades of experience in the field of pharmaceutical sciences, including pharmaceutics and formulation science, biopharmaceutics, pharmacokinetics, and pharmacodynamics. I have also relied on the materials listed in Attachment B.

C. Retention and Compensation

12. I am being compensated for my consulting work on this case at my usual rate of $800.00 per hour plus expenses. My compensation in this proceeding is not dependent on its outcome.

III. Legal Standards

13. Counsel has informed me that certain legal principles should guide me in my analysis. Counsel has informed me that Mylan carries the burden of proving

unpatentability by a preponderance of the evidence, which means Mylan must show that unpatentability is more likely than not.

14. Counsel has informed me that the question of whether the claims of a patent are anticipated by, or obvious in view of, the prior art is to be considered from the perspective of the person of ordinary skill in the art ("POSA"). Counsel has further informed me that the answer to this question is ascertained as of the time the invention was made.

15. Counsel has informed me that performing an obviousness analysis involves ascertaining, as of the time the invention was made, the scope and content of the prior art, the level of skill of the POSA, the differences between the claimed invention and the scope and content of the prior art, and whether there are additional factors present that may argue against a conclusion of obviousness (*i.e.*, "secondary considerations"), such as unexpected results attributable to the invention, or whether the invention met a long-felt but unmet need.

16. Counsel has informed me that an invention may be found obvious:

> When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary

> skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103.

17. Counsel has informed me that a prior art reference anticipates a claimed invention if the prior art reference disclosed each of the claimed elements of the invention. A prior art reference not expressly disclosing a claim element may still anticipate the claimed invention if the missing element is necessarily present, or inherent, in the single anticipating reference. The missing element, or characteristic, is inherent in the anticipating reference if the characteristic is a natural result flowing from the reference's explicit disclosure.

18. Counsel has informed me that if a patent claims a composition in terms of a function, property, or characteristic, and the composition itself is in the prior art, then the claim may be anticipated or obvious in view of the prior art reference disclosing the composition.

IV. Definition of a Person of Ordinary Skill in the Art (POSA)

19. The field of art involves the knowledge of a medical doctor and that of a pharmacologist or pharmacokineticist with experience in dosage form design and evaluation. Thus, the hypothetical person of ordinary skill in the art is a collaboration between a pharmacologist or pharmacokineticist having a Ph.D. degree or equivalent training, or a M.S. degree with at least 2 years of some

experience in dosage form design and in *in vitro* and *in vivo* evaluation of dosage form performance, and a medical doctor having at least 2 years of practical experience treating patients in the gastroenterology field.

20. I am offering my analysis from the perspective of the pharmacologist or pharmacokineticist described above.

V. Summary of Opinions

21. *First*, a POSA would have understood that the targeted pharmacokinetic (PK) and pharmacodynamic (PD) values recited in claims 1 and 2 of the ’208 patent are the natural result of administering the pharmaceutical composition disclosed and claimed in U.S. Patent No. 8,557,285 (“’285 patent”). A POSA would have also understood that the targeted PK and PD values recited in claims 1 and 2 of the ’208 patent are a function, property, or characteristic of the pharmaceutical composition disclosed and claimed in the ’285 patent.

22. *Second*, it would have been routine for a POSA to make and test the pharmaceutical composition disclosed and claimed in the ’285 patent as containing 500 mg naproxen and 20 mg esomeprazole. A POSA would have measured and obtained the PK and PD values resulting from administration of the composition described and claimed in the ’285 patent by routine testing and recording methods.

23. *Third*, a POSA would have been motivated to target the claimed PK and PD values recited in the claims of the ’208 patent because these values were

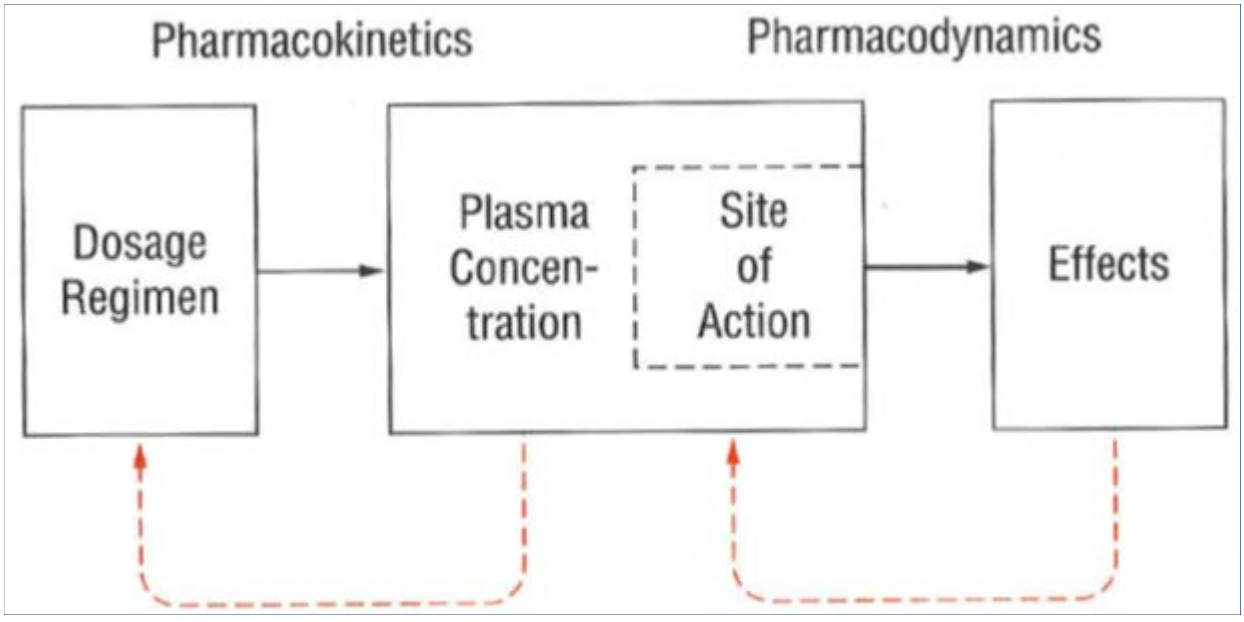
known to be in the therapeutically effective ranges for naproxen and a proton pump inhibitor, such as esomeprazole. Further, a POSA would have had a reasonable expectation of success in targeting the claimed PK and PD values because a skilled artisan would routinely target PK and PD values associated with marketed drugs known to be effective.

24. *Fourth*, all elements recited in the '208 patent's dependent claims were disclosed in the '285 patent, as well as other prior art.

VI. Background on Pharmacokinetics and Pharmacodynamics

25. "Pharmacokinetics" (PK) describes the body processes associated with drug movement into (absorption or input), within (distribution or translocation) and out of (metabolism and excretion) the body. These processes are often referred to by the mnemonic ADME, which stands for Absorption, Distribution, Metabolism and Excretion. Ex. 1021 at 5. While pharmacology is often described as studying the "effect of the drug on the body," PK is often described as the opposite: studying the "effect of the body on the drug." The two areas of study are, however, inextricably connected.

26. "Pharmacodynamics" (PD) describes how the concentration of a drug at its site of action is related to the magnitude of the clinical effect observed. Pharmacodynamics studies the relationship between a drug's biochemical and physiological effects and its mechanism of action. Ex. 1021 at 9.


Pharmacokinetics
Pharmacodynamics
Dosage Regimen
Plasma Concen-tration
Site of Action
Effects

29. As shown, PK/PD events overlap. The driving force for pharmacodynamic (*i.e.*, clinical or toxic) events following drug dosing is generally the concentration of drug in the blood (or plasma). In other words, the PD effects of a drug are driven by its concentration in the plasma, and the time course of the PD effects is driven or controlled by the PK properties of the drug and its dosage form. Ex. 1021 at 5-8. Because of this, it is worthwhile to be able to describe the plasma concentration-time profile of a drug after administering it to a patient. A stylized single-dose plasma concentration-time profile resulting from oral dosing is depicted below.

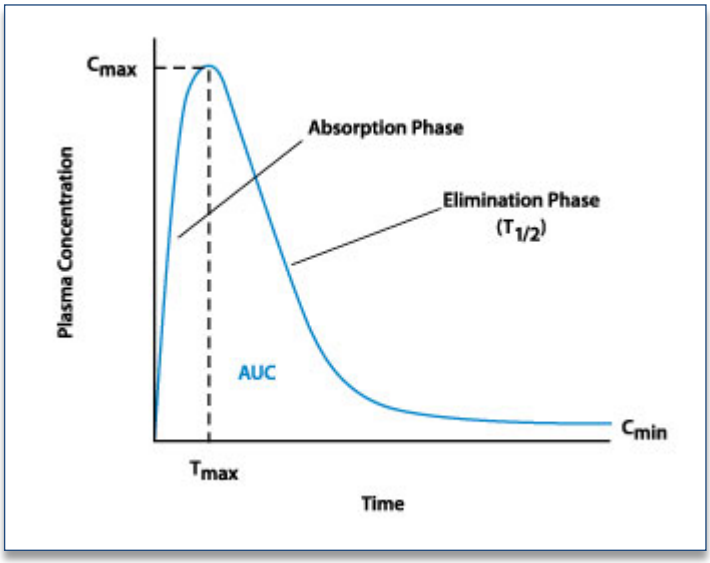


Figure B

See, e.g., Ex. 1022 at 21 (displaying exemplary curve with identified parameters).

30. To develop a single-dose plasma concentration-time profile, the clinical pharmacologist or pharmacokineticist will, after administering a drug (*e.g.*,

administering orally), take frequent blood samples for a time sufficient to characterize the entire profile. The blood samples, or a fluid derived from blood (*e.g.*, plasma or serum), are treated and submitted to an analytical procedure from which one can obtain a quantitative value for the concentration of the drug (and/or metabolites of that drug) in the blood sample. The resulting concentration-time profile can be plotted and analyzed, by using either a computer-based method to obtain a mathematical model that best describes the data, or a model-independent method. Either way, one obtains estimates of the values of the PK parameters for the drug.

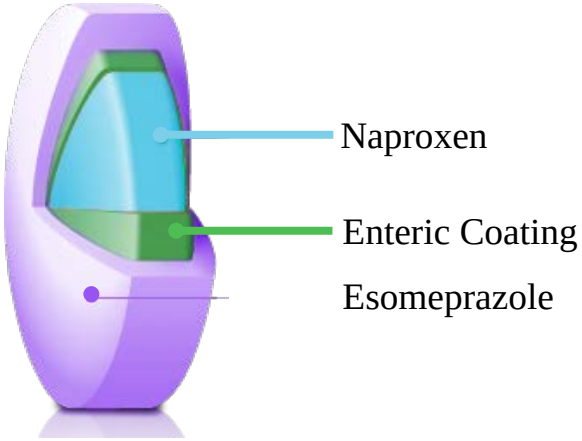
31. Following a single oral dose of a drug, the plasma concentration-time profile can be used to estimate the C_{max} (maximum plasma drug concentration achieved), the T_{max} (time after dosing corresponding to the C_{max}), the $t_{½}$ (half-life of the drug in the body), and the AUC (extent of absorption or total exposure to the drug, as measured by the total area under the plasma concentration *vs* time curve) from time zero to time infinity. The AUC is a function of the amount of drug that gets absorbed into the systemic circulation. The figure above describes a characteristic plasma concentration-time curve for an immediate-release dosage form, *i.e.*, one designed not to delay release and subsequent absorption.

32. Often, a POSA will want to depict graphically the PK profile of a dosage form established in a study of multiple subjects. Placing the profile for

each subject on a single graph may, however, be cumbersome and confusing. It is therefore common for a POSA to prepare an average plasma concentration-time profile by plotting the average plasma concentrations over all subjects at each sample time. Such a graph provides a useful depiction of the PK behavior of the dosage form across multiple subjects. A graph of this type is similar to the one included in ¶ 29, but derives its data from a population (as described), rather than an individual.

33. The drug's dosage form and its formulation affect the shape of the plasma concentration-time curve. In other words, immediate-release solid drug dosage forms will result in a relatively high C_{max} that occurs a short time after dosing (*i.e.*, small T_{max}). In contrast, a "delayed-release" solid drug dosage form will have a T_{max} typically occurring later than that of an immediate-release dosage form. Delayed release often is accomplished by coating a solid dosage form with an enteric (typically, a polymer) layer, which is designed not to dissolve and release the drug until the dosage form reaches the relatively higher pH of the small intestine. For an enteric-coated dosage form, the delay in absorption can be quite prolonged, governed by the nature and characteristics of the enteric coating, the time needed for gastric emptying to occur, and the presence of food in the stomach.

34. Some single unit dosage forms, like Vimovo®, provide "pulsatile" release; *i.e.*, multiple drug releases occurring at different times after ingestion, for


Naproxen
Enteric Coating
Esomeprazole

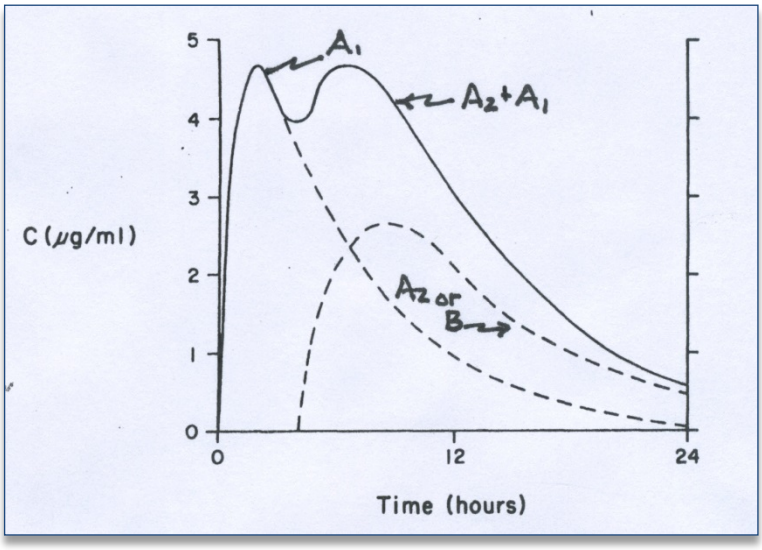
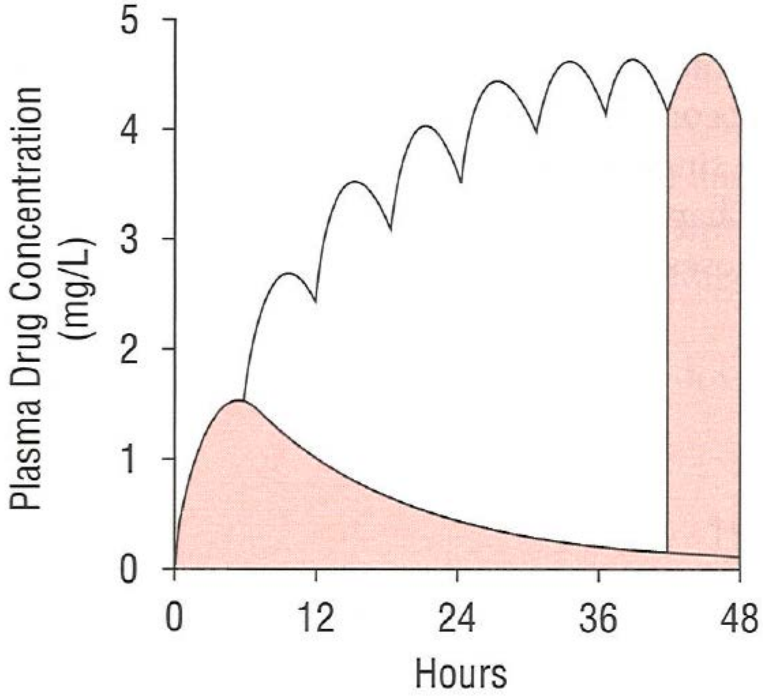


Figure D

36. The solid line represents the total drug plasma concentration for a repeat action or pulsatile dose form. Thus, the drug concentration first rises from immediate release of drug A_1 from the outer coating of the tablet. Total drug concentration then declines until release of drug A_2 (second pulse of A) or B (first pulse of new drug—as with the dosage form shown in Figure C above) from the enteric-coated inner core. The dashed line concentration shown as A_2 or B is added to the A_1 concentration curve to produce the total drug concentration-time solid line. Note that for a pulsatile dosage form, one would see the A_1 drug concentration line continue to decrease according to the descending dashed line; and some time later, concentrations from the other drug, B, will rise and decline (second dashed line), with plasma concentrations for drug B being delayed relative to plasma concentrations for drug A.

37. Many times, it is useful to characterize the pharmacokinetics of a drug and its dosage form after multiple oral dosing. With multiple dosing, a drug accumulates in the body until a maximum plasma concentration is achieved, such that the concentration-time profile repeats after every dosing interval. When this occurs, commonly after about 4 or 5 half-lives, a so-called "steady state" has been obtained. This is a fluctuating steady state in which the drug concentrations repeat but rise and fall periodically. A true steady state involves constant drug concentrations with time, occurring when the rate of drug entry into the body equals the rate of elimination of drug from the body. A stylized plasma concentration-time profile, showing the rise from initial dosing to a fluctuating steady state, is depicted below (Figure E). C_{max}, T_{max}, and $AUC_{(0-t)}$[1] are added as illustrated.

[1] "$AUC_{(0-t)}$" refers to the area under the curve from time zero to an arbitrary time, t.



C_{max}

$AUC_{(t)}$

T_{max}

concentration. For example, if the dosage interval is 24 hours, C_{ave} will refer to the area under the curve for the 24-hour dosing period, divided by 24, *i.e.*, $AUC_{24}/24$.

39. During a dosing interval at steady state, one can characterize different dosage forms of a given drug by these PK parameters. For example, an immediate-release product may have a rapidly-achieved C_{max} and a low C_{min}, depending upon the dosing interval (the longer the interval, the lower the C_{min}; the shorter the interval, the greater the C_{min}).

VII. U.S. Patent No. 9,393,208 [Ex. 1001]

40. U.S. Patent No. 9,393,208 ("'208 patent") issued on July 19, 2016, and is entitled "Method for Delivering A Pharmaceutical Composition to Patient in Need Thereof." *See* Ex. 1001 at [54]. The '208 patent issued from U.S. Patent Application No. 14/980,639, filed on December 28, 2015. *Id.* at [21], [22]. The '208 patent is a continuation of U.S. Patent No. 9,220,698, filed on September 3, 2009, as U.S. Patent Application No. 12/553,107, which claims priority to U.S. Provisional Patent Application No. 61/095,584, filed on September 9, 2008. *Id.* at [60], [63].

41. The '208 patent names as joint inventors Brian Ault, Everardus Orlemans, John Plachetka, and Mark Sostek. *See id.* at [72]. The '208 patent is assigned on its face to Pozen Inc. and Horizon Pharma USA, Inc. *Id.* at [73].

42. The ’208 patent contains seven claims, of which claim 1 is the only independent claim. Claims 2–7 depend from, and further limit, the subject matter recited in claim 1. *Id.* at 46:33-48:17.

A. The ’208 Patent Specification

43. The ’208 patent relates to methods for treating a patient with a unit dose form containing 500 mg of enteric-coated naproxen and 20 mg of immediate-release esomeprazole to target a range of PK and PD values for naproxen and esomeprazole. Ex. 1001 at 46:32-47:9. The ’208 patent refers to an exemplary dosage form, having 500 mg naproxen and 20 mg esomeprazole, as “PN400/E20,” Ex. 1001 at 26:1-2. The ’208 patent describes the results of treating a patient population with PN400/E20, and the claims recite the reported PK/PD values. *See, e.g.*, Ex. 1001 at cols. 24-46, Tbls. 6, 8, 11, 13; 46:32-47:9 (claim 1).

44. The ’208 patent describes and claims PK parameters for the dosage forms that were well-known to a POSA, including “C_{max},” “T_{max},” and “AUC,” each of which is described and explained above. *See, e.g.*, Ex. 1001 at 46:32-47:9 (claim 1). The ’208 patent also reports these PK parameters as the average (mean) or median values plus or minus a variation. *Id.* The ’208 patent also describes and claims the variation in these parameters as coefficients of variation (*e.g.*, claiming ±20% variation), which reflects the variability inherent in biological and analytical processes both within a patient, across multiple measurements, and between

patients in a population. *Id.* The percentage coefficient of variation (%CV) is calculated as the standard deviation (SD) divided by the mean or average value, multiplied by 100. Ex. 1001 at 5:34-37.

45. The '208 patent acknowledges that NSAIDs were known to increase the risk of gastrointestinal injury, such as ulcers, when used long-term. Ex. 1001 at 1:19-24. A POSA would have known, and the '208 patent states, that stomach acid was "[a] major factor contributing to the development of gastrointestinal lesions" in these circumstances. *Id.* at 1:24-26. The '208 patent also states that strategies were known "to reduce the gastrointestinal risk associated with taking NSAIDs by administering agents that inhibit stomach acid secretion, such as, for example, proton pump inhibitors with the NSAID." *Id.* at 1:27-30.

46. The '208 patent specifically identifies U.S. Patent No. 6,926,907 ("'907 patent") [Ex. 1004], as directed to a drug dosage form that includes a proton pump inhibitor ("PPI"), that is "effective in improving NSAID tolerability through dosages of esomeprazole and naproxen that produce the desired pharmacodynamic response and pharmacokinetic values." *Id.* at 1:34-37.

47. The '285 patent and the '907 patent disclose the same combined dosage form claimed in the '208 patent, used in the same way: a unit dosage form containing 500 mg of delayed-release naproxen and 20 mg of immediate-release

esomeprazole. The elements of the ’208 patent’s claim 1 that were disclosed by the prior art ’285 patent are shown in the table below:

Claimed by the ’208 Patent	Disclosed by the Prior Art ’285 Patent (Ex. 1005)
Method for delivering a pharmaceutical composition to a patient	Although the method may be used for any condition in which an NSAID is effective, it is expected that it will be particularly useful in patients with *osteoarthritis* or *rheumatoid arthritis*. Other conditions that may be treated include … *ankylosing spondylitis*[.] 5:22-29.
Orally administering to a patient	The invention is directed to a pharmaceutical composition in unit dosage form suitable for *oral administration* to a patient. 3:27-29.
An AM unit dose form and, 10 hours (±20%) later, a PM unit dose form	The following three groups were administered study medication *twice daily*. 20:44-46.

Naproxen, or a pharmaceutically acceptable salt thereof, in an amount to provide 500 mg of naproxen	*Naproxen* surrounded by a coating that inhibits its release from said unit dosage form unless said dosage form is in a medium with a pH of 3.5 or higher; naproxen is present in said unit dosage form in an amount of *200-600 mg*. 22:12-14, 19-21, 25-27. *Naproxen* is particularly useful when contained in tablets or capsules in an amount of from 250 to *500 mg*. 7:9-10. Examples 1, 2, 4, 5, 6, 10 (all with 500 mg naproxen).
Esomeprazole, or a pharmaceutically acceptable salt thereof, in an amount to provide 20 mg of esomeprazole	*Esomeprazole*, wherein at least a portion of said esomeprazole is not surrounded by an enteric coating; esomeprazole is present in said unit dosage form *in an amount of from 5 to 100 mg*. 22:10-11, 22-24, 27-28.
Esomeprazole … is released from said	Upon introduction of said unit dosage

AM and PM unit dose forms at a pH of 0 or greater	form into a medium, at least a portion of said *esomeprazole* is released *regardless of the pH of the medium*. 22:16-18.

48. The ’208 patent provides abbreviations and definitions for PK, PD, and other terms used in the claims. Ex. 1001 at 3:15-6:10, Table 1. These terms include: “AUC,” “C_{max},” and “T_{max},” as described above, as well as “CV” (the coefficients of variation as a percentage of the average PK values), “SD” (standard deviation), “PPI” (proton pump inhibitor, such as esomeprazole or omeprazole), and “unit dose form” (“a single entity for drug administration,” such as a single tablet containing naproxen and esomeprazole). *Id*. at Table 1, 5:18-30. The ’208 patent also states that the term “about,” which is used in the claims to describe the PK/PD values, indicates that “a given number may vary by at least 5%, with variations of 10%, 15% or 20% being possible.” *Id*. at 5:31-33. The ’208 patent further states that “[w]ith regard to the pharmacokinetic and/or pharmacodynamic values provided herein, the degree of variation is reflected in SDs and % CV values.” *Id*. at 5:34-36. The ’208 patent then explains that “[t]he pharmacokinetic and pharmacodynamic values presented herein are average values, rounded to the nearest whole number, and are based upon results obtained from multiple

individuals. As a result, the values presented herein may vary from one patient to another. This variation is reflected in the term 'about.'" *Id*. at 5:40-45. The '208 patent defines "about" in several other contexts, including the following:

> With regard to time periods referred to herein, the term "about" is intended to reflect variations from the specifically identified time periods that are acceptable within the art.
>
> With regard to the numerical % coefficient of variation values and/or ranges used herein, the term "about" is intended to reflect variations above and below the stated numerical value and/or range that that may achieve substantially the same results as the stated number.
>
> With regard to the pH values and/or ranges recited herein, the term "about" is intended to capture variations above and below the stated number that may achieve substantially the same results as the stated number.

Id. at 5:51-62.

49. The '208 patent discloses a clinical trial using the claimed unit dose form. Example 1 is a "randomized, open-label, 4-way crossover study" in 28 healthy adults. *Id*. at 24:5-9, 35. The 4-way crossover study involved evaluating the effect on days 1 and 9 of twice-daily administration of three PN400 formulations (containing delayed-release naproxen 500 mg combined with one of three doses of immediate-release esomeprazole (10, 20, or 30 mg)), versus twice-

daily administration of immediate-release naproxen 500 mg administered separately from once-daily delayed-release esomeprazole 20 mg. *Id*. at 24:7-21. Washout periods of at least 12 days followed each treatment. *Id*. at 24:36-38. On days 1 and 9, numerous blood samples were taken throughout the day to measure PK values. A pH probe was placed to monitor intragastric pH in order to measure the PD values. *Id*. at 26:13-15.

50. The claims recite the PD value of the percent time, in a 24-hour period, during which gastric pH was greater than 4.0. *Id*. at 47:6-9. The ’208 patent reports that the claimed formulation (PN400/E20), given twice daily, yielded a mean of 71.35% of a 24-hour period during which gastric pH was greater than 4.0. *Id*. at Table 4. For PN400/E30 (500 mg naproxen and 30 mg esomeprazole twice daily), that figure was 76.50%, and for PN400/E10 (500 mg naproxen and 10 mg esomeprazole twice daily), that figure was 40.85%. *Id*. The separate-dosing (*i.e*., not a combination formulation) protocol resulted in a value of 56.85%. *Id*.

51. The claims recite PK measurements for mean C_{max} and median T_{max} for naproxen, and mean AUC for esomeprazole. *Id*. at 46:49-47:5. The ’208 patent reports values for the naproxen PK parameters in Table 11, as shown below.

TABLE 11

Naproxen Pharmacokinetic Parameters

Treatment	Day/ Dose Time	C_{max} (µg/mL)	t_{max} (hr)	$AUC_{0-10,\ am}$ or $AUC_{0-14,\ pm}$ (hr*µg/mL)	AUC_{0-24} (hr*µg/mL)	$t_{½}$ (hr)
A	1	48.1	4.00	259		8.52
PN 400/E30	AM	(53)	(2.00-10.0)	(56)		(25)
	1	68.9	14.0	471	730	12.1
	PM	(28)	(0.50-14.0)	(30)	(32)	(30)
	9	80.9	3.00	603		9.17
	AM	(23)	(0.00-8.00)	(21)		(21)
	9	76.2	10.4	648	1251	12.3
	PM	(23)	(0.00-14.0)	(20)	(16)	(27)
B	1	44.4	4.00	231		8.75
PN 400/E20	AM	(68)	(2.00-10.0)	(70)		(33)
	1	71.5	14.0	450	680	11.8
	PM	(26)	(0.00-14.0)	(33)	(36)	(28)
	9	86.2	3.00	607		9.42
	AM	(22)	(0.00-8.05)	(19)		(23)
	9	76.8	10.0	678	1275	11.3
	PM	(18)	(0.00-14.0)	(16)	(15)	(28)
C	1	57.0	4.00	310		9.24
PN 400/E10	AM	(31)	(2.00-10.0)	(35)		(42)
	1	68.6	10.0	508	819	12.7
	PM	(26)	(0.00-14.0)	(29)	(21)	(23)
	9	87.1	2.50	637		9.91
	AM	(21)	(0.00-8.00)	(17)		(26)
	9	78.6	14.0	672	1309	10.5
	PM	(17)	(1.50-14.0)	(19)	(15)	(23)

TABLE 11-continued

Naproxen Pharmacokinetic Parameters

Treatment	Day/ Dose Time	C_{max} (µg/mL)	t_{max} (hr)	$AUC_{0-10,\ am}$ or $AUC_{0-14,\ pm}$ (hr*µg/mL)	AUC_{0-24} (hr*µg/mL)	$t_{½}$ (hr)
D	1	65.5	1.50	409		8.85
EC E20 +	AM	(25)	(0.75-6.00)	(16)		(22)
naproxen	1	81.5	1.50	685	1094	15.4
	PM	(14)	(0.50-2.50)	(10)	(12)	(31)
	9	90.0	1.50	617		9.32
	AM	(19)	(0.50-4.00)	(12)		(23)
	9	86.5	1.50	769	1387	14.4
	PM	(13)	(0.75-4.00)	(10)	(10)	(17)

Values are mean (% CV) for all parameters, except for t_{max}, which are median (range).

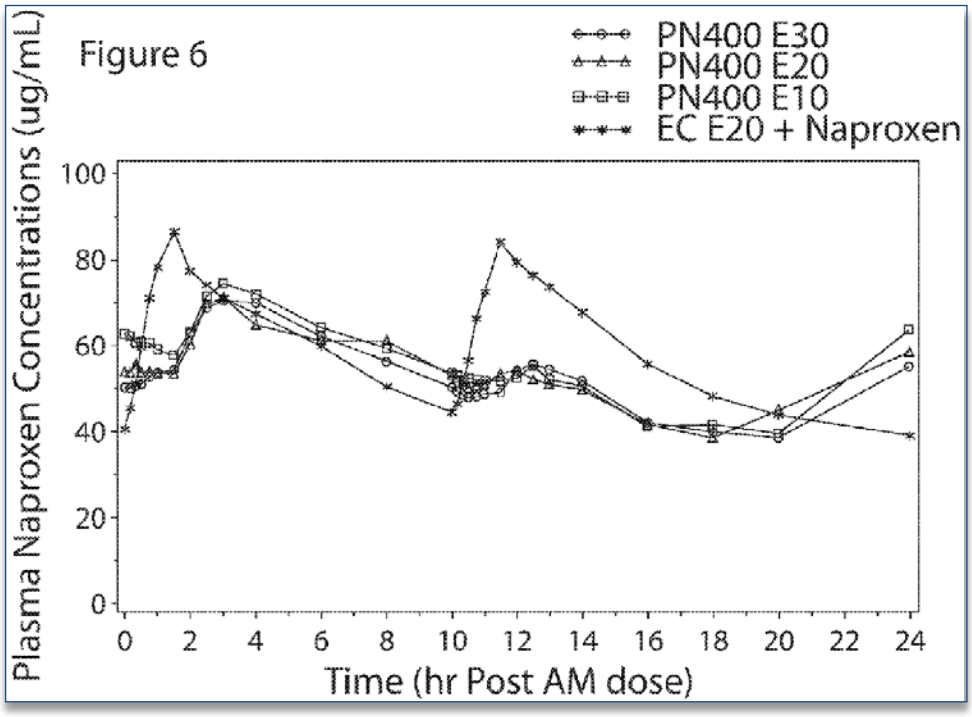


Figure 6
PN400 E30
PN400 E20
PN400 E10
EC E20 + Naproxen
Plasma Naproxen Concentrations (ug/mL)
100
80
60
40
20
0
0
2
4
6
8
10
12
14
16
18
20
22
24
Time (hr Post AM dose)

TABLE 6

Summary of Esomeprazole Pharmacokinetic Results

Treatment	Day/Dose Time	C_{max} (ng/mL)	t_{max} (hr)	$AUC_{0-10,\ am}$ or $AUC_{0-14,\ pm}$ (hr*ng/mL)	AUC_{0-24} (hr*ng/mL)	$t_{1/2}$ (hr)
A	1	487	0.50	591		0.892
PN 400/E30	AM	(82)	(0.33-1.50)	(108)		(35)
	1	187	1.50	388	978	1.11
	PM	(132)	(0.33-4.00)	(137)	(115)	(62)
	9	1584	0.50	2779		1.26
	AM	(39)	(0.17-1.50)	(45)		(25)
	9	810	1.00	2066	4911	1.46
	PM	(59)	(0.33-8.00)	(53)	(42)	(34)
B	1	292	0.50	350		0.846
PN 400/E20	AM	(77)	(0.20-1.50)	(113)		(42)
	1	96.6	1.49	206	556	0.994
	PM	(104)	(0.33-3.00)	(141)	(119)	(55)
	9	715	0.50	1216		1.12
	AM	(52)	(0.17-1.50)	(69)		(33)
	9	428	0.75	919	2134	1.31
	PM	(73)	(0.33-3.00)	(84)	(74)	(42)

TABLE 6-continued

Summary of Esomeprazole Pharmacokinetic Results

Treatment	Day/Dose Time	C_{max} (ng/mL)	t_{max} (hr)	$AUC_{0-10,\ am}$ or $AUC_{0-14,\ pm}$ (hr*ng/mL)	AUC_{0-24} (hr*ng/mL)	t½ (hr)
C	1	138	0.33	148		0.810
PN 400/E10	AM	(71)	(0.17-3.10)	(111)		(48)
	1	35.3	1.50	85.7	237	0.878
	PM	(84)	(0.33-3.00)	(179)	(133)	(50)
	9	278	0.33	368		0.860
	AM	(57)	(0.17-1.00)	(89)		(41)
	9	97.6	1.00	223	602	1.09
	PM	(136)	(0.33-2.00)	(134)	(103)	(47)
D	1	282	1.50	520	580	1.09
EC E20 +	AM	(66)	(1.00-16.0)	(64)	(67)	(44)
naproxen	9	435	1.50	1046	1212	1.27
	AM	(48)	(1.00-14.0)	(54)	(47)	(36)

Values are mean (% CV) for all parameters, except for tmax, which are median (range).

B. The Challenged Claims

54. The ’208 patent contains seven claims, all of which I understand are challenged in Mylan’s Petition.

55. Claim 1 is the only independent claim. Claims 2-7 depend from claim 1, and add further elements to the subject matter recited in claim 1.

56. Claim 1 recites:

> **1.** A method for delivering a pharmaceutical composition to a patient in need thereof, comprising:
>
> orally administering to the patient an AM unit dose form and, 10 hours (±20%) later, a PM unit dose form, wherein:
>
> the AM and PM unit dose forms each comprises:

i) naproxen, or a pharmaceutically acceptable salt thereof, in an amount to provide 500 mg of naproxen, and

ii) esomeprazole, or a pharmaceutically acceptable salt thereof, in an amount to provide 20 mg of esomeprazole;

said esomeprazole, or pharmaceutically acceptable salt thereof, is released from said AM and PM unit dose forms at a pH of 0 or greater,

the AM and PM unit dose forms target:

i) a pharmacokinetic (pk) profile for naproxen where:

a) for the AM dose of naproxen, the mean C_{max} is 86.2 μg/mL (±20%) and the median T_{max} is 3.0 hours (±20%); and

b) for the PM dose of naproxen, the mean C_{max} is 76.8 μg/mL (±20%) and the median T_{max} is 10 hours (±20%); and

ii) a pharmacokinetic (pk) profile for esomeprazole where:

a) for the AM dose of esomeprazole, the mean area under the plasma concentration-time curve from when the AM dose is administered to 10 hours (±20%) after the AM dose is administered (AUC0-10,am) is 1216 hr*ng/mL (±20%),

b) for the PM dose of esomeprazole, the mean area under the plasma concentration-time curve from when the PM dose is administered to 14 hours (±20%) after the PM dose is administered (AUC0-14,pm) is 919 hr*ng/mL (±20%), and

c) the total mean area under the plasma concentration-time curve for esomeprazole from when the AM dose is administered to 24 hours

(±20%) after the AM dose is administered (AUC0-24) is 2000 hr*ng/ mL (±20%); and

the AM and PM unit dose forms further target a mean % time at which intragastric pH remains at about 4.0 or greater for about a 24 hour period after reaching steady state that is at least about 60%.

57. Claim 2 recites:

2. The method according to claim 1, wherein the mean % time at which intragastric pH remains at about 4.0 or greater for about a 24 hour period is at least about 71%.

58. Claim 3 recites:

3. The method according to claim 1, wherein said unit dose form is administered for a period of at least about 6 days.

59. Claim 4 recites:

4. The method according to claim 2, wherein said unit dose form is administered for a period of at least about 9 days.

60. Claim 5 recites:

5. The method according to claim 1, wherein said AM and PM unit dose forms are each a multilayer tablet comprising at least one core and at least a first layer and a second layer, wherein:

i) said core comprises naproxen, or pharmaceutically acceptable salt thereof;

ii) said first layer is a coating that at least begins to release the naproxen, or pharmaceutically acceptable salt thereof, when the pH of the surrounding medium is about 3.5 or greater; and

> iii) said second layer comprises esomeprazole or a pharmaceutically acceptable salt thereof, wherein said esomeprazole or pharmaceutically acceptable salt thereof is released at a pH of from about 0 or greater.

61. Claim 6 recites:

> **6.** The method according to claim 5, wherein said esomeprazole is released at a pH of from about 0 to about 2.

62. Claim 7 recites:

> **7.** The method according to claim 5, wherein said multi-layer tablet is substantially free of sodium bicarbonate.

VIII. Claim Construction

A. Legal Standard

63. I understand that a claim in an unexpired patent, like the ’208 patent, is given its broadest reasonable construction to a person of ordinary skill in the art in light of the specification of the patent in which it appears.

64. I also understand that, unless the inventors gave a term a specific definition in the context of the patent, claim terms are given their ordinary meaning.

65. I further understand that to determine a claim term’s ordinary meaning, courts look first to intrinsic evidence—the claims, specification, and prosecution history—and secondarily to extrinsic evidence, such as dictionary definitions, publications in the relevant field, and expert testimony.

B. The Term "Target" Means "With The Goal of Obtaining"

66. I have reviewed the claims of the '208 patent and conclude that the term "target" should be construed to mean "with the goal of obtaining." The claims of the '208 patent recite administering AM and PM unit dose forms of a naproxen/esomeprazole combination to "target" certain PK/PD properties or PK/PD elements. Ex. 1001 at 46:33-47:9; *id.* at 46:48.

67. The term "target" appears in the '208 patent in several places, but only when repeating language used in the claims, or in phrases that echo the language of the claims. Ex. 1001 at 1:57; 2:3; 6:25, 41, 55; 7:1, 17, 32, 51; 8:1, 13, 25, 54; 9:20, 48, 67; 10:18, 42, 64; 11:33, 64; 12:21, 41, 67; 13:25, 67; 14:36; 15:7, 40; 16:3, 30, 56; 17:11, 44; 18:7, 35.

68. Thus, the many mentions of the term "target" in the patent do not ascribe any particular meaning to the term.

69. Discussions of the PK/PD data in the '208 patent, even beyond use of the term "target," also show that the term should not be understood in a special way for purposes of the '208 patent. Instead, the patent specification, which includes the clinical study described in the example, and the data reported from that study, support Mylan's proposed claim construction.

70. After reviewing the data disclosed in the '208 patent, a POSA would understand that the patentee used the term "target" to describe wider variations in

the PK values than the "±20%" variation recited in the claims. For example, the '208 patent discloses the claimed PK values, among many others, but does so with substantially greater variation than is claimed. *See, e.g.*, Ex. 1001 at Tbl. 6, Tbl. 8 (disclosing PK parameters with coefficients of variation that often exceed 100%). Thus, the term "target" has to mean, to a POSA, something broader than simply yielding or directly producing the claimed PK and PD values.

71. This point is reinforced when one looks at the data in the '208 patent more carefully, and notices that the claimed PK values, those to be "targeted," are copied from experimental results disclosed in the specification. *Id.* at Tbl. 6. In Example 1, the investigators dosed the claimed PN400 formulation (*i.e.*, enteric-coated naproxen 500 mg combined with non-enteric coated esomeprazole 10, 20, or 30 mg) to 28 patients according to the claimed method, and the resulting 24-hour intragastric pH and numerous PK values were measured. *Id.* at 24:7-21; 24:66-25:1; and 25:62-26:8. For the PK parameters, the '208 patent reports both the mean PK values, and the variation associated with that mean value. For example, Table 6 in the '208 patent discloses that the mean AUC for the AM dose of 20 mg of esomeprazole was 1216 hr*ng/mL, with a coefficient of variation of ±69%. *Id.* at Tbl. 6 (Treatment B). Table 6 further discloses that the mean AUC for the PM dose of 20 mg of esomeprazole was 919 hr*ng/mL, with a coefficient of variation of ±84%. A portion of Table 6 is reproduced below (left) with a

TABLE 6

Summary of Esomeprazole Pharmacokinetic Results

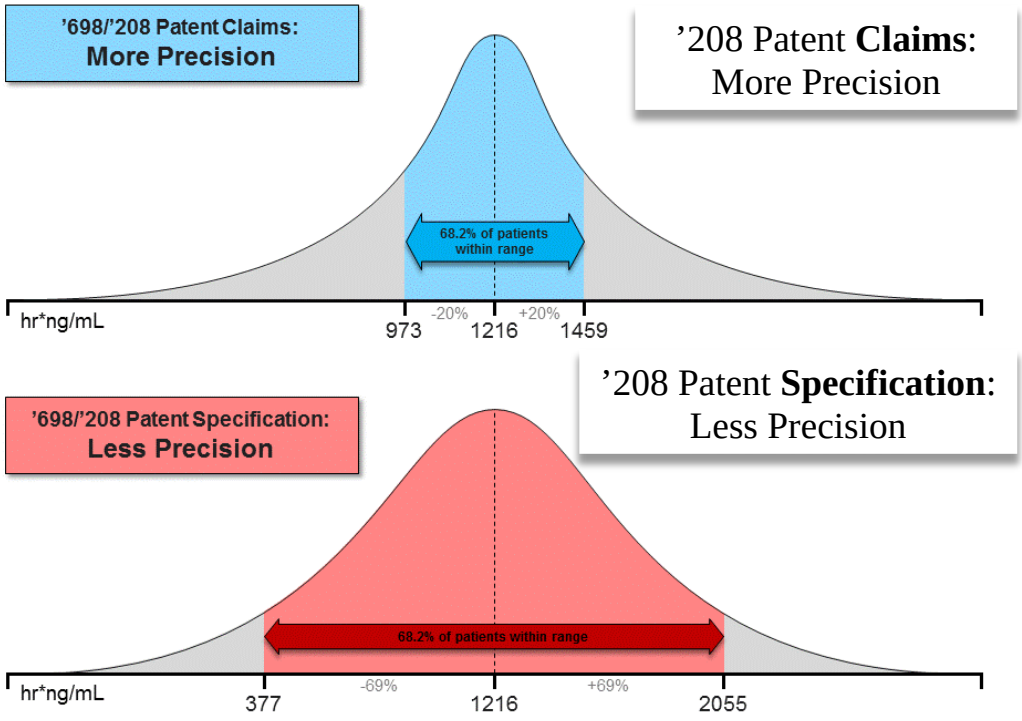
Treatment	Day/Dose Time	C_{max} (ng/mL)	t_{max} (hr)	$AUC_{0\text{-}10,am}$ or $AUC_{0\text{-}14,pm}$ (hr*ng/mL)	$AUC_{0\text{-}24}$ (hr*ng/mL)	t½ (hr)
A	1	487	0.50	591		0.892
PN 400/E30	AM	(82)	(0.33-1.50)	(108)		(35)
	1	187	1.50	388	978	1.11
	PM	(132)	(0.33-4.00)	(137)	(115)	(62)
	9	1584	0.50	2779		1.26
	AM	(39)	(0.17-1.50)	(45)		(25)
	9	810	1.00	2066	4911	1.46
	PM	(59)	(0.33-8.00)	(53)	(42)	(34)
B	1	292	0.50	350		0.846
PN 400/E20	AM	(77)	(0.20-1.50)	(113)		(42)
	1	96.6	1.49	206	556	0.994
	PM	(104)	(0.33-3.00)	(141)	(119)	(55)
	9	715	0.50	1216		1.12
	AM	(52)	(0.17-1.50)	(69)		(33)
	9	428	0.75	919	2134	1.31
	PM	(73)	(0.33-3.00)	(84)	(74)	(42)

ii) a pharmacokinetic (pk) profile for esomeprazole where:

a) for the AM dose of esomeprazole, the mean area under the plasma concentration-time curve from when the AM dose is administered to 10 hours (±20%) after the AM dose is administered (AUC0-10,am) is 1216 hr*ng/mL (±20%),

b) for the PM dose of esomeprazole, the mean area under the plasma concentration-time curve from when the PM dose is administered to 14 hours (±20%) after the PM dose is administered (AUC0-14,pm) is 919 hr*ng/mL (±20%), and

c) the total mean area under the plasma concentration-time curve for esomeprazole from when the AM dose is administered to 24 hours (±20%) after the AM dose is administered (AUC0-24) is 2000 hr*ng/mL (±20%); and


'698/'208 Patent Claims:
More Precision
'208 Patent Claims:
More Precision
68.2% of patients within range
hr*ng/mL
973
-20%
1216
+20%
1459
'698/'208 Patent Specification:
Less Precision
'208 Patent Specification:
Less Precision
68.2% of patients within range
hr*ng/mL
377
-69%
1216
+69%
2055

74. Here, the fact that the experimental data in Example 1 (reported in Table 6; Figure F, bottom panel) have wider variation than the data in claim 1 (Figure F, top panel) means that repeating Example 1 may produce results that fall outside of the range of AUC values claimed in the ’208 patent. A narrow construction of the term “target” would potentially result in the disclosed embodiments, and even the Patent Owner’s commercial Vimovo product, falling outside the scope of claim 1. I understand that claim constructions should generally not exclude preferred embodiments. Thus, the data in Table 6, read in view of the ranges of AUC values recited in the claims, would serve to reinforce to the POSA that the term “target” is properly construed as “with the goal of obtaining.” This plain meaning encompasses both the PK/PD values recited in the claims and the PK/PD values reported in the specification.

75. I have reviewed the substantive portions of the prosecution history of the ’208 patent. The prosecution history does not discuss or inform the meaning of the term “target,” and does not ascribe to the term “target” any special meaning.

76. The patent and its prosecution history therefore supply the POSA no reason to ascribe a special meaning to the term “target,” and it is not a term of art, so the term “target” must therefore carry its ordinary meaning.

77. Reflecting an understanding of the term “target,” the American Heritage Dictionary defines “target” as “to establish as a target or goal.” Ex. 1032.

Similarly, Merriam-Webster's Concise Dictionary defines "target" as "establish as a goal," and Webster's New World College Dictionary defines "target" as "to establish as a target, goal, etc." Exs. 1031 (Webster's), 1033 (Merriam-Webster's). In light of these sources, the ordinary meaning of "target" is best understood as "with the goal of obtaining."

78. I conclude from this analysis that the broadest reasonable construction of the term "target" is "with the goal of obtaining," which reflects the plain meaning of the term "target" in view of the intrinsic and extrinsic evidence.[2]

IX. The Prior Art

A. Prior Art References Disclosed A Combined Dosage Form With Naproxen and Esomeprazole

79. A number of references disclosed a combined dosage form of naproxen and esomeprazole, or NSAID and PPI, more generally, and its use for treating chronic painful and inflammatory conditions. For example, the '285 patent and the '907 patent claim dosage forms of naproxen and esomeprazole. Hochberg and Goldstein disclosed immediate-release omeprazole with naproxen, and Hassan-Alin confirmed that esomeprazole and naproxen could be combined in

[2] Consistent with Petitioner's proposed construction, in related district court litigation, the Court construed "target" as "set as a goal," over Patent Owner's objection. *See* Exhibit 1045 at 11.

a drug combination with no adverse effect on either drug's behavior (compatibility already shown for the combination of omeprazole and naproxen). These references therefore disclosed the use of a naproxen/esomeprazole combined dosage form.

(a) U.S. Patent No. 8,557,285 ("'285 Patent") [Ex. 1005]

80. The '285 patent is entitled "Pharmaceutical Compositions for the Coordinated Delivery of NSAIDs." Ex. 1005. The application that yielded the '285 patent was filed on August 23, 2011, and the '285 patent issued on October 15, 2013. *Id.* However, the '285 patent claims ultimate priority to U.S. Provisional Patent Application No. 60/294,588, which was filed on June 1, 2001. *Id.* The sole named inventor of the '285 patent is John Plachetka, one of the inventors of the '208 patent. *Id.*

81. The abstract of the '285 patent describes the invention as "drug dosage forms that release an agent that raises the pH of a patient's gastrointestinal tract, followed by a non-steroidal anti-inflammatory drug. The dosage form is designed so that the NSAID is not released until the intragastric pH has been raised to a safe level. The invention also encompasses methods of treating patients by administering this coordinated release, gastroprotective, antiarthritic/analgesic combination unit dosage form." *Id.* at Abstract. The '285 patent claims a "pharmaceutical composition in unit dosage form comprising therapeutically

effective amounts" of both esomeprazole and naproxen, where the naproxen is "surrounded by a coating that inhibits its release from said unit dosage form unless said dosage form is in a medium with a pH of 3.5 or higher" and "at least a portion of [the] esomeprazole is not surrounded by an enteric coating." *See* Ex. 1005, at 22:8-18.

82. The '285 patent incorporates by reference each of the patents and patent applications to which it claims priority, including the '907 patent. *Id.* at 1:7-16. The '285 patent acknowledges that use of non-steroidal anti-inflammatory drugs (NSAIDs), like naproxen, carries a risk of gastric injury. *Id.* at 1:30-47 (citing relevant prior art). The '285 patent further stated that it was known in the art that potent and long-lasting proton pump inhibitors (PPIs) could be protective during NSAID use, and more protective than shorter-acting agents, like H_2-receptor antagonists. *Id.* at 1:48-53 (citing prior art).

83. The '285 patent goes on to state that its invention is a "pharmaceutical composition in unit dosage form suitable for oral administration." *Id.* at 3:27-29. The dosage form includes both an acid inhibitor (a preferred agent is a PPI like esomeprazole) and an NSAID (most preferably naproxen). *Id.* at 3:29-33, 44-46, and 4:11-14. The dosage form can be a tablet with effective amounts of NSAID and PPI, with a delayed-release NSAID in the core of the tablet, and an outer layer

of immediate-release acid inhibitor surrounding the core. *Id.* at 4:22-41; *see also id.* at 4:52-59.

84. The ’285 patent disclosed that the claimed dosage form can be used to treat osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis. *Id.* at 5:20-29. The ’285 patent also disclosed that the dosage form can be administered twice daily (*i.e.*, with spacing of 10 hours ±20%). *Id.* at Examples 9, 10. The ’285 patent further disclosed that “[n]aproxen is particularly useful when contained in tablets or capsules in an amount of from 250 to 500 mg,” Ex. 1005 at 7:9-10, and that “about 40 mg” of esomeprazole is a “preferred” amount of the proton pump inhibitor, *id.* at 8:5-10; *see also* Ex. 1004 at 6:6-7, 7:12-13. I also note that the prior art disclosed the use of 20- and 40-mg doses of esomeprazole as particular options because AstraZeneca commercially marketed those strengths as Nexium®, long before the filing date of the ’208 patent. *See, e.g.*, Ex. 1043 at 1, 22. Similarly, AstraZeneca commercially marketed omeprazole as Prilosec®, in strengths of 10, 20, and 40 mg, well before the priority date of the ’208 patent. *See, e.g.*, Ex. 1044 at 1.

85. The ’285 patent noted that the disclosed combination dosage forms “can be made in accordance with methods that are standard in the art,” using “conventional excipients,” and “standard coating techniques.” Ex. 1005 at 8:17-21

(citing a classic formulation treatise, Remington's Pharmaceutical Sciences (1980)), 22-23, and 35-36.

86. In dependent claim 2, the '285 patent claims the pharmaceutical composition of claim 1, having 200–600 mg of naproxen, and in dependent claim 3, having 5–100 mg of esomeprazole. *See id.* at 22:19-21; 22:22-24.

87. In dependent claim 4, the '285 patent claims the pharmaceutical composition of claim 1, having 200-600 mg of naproxen and 5-100 mg of esomeprazole per unit dosage form. *See id.* at 22:25-28.

(b) U.S. Patent No. 6,926,907 ("'907 Patent") [Ex. 1004]

88. The '907 patent is entitled "Pharmaceutical Compositions for the Coordinated Delivery of NSAIDs." The application that yielded the '907 patent was filed on May 31, 2002, and the '907 patent issued on August 9, 2005. The '907 patent claims ultimate priority to U.S. Provisional Patent Application No. 60/294,588, which was filed on June 1, 2001.

89. The '907 patent claims, generally, a unit dosage form of a pharmaceutical composition for oral administration, comprising an immediate-release acid inhibitor and a delayed-release NSAID, where the NSAID is released at a pH of 3.5 or higher and the esomeprazole is released at any pH. Ex. 1004 at 20:9-32.

90. The ’907 patent also claims methods of administering the combined pharmaceutical composition of a proton pump inhibitor and an NSAID. *Id.* at 21:41-23:13. For example, claim 47 of the ’907 patent (*via* claims 37, 41, 42, 45, and 46) recites a method of treating a patient for pain or inflammation comprising administering an effective dose of immediate-release esomeprazole and 200-600 mg of delayed-release naproxen. *Id.* at 22:62-63.

91. The ’907 patent taught administering a drug to treat osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis. *See* Ex. 1004 at claims 23, 52; *id.* at 4:18-27.

92. Importantly, the ’208 patent refers to the ’907 patent and describes it as a reference that “is directed to at least one drug dosage form comprising a proton pump inhibitor that raises the pH of a patient's gastrointestinal tract, followed by an NSAID.” Ex. 1001 at 1:30-34. The ’208 patent also states, referring to the ’907 patent, that “[t]his, and similar, formulations can be effective in improving NSAID tolerability through dosages of esomeprazole and naproxen that produce the desired pharmacodynamic response and pharmacokinetic values.” Ex. 1001 at 1:34-37.

(c) Goldstein [Ex. 1011]

93. Goldstein is a meeting abstract from Digestive Disease Week and the 109th Annual Meeting of the AGA Institute, held in 2008. Goldstein is entitled “A

Single Tablet Multilayer Formulation of Enteric-Coated Naproxen Coupled with Non-Enteric-Coated OMEPRAZOLE Is Associated with a Significantly Reduced Incidence of Gastric Ulcers vs. Enteric-Coated Naproxen: A Prospective, Randomized, Double-Blind Study." Goldstein was published in an April 2008 supplement to the journal Gastroenterology, was received by the public no later than April 30, 2008, and is therefore prior art to the '208 patent.

94. Goldstein reported on a clinical trial (also reported in Hochberg, below) studying "[t]he efficacy and safety of a single tablet formulation, PN200, which provides sequential delivery of non-EC omeprazole 20 mg + EC naproxen 500 mg was compared with EC naproxen 500 mg alone (twice daily use for both)." Ex. 1011 at 4. In the study, 409 patients were randomized to take either twice-daily PN200 (a combined tablet of immediate-release omeprazole 20 mg and delayed-release naproxen 500 mg) or twice-daily delayed-release naproxen 500 mg, and then followed for six months. *Id.* At the conclusion of the study period, the investigators found that PN200 significantly reduced the incidence of ulcers in the PN200 group versus the EC naproxen group for both gastric ulcers (8.3% and 29.4%, respectively), and duodenal ulcers (0.5% and 10.8%, respectively). *Id.* Goldstein concluded that the combined formulation of omeprazole and enteric-coated naproxen "may add to the treatment armamentarium for patients at risk of

NSAID-associated GU, and address adherence to [NSAID and PPI] co-therapy." *Id.*

(d) Hochberg [Ex. 1012]

95. Hochberg is a poster presentation entitled "A novel, single-tablet formulation that delivers immediate-release omeprazole followed by enteric-coated (EC) naproxen significantly reduces the incidence of gastric ulcers compared with EC naproxen alone: results of a prospective, randomised, double-blind, 6-month study including patients with OA [i.e., osteoarthritis] and RA [i.e., rheumatoid arthritis]." Hochberg was presented at the EULAR 2008 Conference in Paris, France, held June 11-14, 2008, and is therefore prior art to the '208 patent. Ex. 1012.

96. Hochberg disclosed that the PN200 single-tablet formulation, containing non-enteric-coated (*i.e.*, immediate-release) omeprazole and enteric-coated (*i.e.*, delayed-release) naproxen delivers omeprazole to the bloodstream before naproxen. Ex. 1012, Introduction and Fig. 1. Hochberg's Figure 1 shows that the concentrations of omeprazole rise and peak much earlier than do the concentrations of naproxen. *Id.* Hochberg, therefore, taught a PK profile for PN200, which matches the formulation claimed in the '208 patent, but with racemic omeprazole substituting for its constituent molecule, esomeprazole. Ex. 1012 at Introduction. One of skill in the art would not expect the difference to

affect the PK performance of the disclosed dosage form. *See*, *e.g.*, Ex. 1023 at 3-4, 18 (significant correlation between antisecretory activity and area under the plasma concentration-time curve).

97. Hochberg also disclosed that the immediate-release omeprazole/enteric-coated naproxen formulation was effective in reducing the risk of NSAID-induced gastric ulcers. Hochberg reported on the results of a study called PN200-301, which was "a 6-month, randomised, double-blind, parallel-group, multicentre study in patients with arthritis requiring chronic NSAID treatment." Ex. 1012 at Methods. Patients were randomized to receive, twice daily, either the combined omeprazole/naproxen formulation or 500 mg enteric-coated naproxen alone. Ex. 1012 at Methods, Fig. 2. Hochberg reported that after six months, in its study population of 290 individuals, "[t]he incidence of gastric ulcers during the course of the study was significantly lower in the PN200 group compared with the EC naproxen group (8.3% vs. 29.4% for PN200 and EC naproxen, respectively)." Ex. 1012 at Results. Hochberg concludes that "[c]ompared with EC naproxen, PN200 was associated with a significantly lower incidence of both gastric ulcers and duodenal ulcers." Ex. 1012 at Conclusions. Hochberg further concluded that "[t]he PN formulation may offer a potential treatment option for patients at risk of NSAID-associated gastric ulcers or

duodenal ulcers and may help address issues of persistence of use and compliance with gastroprotective agents." *Id.*

(e) Hassan-Alin [Ex. 1016]

98. Hassan-Alin, a report of two studies, is an article entitled "Lack of Pharmacokinetic Interaction between Esomeprazole and the Nonsteroidal Anti-Inflammatory Drugs Naproxen and Rofecoxib in Healthy Subjects." Hassan-Alin was published in the journal Clinical Drug Investigation in 2005, and is therefore prior art to the '208 patent.

99. Hassan-Alin taught that "[n]onsteroidal anti-inflammatory drugs (NSAIDS) are widely used for the treatment of rheumatoid arthritis (RA), osteoarthritis (OA) and a wide variety of other acute and chronic painful musculoskeletal disorders." Ex. 1016 at 2. Hassan-Alin noted that "[t]he use of NSAIDs is expected to increase further in the future," but that "[a]ll NSAIDs are, however, associated with a substantial number of adverse events." *Id.* Hassan-Alin stated that "15-40% of NSAID users report upper [gastrointestinal] symptoms and 10-30% of long-term NSAID users will develop a peptic ulcer, predominantly in the stomach. NSAID use increases the risk of peptic ulcer complications by 3- to 5-fold, and 15-35% of all peptic ulcer complications are reported to be caused by NSAID use." *Id.*

100. Hassan-Alin stated that "[e]someprazole, which confers a longer time with intragastric pH >4 than all other PPIs, is expected to be effective for the prevention of NSAID-associated ulcers." *Id.* at 3. And, "[e]someprazole is expected to be widely used in the management of upper GI symptoms, and to heal and prevent gastric and duodenal ulcers associated with continued NSAID use. Therefore, esomeprazole will commonly be used in combination with NSAIDs." *Id.* at 7.

101. Hassan-Alin studied whether the pharmacokinetics of esomeprazole and naproxen are affected by administering the two drugs together. Hassan-Alin hypothesized that "a drug interaction would not be expected between esomeprazole and the NSAIDs" because they are metabolized by different enzymes. *Id.* at 9. Hassan-Alin tested the hypothesis using a randomized, three-way crossover trial in which patients received naproxen 250 mg twice daily, esomeprazole 40 mg once daily, or the two together. *Id.* at 3. Each treatment period lasted 7 days, followed by a washout period of at least 14 days. *Id.* PK measurements were taken on day 7. *Id.*

102. The results of the trial showed that naproxen has no "effect on the pharmacokinetics of esomeprazole, and esomeprazole does not have any effect on the pharmacokinetics of naproxen." *Id.* at 9. Therefore, "esomeprazole can be used together with naproxen . . . without pharmacokinetic drug interaction safety

concerns for the healing and prevention of gastric and duodenal ulcers in patients needing continuous NSAID treatment to relieve inflammation and pain." *Id.* Hassan-Alin noted that these results were "in agreement with previous studies involving omeprazole, which showed no drug-drug interactions between omeprazole and three different NSAIDs," including naproxen. *Id.*

B. Prior art references disclosed the target pharmacokinetics of naproxen

103. Several references disclosed PK values for naproxen in both immediate-release and enteric-coated forms. These references therefore provided target PK (*i.e.*, C_{max}) values for the naproxen element of the combination used in the '208 patent's claimed method.

(a) EC-Naprosyn label [Ex. 1009]

104. The 500 mg enteric-coated (*i.e.*, delayed-release) naproxen dosage form included in the formulation claimed in the '208 patent was sold publicly, long before the priority date of the '208 patent, as EC-Naprosyn. The EC-Naprosyn label, last revised before the priority date in January 2007, taught that EC-Naprosyn is indicated for the relief of the signs and symptoms of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, and juvenile arthritis. Ex. 1009 at 6, 8. The label further disclosed PK information about delayed-release naproxen 500 mg, including that delayed-release naproxen 500 mg, dosed twice daily, provided a mean C_{max} of 94.9 µg/mL (with an 18% coefficient of variation; i.e.,

77.8 µg/mL to 112.0 µg/mL) and a mean T_{max} of 4 hours (with a 39% coefficient of variation). *Id*. at 4. The label further stated that "[w]hen EC-NAPROSYN was given to fasted subjects, peak plasma levels were attained about 4 to 6 hours following the first dose (range: 2 to 12 hours)". *Id*. at 3. The label reported that "[a]n in vivo study in man using radiolabeled EC-NAPROSYN tablets demonstrated that EC-NAPROSYN dissolves primarily in the small intestine rather than the stomach, so the absorption of the drug is delayed until the stomach is emptied." *Id*. Additionally, the label disclosed that "[t]he different dosage forms of NAPROSYN are bioequivalent in terms of extent of absorption (AUC) and peak concentration (C_{max}); however, the products do differ in their pattern of absorption." *Id*. at 3.

(b) Khosravan [Ex. 1017]

105. Khosravan is an article entitled "Pharmacokinetic Interactions of Concomitant Administration of Febuxostat and NSAIDs." Khosravan was published in the Journal of Clinical Pharmacology in 2006, two years before the '208 patent's priority date. Khosravan reported on two studies investigating whether febuxostat, a treatment for gout, has any PK interactions with indomethacin and naproxen. One arm of one of the Khosravan studies (study 2) involved administering naproxen 500 mg twice daily, at 8:00 a.m. and 8:00 p.m., for seven days. Ex. 1017 at 3. On day 7, numerous blood samples were taken,

from 0.25 to 24 hours after administering naproxen, to create a PK profile for naproxen. *Id*. at 4. Khosravan's results showed that the naproxen 500 mg AM dose yielded a C_{max} of 93.7 µg/mL (±7.1) and T_{max} of 1.5 hours (range from 1.0 - 4.0 hours). *Id*. at 9 (Table IV). Further, Khosravan's naproxen 500 mg PM dose yielded a C_{max} of 86.9 µg/mL (±8.9) and a T_{max} of 2.5 hours (range from 1.5 - 6.0 hours). *Id*.

(c) Jung [Ex. 1018]

106. Jung [Ex. 1018] is an article entitled "Steady-State Pharmacokinetics of Enteric-Coated Naproxen Tablets Compared with Standard Naproxen Tablets." Jung was published in Clinical Therapeutics in 1994, prior to the earliest priority date for the '208 patent.

107. Jung is a report of a clinical study involving dosing enteric-coated or standard naproxen tablets, 500 mg, twice daily for seven days. Ex. 1018 at 3. Jung then began blood sampling on day 8, after the last dose of study drug, "to determine and compare the steady-state pharmacokinetics for each of the two naproxen formulations." *Id.* Jung reported that the "[m]ean time to maximum plasma concentration (T_{max}) was greater for EC naproxen than for standard naproxen (4.0 vs 1.9 hours)," while the "maximum observed plasma concentration (C_{max})" was 94.9 µg/mL. *Id.* Jung further reported that "[a]n enteric-coated (EC) formulation of naproxen was developed to release naproxen at the pH level of the

small intestine, where dissolution takes place." *Id.* at 4. The standard deviation for the T_{max} of EC naproxen was ±1.6, and for C_{max} was ±17.5. *Id.* at 8, Table III.

(d) Davies [Ex. 1019]

108. Davies [Ex. 1019] is an article entitled "Clinical Pharmacokinetics of Naproxen," which was published in the journal Clinical Pharmacokinetics in 1997. Davies was therefore published before the earliest priority date for the '208 patent.

109. Davies is a review article that compiled detailed information on the clinical pharmacokinetics of naproxen and its metabolism. Ex. 1019 at 1. Davies reported that "[t]he area under the plasma concentration-time curve (AUC) of naproxen is linearly proportional to the dose for oral doses up to a total dose of 500mg." *Id.* Davies also reported that "[n]aproxen is prescribed for the treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, and acute gouty arthritis." *Id.* at 2. Davies noted that "[m]ultiple dose administration yields absorption characteristics similar to those seen after single doses." *Id.* Davies compiled, in Table I, the results of numerous studies on the pharmacokinetics of naproxen, in a variety of dosage forms, strengths, and dosing regimens. *Id.* at 3-6 (Table I).

C. Prior Art References Disclosed The Target Pharmacokinetics of, and Pharmacodynamic Response To, Esomeprazole

110. A number of references disclosed the PK/PD values associated with esomeprazole by analogy to omeprazole. For example, both Howden 2005 and the

Zegerid label discussed an approved immediate-release omeprazole product, with data regarding its PK and PD parameters after one day and repeated days of dosing. These references, therefore, provided target PK and PD (*i.e.*, AUC and pH) values for the esomeprazole element of the combination used in the '208 patent's claimed method.

(a) Howden 2005 [Ex. 1006]

111. Howden 2005 [Ex. 1006] is a publication entitled "Review article: immediate-release proton-pump inhibitor therapy - potential advantages." Howden 2005 was published in the journal Alimentary Pharmacology and Therapeutics in 2005, which is prior to the earliest priority date for the '208 patent.

112. Howden 2005 stated in its Summary that it "provides an overview of the pharmacokinetics and pharmacodynamics of a new immediate-release omeprazole," in the form of Zegerid powder for oral suspension, and the potential advantages that the dosage form has over delayed-release PPIs. Ex. 1006 at 1. Howden 2005 reported that Zegerid is available in two strengths, 40 mg or 20 mg omeprazole per unit dose. *Id.* at 2. Howden 2005 disclosed PK parameters of T_{max}, C_{max}, and AUC on day 1 and day 7 after administering Zegerid. *Id.* at 2-3. Howden 2005 also disclosed the results of pharmacodynamic studies with Zegerid. *Id.* at 3-4. Howden 2005 disclosed that the mean AUCs for immediate-release omeprazole after once-daily dosing of 20 mg for one and seven days are 825 and

1446 ng*hr/mL, respectively. *Id.* at 2. For 40 mg dosing, the corresponding values are 2228 and 4640 ng*hr/mL, respectively. *Id.* Howden 2005 further disclosed that after seven days of once-daily dosing of 40 mg of omeprazole, gastric pH remained above four for 77% of a 24-hour period. *Id.* at 3, Fig. 2. Figure 2 of Howden 2005 shows a significant drop in gastric pH after about 15 hours with once-daily dosing. *Id.* at 3. Finally, Howden 2005 showed that gastric pH could be maintained over 4 for more than 80% of a 24-hour period if seven days of once-daily dosing of 20 mg is followed by twice-daily dosing on the eighth day. *Id.* at 4 (citing Goldlust *et al.* (Ex. 1042)).

(b) Zegerid label [Ex. 1010]

113. The Zegerid® label [Ex. 1010] was published in 2004, prior to the earliest priority date for the '208 patent.

114. According to its label, Zegerid is indicated for several uses:

- Duodenal Ulcer

  Zegerid is indicated for short-term treatment of active duodenal ulcer. Most patients heal within four weeks. Some patients may require an additional four weeks of therapy.

- Treatment of Gastroesophageal Reflux Disease (GERD)

  Symptomatic GERD: Zegerid is indicated for the treatment of heartburn and other symptoms associated with GERD.

> Erosive Esophagitis: Zegerid is indicated for the short-term treatment (4-8 weeks) of erosive esophagitis which has been diagnosed by endoscopy.
>
> - Maintenance of Healing of Erosive Esophagitis
>
> Zegerid Powder for Oral Suspension is indicated to maintain healing of erosive esophagitis.

Ex. 1010 at 10.

115. The Zegerid label disclosed that Zegerid is a "powder for oral suspension" containing omeprazole as its active ingredient. Ex. 1010 at 4.

116. The Zegerid label reported several PK parameters following from "oral 20 mg once-daily dosing for 1 and 7 days." *Id.* at 5. In particular, the Zegerid label reported that the AUC(0-inf)[3] for the dose on day 1 is 825 ng*hr/mL, with a 72% coefficient of variation; the AUC(0-inf) for the dose on day 7 is 1446 ng*hr/mL, with a 61% coefficient of variation. *Id.*

[3] "$AUC_{(0\text{-}inf)}$" means the total area under the plasma concentration-time curve from time zero to infinity. In other words, $AUC_{(0\text{-}inf)}$ represents the total amount of drug delivered by the dose in question. A POSA would use Zegerid's $AUC_{(0\text{-}inf)}$ data to inform their understanding of the AUC produced from hours zero to ten, and ten to twenty-four. The figures accompanying the AUC data in the Zegerid label show little absorption after hour eight. Ex. 1010 at 4, Figures. The Zegerid label also reported that, "absorption of omeprazole is rapid, with mean peak plasma levels of omeprazole occurring at around 30 minutes (range 10 to 90 minutes) after a single dose or repeated once-daily administration." Ex. 1010 at 4.

117. The Zegerid label also reported the pharmacodynamic (*i.e.*, antisecretory) effect of repeated once-daily dosing of 20 mg of Zegerid on intragastric pH on day 7. *Id.* at 6-7.

118. The Zegerid label further noted that "[r]epeated single daily oral doses of Zegerid 20 mg have produced nearly 100% inhibition of 24-hour integrated intragastric acidity in some subjects." *Id.* at 7.

D. Esomeprazole is a Component of Omeprazole

119. Omeprazole is a prior art PPI effective in inhibiting gastric acid secretion that was known to be useful as an antiulcer agent. Ex. 1024 at 1:25-34. Omeprazole was known as a racemic mixture of its two single enantiomers,[4] the R- and S- enantiomers of omeprazole, herein referred to as R-omeprazole and S-omeprazole. *Id*. at 1:35-49. The S-enantiomer of omeprazole was known to have improved pharmacokinetic properties over racemic omeprazole. *Id.* at 1:50-54; Ex. 1025 at 1:50-55.

120. Esomeprazole, as the S-enantiomer of omeprazole, has long been known as an effective inhibitor of gastric acid secretion. *See generally* Ex. 1007; *id*. at 2:38-45. Further, it was known before the priority date of the '208 patent that the AUC of esomeprazole is higher than the AUC of omeprazole, given the same

[4] Enantiomers are optical isomers (chemically identical and with the same connectivity of atoms, but differing in their three-dimensional arrangements), and are therefore non-superimposable, mirror images of each other.

drug dose (*e.g.*, 20 mg each), and a POSA could quantify the difference between the AUCs for omeprazole and esomeprazole. *Id.*

X. All Claims of the '208 Patent Are Unpatentable

A. The '285 Patent Anticipated the Claims of the '208 Patent

(a) The '285 Patent anticipated independent claim 1

121. Claim 1 recites:[5]

> 1. *A method for delivering a pharmaceutical composition to a patient in need thereof, comprising:*
>
> *orally administering to the patient an AM unit dose form and, 10 hours (±20%) later, a PM unit dose form, wherein:*
>
> *the AM and PM unit dose forms each comprises:*
>
> *i) naproxen, or a pharmaceutically acceptable salt thereof, in an amount to provide 500 mg of naproxen, and*
>
> *ii) esomeprazole, or a pharmaceutically acceptable salt thereof, in an amount to provide 20 mg of esomeprazole;*
>
> *said esomeprazole, or pharmaceutically acceptable salt thereof, is released from said AM and PM unit dose forms at a pH of 0 or greater,*
>
> **the AM and PM unit dose forms target:**
>
> **i) a pharmacokinetic (pk) profile for naproxen where:**

[5] Given the length of claim 1, and for purposes of aiding presentation of my discussion, I refer to the *italicized* portion of claim 1 as the "dosing element" and the **bolded** portion of claim 1 as the "PK/PD elements."

a) for the AM dose of naproxen, the mean C_{max} is 86.2 µg/mL (±20%) and the median T_{max} is 3.0 hours (±20%); and

b) for the PM dose of naproxen, the mean C_{max} is 76.8 µg/mL (±20%) and the median T_{max} is 10 hours (±20%); and

ii) a pharmacokinetic (pk) profile for esomeprazole where:

a) for the AM dose of esomeprazole, the mean area under the plasma concentration-time curve from when the AM dose is administered to 10 hours (±20%) after the AM dose is administered (AUC0-10,am) is 1216 hr*ng/mL (±20%),

b) for the PM dose of esomeprazole, the mean area under the plasma concentration-time curve from when the PM dose is administered to 14 hours (±20%) after the PM dose is administered (AUC0-14,pm) is 919 hr*ng/mL (±20%), and

c) the total mean area under the plasma concentration-time curve for esomeprazole from when the AM dose is administered to 24 hours (±20%) after the AM dose is administered (AUC0-24) is 2000 hr*ng/mL (±20%); and

the AM and PM unit dose forms further target a mean % time at which intragastric pH remains at about 4.0 or greater for about a 24 hour period after reaching steady state that is at least about 60%.

Ex. 1001 at 46:33-47:9.

122. As explained below, the prior art '285 patent disclosed each element of claim 1.

1. The '285 patent taught a combined dosage form of naproxen and esomeprazole and its twice daily administration.

123. In the dosing element of claim 1, the claim recites a method for delivering a pharmaceutical composition to a patient in need thereof by orally administering to the patient an AM unit dose form and, 10 hours (±20%) later, a PM unit dose form, where each unit dose form comprises 500 mg of naproxen and 20 mg of esomeprazole. *See id.* at 46:33-44.

124. Claim 1 also recites that the esomeprazole component "is released from said AM and PM unit dose forms at a pH of 0 or greater." *See* Ex. 1001 at 46:46-47.

125. The '285 patent disclosed each of these elements.

126. ***First***, the '285 patent disclosed administering a combination pharmaceutical dosage form to a patient needing the unit dose form. Ex. 1005 at claim 1, 5:20-29; *see also* Ex. 1004 at claims 23, 52, 4:18-27.

127. The '285 patent also disclosed orally administering the unit dose form twice daily. Ex. 1005 at Examples 9, 10. A POSA would have known that EC-naproxen was dosed twice daily. Ex. 1009 at 24; Ex. 1005 at 6:24-33, Example 9.

128. The ’285 patent also disclosed the claimed amounts of naproxen (500 mg) and esomeprazole (20 mg) because the ’285 patent claims a unit dose form combining naproxen and esomeprazole, where the amount of naproxen is between 200 and 600 mg, and the amount of esomeprazole is between 5 and 100 mg. Ex. 1005 at claims 2-4. The ’285 patent disclosed that 250 to 500 mg of naproxen is preferred. Ex. 1005 at 7:9-10.

129. ***Second***, the ’285 patent disclosed a naproxen/esomeprazole combination tablet “wherein at least a portion of said esomeprazole is not surrounded by an enteric coating.” Ex. 1005 at 22:10-11; *see also id.* at Example 6 (disclosing a tablet including immediate-release omeprazole), Figs. 1-2. A POSA would have known that non-enteric-coated (*i.e.*, immediate release) esomeprazole would release from the unit dose form immediately, which is “at a pH of 0 or greater.”

130. Therefore, I conclude that the prior art ’285 patent disclosed the dosing element of claim 1.

2. The PK/PD elements are inherent in the twice-daily administration of the dosage forms disclosed in the ’285 patent.

131. Claim 1 of the ’208 patent recites a number of PK/PD elements, which I refer to, collectively, as the PK/PD limitations. As noted in footnote 5, these are the bolded aspects of claim 1.

132. The PK/PD elements are directed to:

- the C_{max} and T_{max} of the naproxen component of the unit dose form,
- the 10-, 14-, and 24-hour AUC of the esomeprazole component of the unit dose form, and
- the pharmacodynamic effect of dosing esomeprazole (*i.e.*, the percent of a 24-hour period for which the gastric pH is over 4).

Ex. 1001 at 46:49-47:9.

133. These PK/PD elements are characteristics of the administration of the dosage forms disclosed in the ’285 patent. To achieve the PK/PD limitations of claim 1, the POSA need only have administered the dosage forms disclosed in the ’285 patent. No further manipulation or adjustment by the patient or physician would have been required.

134. Given an oral drug formulation with certain release characteristics for its components, and a method of administering the drug, the dosage form will produce a certain PK/PD profile. This profile, combined, and for each component, is the natural result of basic biological processes: the drug is absorbed into the body, distributed throughout the body, metabolized by the body, and excreted from the body as described earlier. *See* Ex. 1026 at 3 (the primary factors influencing drug absorption and efficacy are physicochemical variables, physiological variables, and dosage form variables). The PK/PD profile recited in claim 1 is

therefore an inherent property of the claimed formulation and its method of administration, resulting from natural processes acting on the dosage form.

135. For example, once the dosage form is constructed, the availability of the included drug will be a function of the anatomy of the gastrointestinal tract, *id.* at 4-11, the physicochemical characteristics of the drug and the way it interacts with and is absorbed by the body, *id.* at 11-23, and physiological factors affecting drug absorption from the dosage form (including the step of dissolution), *id.* at 23-37. The ’208 patent acknowledges that the factors influencing the PK/PD outcomes are the drug dosage form (dosage of each drug and duration of drug administration), and natural biological processes (extent of drug absorption and drug distribution). Ex. 1001 at 1:37-41.

136. In my opinion, the inventors of the ’208 patent did not invent something new. Rather, they administered a dosage form known from the ’285 patent and claimed the PK/PD parameters resulting from the body’s natural metabolic processes acting on the drugs and the dosage form. That the inventors did so using coefficients of variation means that they simply accounted for the intra- and inter-patient variability that is the natural result of variations in inherent biological processes. This is confirmed by the fact that the ’208 patent cites to the earlier ’907 patent, stating that it describes a formulation that is “effective” and

"that produce[s] the desired pharmacodynamic response and pharmacokinetic values." Ex. 1001 at 1:27-41.

* * *

137. In short, the '285 patent disclosed the claimed unit dose formulation of naproxen and immediate-release esomeprazole, and the claimed method of administering it. The PK/PD elements claimed in the '208 patent are inherent characteristics of the formulation disclosed in the '285 patent, and were therefore disclosed with the formulation and the method.

138. Thus, it is my opinion that the '285 patent anticipated claim 1.

(b) Dependent claim 2 was anticipated

139. Claim 2 recites "[t]he method according to claim 1, wherein the mean % time at which intragastric pH remains at about 4.0 or greater for about a 24 hour period is at least about 71%."

140. For the same reasons as detailed above with respect to claim 1, claim 2's slightly heightened PD requirement is also inherent in the '285 patent's formulation.

141. Thus, it is my opinion that claim 2 was anticipated by the '285 patent.

(c) Dependent claims 3 and 4 were anticipated

142. Dependent claim 3 recites: "[t]he method according to claim 1, wherein said unit dose form is administered for a period of at least about 6 days."

143. Dependent claim 4 recites: "[t]he method according to claim 2, wherein said unit dose form is administered for a period of at least about 9 days."

144. In my opinion, the elements of claims 3 and 4 are met by the '285 patent's disclosure that "[t]he present invention" of the '285 patent is "a new method for reducing the risk of gastrointestinal side effects in people taking NSAIDs … particularly during chronic treatment." Ex. 1005 at 3:11-14; *see also* Ex. 1005 at 1:50, 3:2-3. A POSA would understand that "chronic treatment" refers to treatment for at least nine days.

145. In addition, the '285 patent disclosed, in Example 9, a study of the relationship between gastric pH and NSAID-induced gastric ulcers. In that study, the therapeutic treatments were given for five days. Ex. 1005 at 20:38-50. It is my opinion that the five-day period recited in the '285 patent is "at least about 6 days," as recited in claim 3 of the '208 patent. *See above* ¶ 48 (discussing the '208 patent's definition for the term "about," including "variations from the specifically identified time periods that are acceptable within the art").

146. Thus, it is my opinion that the '285 patent anticipated claims 3 and 4.

(d) Dependent claims 5-7 were anticipated

147. Dependent claim 5 recites: "[t]he method according to claim 1, wherein said AM and PM unit dose forms are each a multilayer tablet comprising at least one core and at least a first layer and a second layer, wherein:

> i) said core comprises naproxen, or pharmaceutically acceptable salt thereof;
>
> ii) said first layer is a coating that at least begins to release the naproxen, or pharmaceutically acceptable salt thereof, when the pH of the surrounding medium is about 3.5 or greater; and
>
> iii) said second layer comprises esomeprazole or a pharmaceutically acceptable salt thereof, wherein said esomeprazole or pharmaceutically acceptable salt thereof is released at a pH of from about 0 or greater."

148. Dependent claim 6 recites: "[t]he method according to claim 5, wherein said esomeprazole is released at a pH of from about 0 to about 2."

149. Dependent claim 7 recites: "[t]he method according to claim 5, wherein said multi-layer tablet is substantially free of sodium bicarbonate."

150. The '285 patent disclosed a multilayer tablet having at least a core and first and second layers. Ex. 1005 at Figs. 1, 2. The '285 patent further disclosed that the core is naproxen or a salt thereof, surrounded by an enteric coating, and a second layer of immediate-release esomeprazole, meaning that the esomeprazole "is released at a pH of from about 0 or greater." *Id.* at Figs. 1, 2, Example 6 (16:1-17:47), and claim 1. It is therefore my opinion that the '285 patent disclosed each element of claim 5 of the '208 patent.

151. The '285 patent disclosed a combination dosage form with a second layer of immediate-release esomeprazole, which a POSA would understand to release esomeprazole at a pH of from about 0 to about 2. *Id.* at Figs. 1, 2, and

claim 1. It is therefore my opinion that the '285 patent disclosed the element of claim 6 of the '208 patent.

152. The '285 patent disclosed a combination dosage form including an immediate-release omeprazole layer without additional sodium bicarbonate. Ex. 1005 at 16:1-17:47. It is therefore my opinion that the '285 patent disclosed the element of claim 7 of the '208 patent.

153. Thus, it is my opinion that the '285 patent anticipated claims 5-7.

B. Ground 2: U.S. Patent No. 8,557,285 Rendered Obvious the Claims of the '208 Patent

(a) The pharmacokinetic and pharmacodynamic properties of the claimed unit dose form would have been obvious

154. As described above, the '285 patent anticipates all of the structural and method elements of claim 1 of the '208 patent. The '285 patent disclosed the combined dosage form, having 500 mg of naproxen and 20 mg of immediate-release esomeprazole, which is dosed twice daily. Ex. 1005 at claims 1-4; 5:20-29; Figures 1-2; and Examples 6, 9, and 10. Further, to the extent that the 20 mg esomeprazole dose was not anticipated by the '285 patent, then it would have been obvious: 1) the '285 patent disclosed an esomeprazole-dose range of 5 mg to 100 mg, and stated that a 40 mg dose was "preferred," Ex. 1005 at 8:9-10; 2) 20- and 40-mg esomeprazole doses were approved and on the market in the prior art as Nexium®, Ex. 1043 at, *e.g.*, 1, 22; and 3) a skilled artisan would have known from

Goldstein and Hochberg that 20 mg of omeprazole—a compound known to be somewhat less effective than esomeprazole—was effective when dosed in a tablet having the structure taught by the ’285 patent, Exs. 1011, 1012. To the extent that the 500 mg naproxen dose was not anticipated by the ’285 patent, then it would have been obvious because the 500-mg naproxen dose was approved and on the market in the prior art as EC-Naprosyn®. *See, e.g.*, Ex. 1009 at 2.

155. In addition, even if the PK/PD elements of claim 1 are not inherent in the disclosed and claimed dosage form, as set forth above, then they were obvious over the ’285 patent because they are the product of routine testing. As noted above, one of the most basic skills that a pharmacokineticist will possess is the ability to test quantitatively a drug or dosage form’s behavior in the body, gathering the PK/PD data that describe the drug’s absorption, distribution, metabolism, and excretion. That is all the alleged inventors of the ’208 patent did here: they tested a known combination dosage form, according to known methods, and recorded the results of the drug trial. The analysis required no undue experimentation—PK/PD data were certain to result from the routine testing, and the specific values recited in claim 1 are merely the unsurprising and expected results of the data collection.

156. For example, in the ’208 patent, the trial in Example 1 involved a “randomized, open-label, 4-way cross-over study to evaluate the effect on days 1

and 9 of twice daily oral administration" of the chosen dosage forms. Ex. 1001 at 24:7-9. The study protocol involved randomizing patients, dosing with a study treatment, taking blood samples, analyzing the samples, and monitoring gastric pH. *Id.* at 25:62-26:34. This study design and collection process were well known to a POSA as routine administration and analysis. Further, the '208 patent notes that the formulation disclosed in at least the '907 patent (and, for that matter, the '285 patent, which shares a materially-identical specification) "produce[s] the desired pharmacodynamic response and pharmacokinetic values." Ex. 1001 at 1:30-37. Analyzing the relevant biological data to determine the "desired pharmacodynamic response and pharmacokinetic values" was well within the skill of a POSA, and was routine.

* * *

157. In short, the '285 patent disclosed the claimed unit dose formulation of naproxen and immediate-release esomeprazole, and the claimed method of administering it. The PK/PD elements claimed in the '208 patent are the products of routine testing of the claimed formulation, disclosed in the '285 patent, and would have been easily accessible to a POSA.

158. Thus, it is my opinion that the PK/PD element in claim 1 would have been obvious in view of the '285 patent.

(b) Dependent claim 2 would have been obvious

159. Claim 2 recites "[t]he method according to claim 1, wherein the mean % time at which intragastric pH remains at about 4.0 or greater for about a 24 hour period is at least about 71%."

160. For the same reasons the pharmacodynamic element in claim 1 is inherent in the formulation disclosed in the '285 patent, claim 2's slightly heightened PD requirement is also inherent in the '285 patent's formulation. *See above*.

161. Thus, it is my opinion that the pharmacodynamic element in claim 2 would have been obvious in view of the '285 patent.

(c) Dependent claims 3 and 4 would have been obvious

162. Dependent claim 3 recites: "[t]he method according to claim 1, wherein said unit dose form is administered for a period of at least about 6 days."

163. Dependent claim 4 recites: "[t]he method according to claim 2, wherein said unit dose form is administered for a period of at least about 9 days."

164. In my opinion, as discussed above, the elements of claims 3 and 4 are met by the '285 patent's disclosure that "[t]he present invention" of the '285 patent is "a new method for reducing the risk of gastrointestinal side effects in people taking NSAIDs … particularly during chronic treatment." Ex. 1005 at 3:11-14; *see*

also Ex. 1005 at 1:50, 3:2-3. A POSA would understand that "chronic treatment" refers to treatment for at least nine days.

165. In addition, the '285 patent disclosed, in Example 9, a study of the relationship between gastric pH and NSAID-induced gastric ulcers. In that study, the therapeutic treatments were given for five days. Ex. 1005 at 20:38-50. It is my opinion that the five-day period recited in the '285 patent is "at least about 6 days," as recited in claim 3 of the '208 patent.

166. The '285 patent further disclosed that the antisecretory effect of proton pump inhibitors, like the esomeprazole recited in claim 1, "may be delayed for several hours and may not take full effect for several days." Ex. 1005 at 2:1-2. To support this statement, the '285 patent cites to a 1991 publication by Howden. *Id.* at 2:2 (citing *Clin. Pharmacokinet.* 20:38-49). A POSA would have known that this publication by Howden at least disclosed trials involving seven, eight, nine, and 28 days of dosing with omeprazole. Ex 1027 at 4. It is my opinion that the seven-, eight-, nine-, and 28-day periods disclosed in Howden 1991 are each "at least about 9 days," as recited in claim 4 of the '208 patent.

167. Thus, it is my opinion that the '285 patent disclosed each of the time periods recited in claims 3 and 4, and each of those claims would have been obvious to a POSA.

(d) Dependent claims 5-7 would have been obvious

168. Dependent claim 5 recites: "[t]he method according to claim 1, wherein said AM and PM unit dose forms are each a multilayer tablet comprising at least one core and at least a first layer and a second layer, wherein:

> i) said core comprises naproxen, or pharmaceutically acceptable salt thereof;
>
> ii) said first layer is a coating that at least begins to release the naproxen, or pharmaceutically acceptable salt thereof, when the pH of the surrounding medium is about 3.5 or greater; and
>
> iii) said second layer comprises esomeprazole or a pharmaceutically acceptable salt thereof, wherein said esomeprazole or pharmaceutically acceptable salt thereof is released at a pH of from about 0 or greater."

169. Dependent claim 6 recites: "[t]he method according to claim 5, wherein said esomeprazole is released at a pH of from about 0 to about 2."

170. Dependent claim 7 recites: "[t]he method according to claim 5, wherein said multi-layer tablet is substantially free of sodium bicarbonate."

171. The '285 patent disclosed a multilayer tablet having at least a core and first and second layers. Ex. 1005 at Figs. 1, 2. The '285 patent further disclosed that the core is naproxen or a salt thereof, surrounded by an enteric coating, and a second layer of immediate-release esomeprazole, meaning that the esomeprazole "is released at a pH of from about 0 or greater." *Id.* at Figs. 1, 2, Example 6 (16:1-

17:47), and claim 1. It is therefore my opinion that the ’285 patent disclosed each element of claim 5 of the ’208 patent.

172. The ’285 patent disclosed a combination dosage form with a second layer of immediate-release esomeprazole, which a POSA would understand to release esomeprazole at a pH of from about 0 to about 2. *Id.* at Figs. 1, 2, and claim 1. It is therefore my opinion that the ’285 patent disclosed the element of claim 6 of the ’208 patent.

173. The ’285 patent disclosed a combination dosage form including an immediate-release omeprazole layer without additional sodium bicarbonate. Ex. 1005 at 16:1-17:47. It is therefore my opinion that the ’285 patent disclosed the element of claim 7 of the ’208 patent.

174. Thus, it is my opinion that the ’285 patent disclosed each of the elements recited in claims 5-7, and those claims therefore would have been obvious to a POSA in view of the ’285 patent.

C. Ground 3: U.S. Patent No. 8,557,285, in View of Howden 2005 and the EC-Naprosyn Label, Rendered Obvious the Claims of the ’208 Patent

175. As described above, the ’285 patent disclosed all of the structural and method of treatment elements of the claims of the ’208 patent. To the extent that the PK/PD elements are not found to be inherent in the formulation disclosed in the

'285 patent, then it is my opinion that the PK/PD elements would have been obvious in view of EC-Naprosyn and Howden 2005.

(a) Independent claim 1 would have been obvious

176. Claim 1 of the '208 patent requires that "the AM and PM unit dose forms *target*" claimed PK/PD values for naproxen and esomeprazole. Ex. 1001 at 46:33-47:9 (emphasis added). As discussed above, the term "target" is best understood, in the context of the '208 patent, to mean "with the goal of obtaining." The claim language therefore requires that a POSA must simply have "the goal of obtaining" the claimed PK and PD elements when administering the claimed unit dose form.

177. The prior art provided both the motivation to target the claimed PK and PD values, and a reasonable expectation of success in setting those targets as a goal.

1. The prior art provided motivation to target (i.e., have the goal of obtaining) the PK and PD elements.

178. The POSA would have been motivated to target the claimed PK and PD parameters because therapeutically effective drugs were approved and on the market, and established the relevant PK and PD values. For example, EC-Naprosyn, a delayed-release naproxen product identical to the naproxen formulation claimed in the '208 patent, was approved in 1994, and was marketed and sold years before the priority date. Approval would have signaled to a POSA

that the applicants established to the FDA's satisfaction that delayed-release naproxen was safe and effective for its indications, including treating osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis. Ex. 1009 at 6, 8. The approved label further disclosed PK and PD values associated with the approved drug product. *Id.* at 4. These pharmacokinetic parameter values of EC-Naprosyn were well-characterized and fell within the ranges claimed in the '208 patent. Based on disclosures in the EC-Naprosyn label and other references, a skilled artisan would have been motivated to target the claimed naproxen PK values because they were known to be effective. Further, immediate-release omeprazole was approved, marketed, and sold as Zegerid prior to 2008, and references describing Zegerid disclosed that immediate-release omeprazole produced PK and PD values within the ranges claimed by the '208 patent. *See above* ¶¶ 111-118. Again, knowing that Zegerid was approved as a therapeutically effective immediate-release proton pump inhibitor, just like the esomeprazole disclosed and claimed in the prior art '285 patent, would have motivated a POSA to *target* Zegerid's PK/PD data using the formulation disclosed in the '285 patent and later claimed in the '208 patent. Thus, it would have been obvious to target the PK/PD values of prior art approved drugs known by the POSA to be effective.

179. For naproxen, claim 1 of the '208 patent claims the following PK elements:

> a) for the AM dose of naproxen, the mean C_{max} is 86.2 µg/mL (±20%) and the median T_{max} is 3.0 hours (±20%); and
>
> b) for the PM dose of naproxen, the mean C_{max} is 76.8 µg/mL (±20%) and the median T_{max} is 10 hours (±20%)

Ex. 1001 at 46:50-55.

180. A POSA would have looked naturally to the EC-Naprosyn label for the PK parameters resulting from administering enteric-coated naproxen to a patient. Like the '285 patent, the EC-Naprosyn label disclosed administering a 500 mg delayed-release naproxen formulation twice daily. The EC-Naprosyn label taught that administering EC-Naprosyn 500 mg twice daily yields in a patient a mean C_{max} of 94.9 µg/mL, with a coefficient of variation of ±18% (±17.1 µg/mL), disclosing an overall range of 77.8 µg/mL to 112.0 µg/mL. Ex. 1009 at 4. This overall range for the EC-Naprosyn C_{max} corresponds to the ranges claimed in the '208 patent because claim 1 requires the dose to "target" a mean C_{max} for the AM dose of 86.2 µg/mL ± 20%, which is between 77.8 µg/mL and 112.0 µg/mL. Ex. 1001 at 46:50-51. Similarly, claim 1 targets a mean C_{max} for the PM dose of 76.8 µg/mL ± 20% (±15.4 µg/mL), which yields a range of 61.4 µg/mL to 92.2 µg/mL. Ex. 1001 at 46:53-54. This range of 61.4 µg/mL to 92.2 µg/mL overlaps with the PK range disclosed in the EC-Naprosyn label, which, as noted above, is 77.8 µg/mL to 112.0 µg/mL. Table 1, below, shows the overlap between the naproxen

C_{max} values claimed in the ’208 patent, and those disclosed in the EC-Naprosyn label:

Table 1: Comparison of Naproxen 500 mg C_{max} Data: ’208 Patent Claims *versus* EC-Naprosyn Label

	’208 Patent	**EC-Naprosyn Label**	**Overlap**
AM dose	69.0 - 103.4 µg/mL	77.8 - 112.0 µg/mL	Yes
PM dose	61.4 - 92.2 µg/mL	77.8 - 112.0 µg/mL	Yes

181. A POSA would have known that when the ranges of values around two identified values overlap, the identified values are statistically equivalent. Therefore, the EC-Naprosyn label disclosed the values claimed in the ’208 patent.

182. Notably, the EC-Naprosyn label characterizes twice daily dosing of 500 mg EC-Naprosyn with a single C_{max}, indicating to a POSA that there is no significant difference between the AM and PM doses of the drug product. Ex. 1009 at 4. Similarly, the mean C_{max} reported by Khosravan as resulting from the AM dose of 500 mg naproxen is 93.7 µg/mL ± 7.1 µg/mL, while the mean C_{max} resulting from the PM dose of 500 mg naproxen is 86.9 µg/mL ± 8.9 µg/mL. *Id.* Both of these AM and PM mean C_{max} ranges overlap with the AM and PM mean C_{max} ranges claimed in the ’208 patent. Ex. 1001 at 46:50-54; Ex. 1017 at 9. While there are no statistically significant differences between the AM and PM

mean C_{max} values reported in both Khosravan and claim 1 of the '208 patent, the mean C_{max} in each is slightly reduced for the PM dose versus the AM dose. Ex. 1001 at 46:50-54; Ex. 1017 at 9. Thus, to the extent the claims of the '208 patent reflect a meaningful decrease in the targeted naproxen PK values between the PM and AM measurements, that decrease was disclosed by Khosravan. It, therefore, would have been obvious to a POSA to target the claimed C_{max} ranges for naproxen because EC-Naprosyn is part of the claimed formulation, and the EC-Naprosyn label and Khosravan disclose the claimed C_{max} values. Furthermore, such concentration differences would not be expected to provide any important clinical differences in the therapeutic activity of the drug.

183. It also would have been obvious to a POSA to target the naproxen T_{max} values recited in the claims of the '208 patent. The EC-Naprosyn label disclosed that dosing 500 mg EC-Naprosyn yields a T_{max} of 4 hours ±39%, with a range of 2 to 12 hours. Ex. 1009 at 3-4. The '208 patent, in turn, recites a T_{max} for the AM dose of naproxen of 3.0 hours ±20%, the same as that taught by the EC-Naprosyn label. Ex. 1001 at 46:51-52; Ex. 1009 at 4. The '208 patent further recites a T_{max} for the PM dose of naproxen of 10 hours ±20%, which provides a range of 8 to 12 hours, also falling within the range of 2 to 12 hours disclosed in the EC-Naprosyn label. Ex. 1001 at 46:54-55; Ex. 1009 at 3.

184. As an aside, the claimed T_{max} for the naproxen PM dose appears to be an artifact in the Example 1 data to which the Patent Owner drafted its claims, even though the claimed range falls within the scope of the prior art. The '208 patent does not refer to the T_{max} for the naproxen PM dose as an unexpected result, or otherwise make any comment on the reported and claimed value. Further, the 2014 Vimovo label stated that "[b]ioequivalence between VIMOVO and enteric-coated naproxen, based on both area under the plasma concentration-time curve (AUC) and maximum plasma concentration (C_{max}) of naproxen, has been demonstrated for both the 375 mg and 500 mg doses," and that "peak plasma concentrations of naproxen are reached on average 3 hours following both the morning and the evening dose." Ex. 1030 at 26-27. As described above, this statement reflects the fact that the claimed naproxen PK values (which are associated with a Vimovo-embodied dosage form), fall easily within the disclosures of naproxen PK values in the prior art. Because the '208 patent describes and claims enteric-coated naproxen (*i.e.*, EC-Naprosyn) in its allegedly inventive formulation, there can be nothing new or nonobvious about the T_{max} of the PM dose.

185. Regarding esomeprazole pharmacokinetics, claim 1 of the '208 patent recites:

> ii) a pharmacokinetic (pk) profile for esomeprazole where:
>
> > a) for the AM dose of esomeprazole, the mean area under the plasma concentration-time curve from when the AM dose is administered to 10 hours (±20%) after the AM dose is administered (AUC0-10,am) is 1216 hr*ng/mL (±20%),
> >
> > b) for the PM dose of esomeprazole, the mean area under the plasma concentration-time curve from when the PM dose is administered to 14 hours (±20%) after the PM dose is administered (AUC0-14,pm) is 919 hr*ng/mL (±20%), and
> >
> > c) the total mean area under the plasma concentration-time curve for esomeprazole from when the AM dose is administered to 24 hours (±20%) after the AM dose is administered (AUC0-24) is 2000 hr*ng/mL (±20%)

Ex. 1001 at 46:56-47:5.

186. A POSA would have been motivated to target the claimed PK values for esomeprazole because Zegerid was known to be an effective immediate-release omeprazole product, it was approved and marketed before the priority date of the '208 patent, and it produced the claimed PK values. Howden 2005, for example, reported on Zegerid. Citing the Zegerid label, Howden 2005 disclosed that the mean steady state omeprazole AUC, resulting from administering 20 mg Zegerid, is 1446 hr*ng/mL. Ex. 1006 at 2. The Zegerid label further disclosed that the reported mean AUC figure came with a coefficient of variation of 61%, yielding a mean AUC range of 564 hr*ng/mL to 2328 hr*ng/mL. Ex. 1010 at 5.

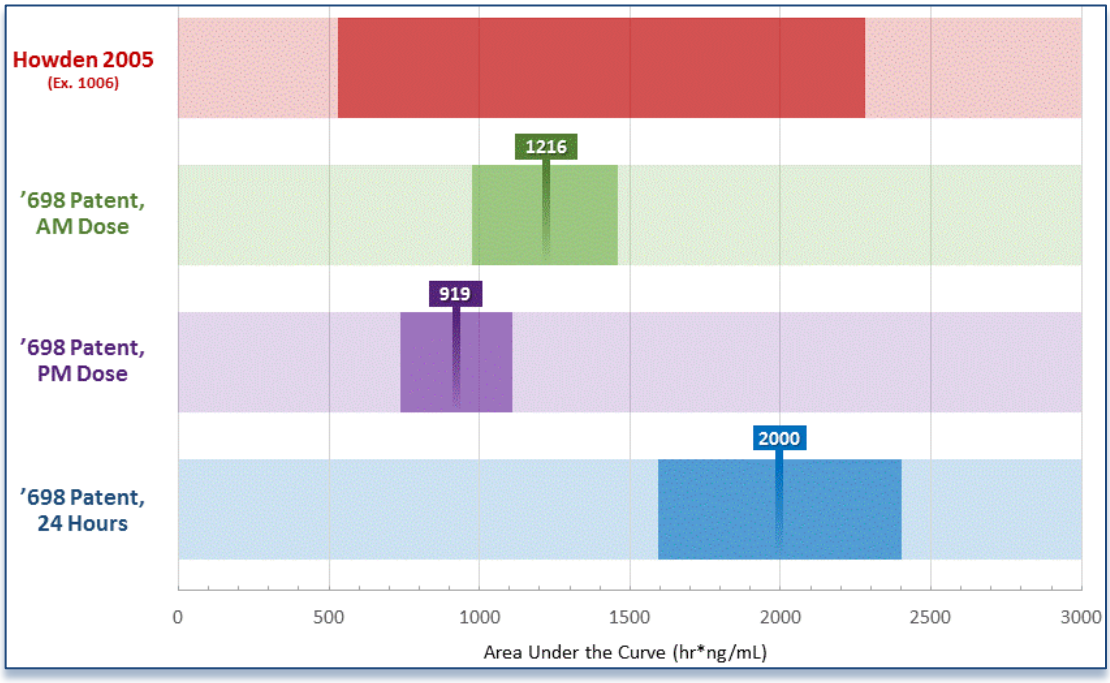

Howden 2005
(Ex. 1006)
'698 Patent,
AM Dose
1216
'698 Patent,
PM Dose
919
'698 Patent,
24 Hours
2000
0
500
1000
1500
2000
2500
3000
Area Under the Curve (hr*ng/mL)

Table 2: Comparison of PPI AUC Data:
'208 Patent Claims *versus* Howden 2005

	'208 Patent	**Howden 2005**	**Overlap**
AM dose	973 - 1459 hr*ng/mL	564 - 2328 hr*ng/mL	Yes
PM dose	735 - 1103 hr*ng/mL	564 - 2328 hr*ng/mL	Yes
24 hours	1600 - 2400 hr*ng/mL	564 - 2328 hr*ng/mL; 1128 - 4656 hr*ng/mL	Yes

188. Howden 2005, therefore, disclosed that the esomeprazole PK values claimed in the '208 patent are values at which esomeprazole would be effective, based on the known values from the prior art. Thus, Howden 2005 would have motivated a POSA to *target* the claimed PK values.

189. Any differences asserted between Zegerid and the formulation claimed in the '208 patent are irrelevant to this analysis. For example, the Patent Owners may argue that because Zegerid is omeprazole, information regarding its PK behavior is inapplicable to the claims, which recite esomeprazole. But a POSA would expect any effective AUC for omeprazole to also be effective for esomeprazole because esomeprazole is a component of the omeprazole racemate.

190. As discussed above, as of the '208 patent's priority date, a POSA would have known that omeprazole is a racemic mixture of R- and S-enantiomers. A POSA would also have known that omeprazole's S-enantiomer, referred to as

esomeprazole, achieves an effective AUC upon proper dosing, which is increased compared to a same dose of omeprazole. *See* Ex. 1007 at Abstract (S-omeprazole is referred to as the (-)-enantiomer of omeprazole). Thus, a POSA would have arrived at an effective dose of esomeprazole simply by targeting the AUC associated with an effective dose of omeprazole. By targeting omeprazole's AUC, a POSA would have been assured of getting an effective AUC for esomeprazole because the prior art showed that esomeprazole was more effective (*i.e.*, yielded a greater AUC) than omeprazole at the same dose. *Id.* (increased plasma AUC for a dose of esomeprazole compared to the same dose of racemic omeprazole).

191. The Patent Owners may also argue that the prior art is inapplicable because Zegerid includes sodium bicarbonate, while the claimed formulation does not (or is substantially free of it). Notably, this argument is relevant only to claim 7 of the '208 patent, which is the only claim expressly excluding sodium bicarbonate from the claimed formulation. But even if the other claims could be read the same way, that Zegerid includes sodium bicarbonate is irrelevant. A POSA would have understood from Howden 2005 that Zegerid disclosed a mean AUC for an effective dose of omeprazole. Ex. 1006 at 2. But a POSA would have known that Zegerid's bicarbonate only enhances omeprazole's stability in the stomach, and does not change either omeprazole's mechanism of action or its effective plasma concentrations. *Id.* at 3-4. A POSA would also have known from

the prior art that achieving an effective AUC, regardless of the mechanism, was the overarching goal in finding an effective therapy. *See* Ex. 1007 (disclosing the use of esomeprazole, rather than omeprazole, to attain an effective AUC for a proton pump inhibitor). Zegerid's disclosed mean AUC was therefore a reliable target for a POSA, who would know that drug effectiveness would follow from achieving the disclosed mean AUC.

192. Finally, the Patent Owners may argue that the teachings of Zegerid are inapplicable because of its once-daily administration, versus the '208 patent's claimed twice-daily administration. Again, this difference is immaterial to the conclusion of obviousness because a POSA would not expect any interaction between the AM and PM doses. A POSA would know that at steady state, each dose of omeprazole (or esomeprazole) has approximately the same PK effect as the last. *See* above ¶¶ 35-39. A POSA would have known to use the AUC resulting from once-daily, steady-state dosing of Zegerid as a target for both the AM and PM doses of the combined formulation recited in the claims, and known from the '285 patent. Further, a POSA would have known that omeprazole and esomeprazole exhibit nonlinear pharmacokinetics, meaning that increasing the dose of active ingredient increases AUC disproportionately. Ex. 1028 at 6; Ex. 1029 at 12-13. Therefore, a POSA could have predicted, easily, the AUC of twice-

daily dosing, from knowledge of the AUC produced by once-daily dosing. Ex. 1028 at 6; Ex. 1029 at 12-13.

193. Accordingly, it is my opinion that the naproxen and esomeprazole values recited as targets in claim 1 of the ’208 patent would have been obvious to a person of ordinary skill in the art.

194. Finally, claim 1 of the ’208 patent recites a pharmacodynamic element resulting from dosing with esomeprazole: “the AM and PM unit dose forms further target a mean % time at which intragastric pH remains at about 4.0 or greater for about a 24 hour period after reaching steady state that is at least about 60%.”

195. Howden 2005 disclosed the pharmacodynamic element of claim 1.

196. Howden 2005 reported the results of the Goldlust study, in which patients received seven consecutive morning doses of Zegerid, followed by morning and bedtime doses of Zegerid on the eighth day. Ex. 1006 at 4. Howden 2005 reported that “[t]he addition of the bedtime dose maintained intragastric pH above 4 for significantly longer than the morning dose alone, over both the nocturnal and entire 24-h period (Figure 3).” *Id.* (citing Goldlust (Ex. 1042)). Figure 3 shows that intragastric pH at steady state remained above 4.0 for about 80% of the 24-hour period. *Id.; see also* Ex. 1015 at 7, Fig. 4 (disclosing intragastric pH>4.0 for more than 60% of a 24-hour period for single-daily doses

of omeprazole in 20, 30, and 60 mg strengths). This result satisfies the "at least about 60%" requirement of claim 1.

197. Howden 2005 further disclosed the results of a second study, in which patients received 40 mg Zegerid once daily—the same total daily dose recited in the claimed method. Howden 2005 reported that the 40 mg dose of Zegerid "kept intragastric pH above 4 for 77% (18.6 h) of the 24-h recording period." Ex. 1006 at 3. Thus, Howden 2005 provides a target pharmacodynamic response for an immediate-release PPI because a POSA would have known, when developing another immediate-release PPI formulation, that Zegerid was an effective drug.

198. It is therefore my opinion that Howden 2005 taught the pharmacodynamic element of claim 1 of the '208 patent.

2. The prior art provided a reasonable expectation of success in setting the PK and PD elements as targets.

199. A POSA would have had a reasonable expectation of success in targeting the claimed PK and PD values, based on the teachings of the prior art.

200. First, delayed-release (*i.e.*, enteric-coated) naproxen was approved and used before the '208 patent's priority date, including at a dose of 500 mg, and its PK at therapeutically effective doses were well-characterized. *See generally* Ex. 1009. In addition to naproxen having been on the market for years, many studies determined and reported the PK values resulting from naproxen's use. *See, e.g.*, Ex. 1019 at 3-6 Table 1; Ex. 1018. Prior art studies reported in these

references consistently found PK values corresponding to those recited in claim 1 of the '208 patent. *See, e.g.*, Ex. 1018 at 3 (Abstract), 7-8. A POSA would therefore have been motivated to target, and had a reasonable expectation of success in targeting, the naproxen PK values recited in claim 1.

201. A POSA would also have had a reasonable expectation of success in targeting the claimed esomeprazole PK and PD values. As discussed, the claim term "target" means "with the goal of obtaining," so the claims do not require actually achieving the claimed PK values. Rather, a reasonable expectation of success is established if the skilled artisan reasonably expects to succeed in setting the claimed PK and PD values as a goal. In that context, it would have been routine for a POSA to target the PK/PD parameters yielded by administering known therapeutically effective drugs. Here, a POSA would have noted that both Howden 2005 and the Zegerid label disclose PK and/or PD data for an effective immediate-release PPI, and would have set these PK and PD values as a goal to be obtained. Further, esomeprazole in the 20- and 40-mg dosage amounts was already in the prior art as an effective proton pump inhibitor, marketed by AstraZeneca as Nexium®, and omeprazole was being marketed in 10-, 20-, and 40-mg dosage amounts as Prilosec®. Ex. 1043 at 1, 22; Ex. 1044 at 1. A POSA would therefore have been motivated to target the claimed esomeprazole PK and PD values with a reasonable expectation of success.

* * *

202. In short, as discussed above, the ’285 patent disclosed the claimed unit dose formulation of naproxen and immediate-release esomeprazole, and the claimed method of administering it. To the extent the PK/PD elements claimed in the ’208 patent were not inherent in the formulation and method, or found not to be the product of routine testing, then the targeted PK/PD elements would have been obvious to a POSA in view of the prior art. Howden 2005 disclosed targets for the PK and PD elements attributable to omeprazole (and, thus, esomeprazole), and the EC-Naprosyn label disclosed targets for the PK elements attributable to naproxen. A POSA would have been motivated to target these values, and would have had a reasonable expectation of success in setting those targets, as discussed above.

203. Thus, it is my opinion that claim 1 of the ’208 patent would have been obvious over the ’285 patent, in view of Howden 2005 and the EC-Naprosyn label.

(b) Dependent claim 2 would have been obvious

204. Claim 2 recites “[t]he method according to claim 1, wherein the mean % time at which intragastric pH remains at about 4.0 or greater for about a 24 hour period is at least about 71%.” Ex. 1001 at 47:10-12.

205. As discussed in detail above, Howden 2005 disclosed that administering 20 mg Zegerid for seven days, with an additional dose given on the eighth day, would yield a mean percent time at which intragastric pH remains at

4.0 or greater in a 24-hour period, after reaching steady state, of about 80%. Ex. 1006 at 4. Howden 2005 also taught that administering 40 mg Zegerid once daily yields a figure of 77%. *Id.* at 3. Both of these pharmacodynamic data points are comfortably above the claimed value of "at least about 71%." *See also* Ex. 1015 at 7, Fig. 4 (disclosing intragastric pH>4.0 for more than 71% of a 24-hour period for single daily doses of omeprazole in 30 and 60 mg strengths). Therefore, claim 2 would have been obvious to a POSA.

(c) Dependent claims 3-4 would have been obvious

206. Dependent claim 3 recites: "[t]he method according to claim 1, wherein said unit dose form is administered for a period of at least about 6 days."

207. Dependent claim 4 recites: "[t]he method according to claim 2, wherein said unit dose form is administered for a period of at least about 9 days."

208. As discussed above, the elements of claims 3 and 4 are met by the '285 patent's disclosure that "[t]he present invention" of the '285 patent is "a new method for reducing the risk of gastrointestinal side effects in people taking NSAIDs … particularly during chronic treatment." Ex. 1005 at 3:11-14; *see also* Ex. 1005 at 1:50, 3:2-3. A POSA would understand that chronic treatment refers to treatment for at least nine days.

209. In addition, as discussed above, the '285 patent disclosed, in Example 9, a study of the relationship between gastric pH and NSAID-induced gastric

ulcers. In that study, the therapeutic treatments were given for five days. Ex. 1005 at 20:38-50. It is my opinion that the five-day period recited in the '285 patent is "at least about 6 days," as recited in claim 3 of the '208 patent.

210. The '285 patent further disclosed that the antisecretory effect of proton pump inhibitors, like the esomeprazole recited in claim 1, "may be delayed for several hours and may not take full effect for several days." Ex. 1005 at 2:1-2. To support this statement, the '285 patent cites to Howden 1991. *Id.* at 2:2 (Clin. Pharmacokinet. 20:38-49). A POSA would have known that Howden 1991, discussed above, at least disclosed that the "several days" of dosing involved trials with seven, eight, nine, and 28 days of dosing with omeprazole. Ex 1027 at 4. It is my opinion that the seven-, eight-, nine-, and 28-day periods disclosed in Howden 1991 are each "at least about 9 days," as recited in claim 4 of the '208 patent, and (to the extent there is doubt) "at least about 6 days," as recited in claim 3.

211. Thus, it is my opinion that each of the time periods recited in claims 3 and 4 is disclosed by the '285 patent, and each of claims 3 and 4 would have been obvious to a POSA.

(d) Dependent claims 5-7 would have been obvious

212. Dependent claim 5 recites: "[t]he method according to claim 1, wherein said AM and PM unit dose forms are each a multilayer tablet comprising at least one core and at least a first layer and a second layer, wherein:

> i) said core comprises naproxen, or pharmaceutically acceptable salt thereof;
>
> ii) said first layer is a coating that at least begins to release the naproxen, or pharmaceutically acceptable salt thereof, when the pH of the surrounding medium is about 3.5 or greater; and
>
> iii) said second layer comprises esomeprazole or a pharmaceutically acceptable salt thereof, wherein said esomeprazole or pharmaceutically acceptable salt thereof is released at a pH of from about 0 or greater."

213. Dependent claim 6 recites: "[t]he method according to claim 5, wherein said esomeprazole is released at a pH of from about 0 to about 2."

214. Dependent claim 7 recites: "[t]he method according to claim 5, wherein said multi-layer tablet is substantially free of sodium bicarbonate."

215. As discussed earlier, the '285 patent disclosed a multilayer tablet having at least a core and first and second layers. Ex. 1005 at Figs. 1, 2. The '285 patent further disclosed that the core is naproxen or a salt thereof, surrounded by an enteric coating, and a second layer of immediate-release esomeprazole, meaning that the esomeprazole "is released at a pH of from about 0 or greater." *Id.* at Figs. 1, 2, Example 6 (16:1-17:47), and claim 1. It is therefore my opinion that the '285 patent disclosed each element of claim 5 of the '208 patent.

216. The '285 patent disclosed a combination dosage form with a second layer of immediate-release esomeprazole, which a POSA would understand to release esomeprazole at a pH of from about 0 to about 2. *Id.* at Figs. 1, 2, and

claim 1. It is therefore my opinion that the '285 patent disclosed the element of claim 6 of the '208 patent.

217. The '285 patent disclosed a combination dosage form including an immediate-release omeprazole layer without additional sodium bicarbonate. Ex. 1005 at 16:1-17:47. It is therefore my opinion that the '285 patent disclosed the element of claim 7 of the '208 patent.

218. Thus, it is my opinion that the '285 patent disclosed each of the elements recited in claims 5-7, and those claims therefore would have been obvious to a POSA.

D. There Are No Unexpected Results Arising From The Claimed Method.

219. I understand that for an invention to demonstrate unexpected results, the claimed invention must exhibit some superior property or advantage that the person of ordinary skill in the art would have found surprising or unexpected. The results must be shown to be unexpected compared with the closest prior art and be a difference in kind and not merely one of degree.

220. In my opinion, a POSA would have expected to target the claimed PK/PD values.

221. The methods claimed in the '208 patent recite administering a unit dose form comprising 500 mg naproxen and 20 mg immediate-release

esomeprazole to "target" particular PK and PD values for naproxen and esomeprazole.

222. As discussed above, prior art such as the '285 patent, the '907 patent, Goldstein, Hochberg, and Hassan-Alin disclosed, described, and/or claimed a combination unit dose form comprising naproxen and an immediate-release proton pump inhibitor, including esomeprazole. *See* ¶¶ 80-102. The prior art also disclosed methods of administering the claimed unit dose form.

223. Further, the prior art, including Khosravan, EC-Naprosyn label, Jung, Davies, Howden 2005, and Zegerid label, disclosed the PK/PD values claimed in the '208 patent as being targeted by administering the claimed unit dose form. *See* ¶¶ 104-118.

224. From these references, a person of ordinary skill in the art would have known that prior art dosage forms were effective and yielded the PK/PD values recited in the claims of the '208 patent. A person of ordinary skill would also have known how to administer the formulation recited in the claims of the '208 patent, which was taught in the '285 and '907 patents. Thus, the PK/PD values targeted by administering the claimed formulation are not unexpected results because both the administered formulation and the results following from its dosing were disclosed and/or claimed in the prior art. In addition, the results would not have been unexpected because, as described earlier, a POSA would have already

possessed the claimed PK/PD values because the POSA knew the claimed formulation and method of administering the formulation, and the claimed PK/PD data are the natural result of following those two disclosures.

225. I am not aware of any evidence either suggesting or demonstrating that the targeted values claimed in the ’208 patent were unexpected.

226. I understand that the applicants for the ’698 patent, which is the “parent” of the ’208 patent, and from which the ’208 patent is derived, attempted to establish, during the ’698 patent’s prosecution at the Patent Office, that the method claimed in the ’698 patent (which targets substantively the same PK/PD values as does the method claimed in the ’208 patent) yielded unexpected results. I have reviewed relevant portions of the ’698 patent’s prosecution history, and compared the claims of the ’698 and ’208 patents, and I conclude that the applicants did not establish unexpected results that would weigh in favor of nonobviousness of the methods claimed in the ’208 patent.

227. During prosecution of the application that led to the ’698 patent, the applicants contended that the claimed invention was superior to the combination of naproxen and famotidine (an H_2-receptor antagonist, which is a different drug class than proton pump inhibitors, like esomeprazole). The applicants argued that the presently claimed invention was superior to the naproxen/famotidine combination disclosed in the ’907 patent because the amount of acid suppression over a 24-hour

period experienced with the claimed invention was 71.35% versus 49% with the prior art combination. Ex. 1013 (Applicant Response from January 30, 2013) at 7. This is not a surprising or unexpected result. At the time of the invention, H_2-receptor blockers (like famotidine) and PPIs (like esomeprazole) were known to suppress gastric acid secretion through different mechanisms. Ex. 1014 at 5-8. A POSA would also have known that PPIs provide greater acid suppression over a 24-hour period than H_2-receptor blockers because the more potent PPIs are longer-acting, and H_2-receptor blockers are shorter-acting, and PPIs were therefore thought to be more protective during chronic NSAID administration. Ex. 1004 at 1:41-58; *see also* Ex. 1014 at 5, 6 ("PPIs are without question the most potent inhibitors of gastric acid secretion available."), 8-10; *see generally* Ex. 1015 (discussing superiority of PPIs over H_2-receptor blockers in acid suppression).

228. But even if this were not true, the patent applicants still would not have established the unexpected superiority of the claimed invention because the combination of naproxen and famotidine is not the closest prior art to the claimed formulation. As described above, the '285 patent claimed a combination dosage form of esomeprazole and naproxen and disclosed a method of administering the dosage form. In addition, the '907 patent claims dosage forms that encompass the unit dose form of esomeprazole and naproxen recited in the claims of the '208 patent, and claims methods of administering the combined dosage form. Plainly,

the results of the claimed method of administering a formulation, set merely in terms of the results themselves, cannot be unexpected when the method was known in the prior art.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

DATED: 11.30.2017 By: Michael Mayersohn

Michael Mayersohn, Ph.D.

ATTACHMENT A

CURRICULUM VITAE

Michael Mayersohn, Ph.D.

PERSONAL INFORMATION

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EDUCATION

College	Date	Degree	Major
College of Pharmaceutical Sciences Columbia University, New York	1961-1966	B.S.	Pharmacy
College of Pharmaceutical Sciences Columbia University, New York	1966-1967	None	Pharmaceutics
School of Pharmacy, State University of New York at Buffalo Dissertation Advisor: Milo Gibaldi, Ph.D.	1967-1970	Ph.D.	Pharmaceutics

ACADEMIC AND PROFESSIONAL APPOINTMENTS

Date	Appointment	Place
9/64 - 6/66	Research Assistant	Department of Pharmaceutics College of Pharmaceutical Sciences Columbia University, New York, NY.
9/66 - 6/67	Harry Taub and Plaut Fellow in Pharmacy	Department of Pharmaceutics, College of Pharmaceutical Sciences, Columbia University, New York, NY.
6/67 - 9/67	Research Trainee	Pharmaceutical Research and Development Division, CIBA Pharmaceutical Co., Summit, New Jersey
9/67 - 10/70	Fellow of the American Foundation for Pharmaceutical Education.	Department of Pharmaceutics, School of Pharmacy, State University of New York at Buffalo, NY.
10/70 - 6/75	Assistant Professor	Faculty of Pharmacy, University of Toronto, Toronto, Ontario, Canada.
6/75 - 6/76	Associate Professor	Faculty of Pharmacy, University of Toronto, Toronto, Ontario, Canada.
6/76 - 6/83	Associate Professor	College of Pharmacy, The University of Arizona, Tucson, Arizona.
6/83 -6/2016	Professor	College of Pharmacy, The University

		of Arizona, Tucson Arizona.
6/2016-Present	Professor Emeritus	College of Pharmacy, The University of Arizona, Tucson, Arizona
7/1 - 12/30/86	Visiting Professor	Department of Pharmaceutical Research, F. Hoffmann-La Roche and Co., Basel, Switzerland.
8/93 -6/2016	Member	Interdisciplinary Graduate Program in Pharmacology and Toxicology, The University of Arizona
8/93- 6/2016	Member	Center for Toxicology, The University of Arizona
8/93 – 6/2016	Member	Southwest Environmental Health Sciences Center, The University of Arizona
7/8 - 7/19/96	Visiting Professor	Sandoz Pharmaceutical Corporation, East Hanover, New Jersey
9/2000-2003	Member	Arizona Center for Phytomedicine Research of Arizona, Tucson Arizona.

MAJOR RESEARCH FIELD

Research training and experience have been in the general area of pharmaceutical sciences with a specialty in pharmaceutics, biopharmaceutics and pharmacokinetics. These specialty areas involve: an examination of the relationship between the physical chemical characteristics of a drug and its dosage form and the fate and performance of that drug in the body; the use and development of analytical procedures to quantitate drugs and metabolites in biological fluids and from these data the development of rigorous mathematical models to quantitate the kinetic processes of drug absorption distribution, elimination and response; the design of rational drug dosing regimens based upon analytical, mathematical and clinical data. Research projects have involved investigations in each of these areas.

ACADEMIC AWARDS AND HONORS

Award	Date	Place
Rho Chi Award	1962	College of Pharmaceutical Sciences Columbia University
Henry Pfeiffer Scholarship	1962	College of Pharmaceutical Sciences Columbia University
Block Memorial Scholarship	1963	College of Pharmaceutical Sciences Columbia University
American Foundation for Pharma-ceutical Education Scholarship	1964	College of Pharmaceutical Sciences Columbia University
Harry Taub Fellowship	1966	College of Pharmaceutical Sciences Columbia University
Plaut Memorial Fellowship	1966	College of Pharmaceutical Sciences Columbia University
Rho Chi Pharmaceutical Honor Society	1966	College of Pharmaceutical Sciences Columbia University

Fellow of the American Foundation for Pharmaceutical Education	1968-1970	School of Pharmacy, State University of New York at Buffalo.
Medical Research Council of Canada, Visiting Professor	1971-1975	Faculty of Pharmacy, University of Alberta Faculty of Pharmacy, University of British Columbia College of Pharmacy, Dalhousie University
Basic Science Educator of the Year	1984	College of Pharmacy, University of Arizona
Fellow, Academy of Pharmaceutical Sciences	1985	American Pharmaceutical Association
Fellow, American Association of Pharmaceutical Scientists	1986	American Association of Pharmaceutical Scientists
Basic Science Educator of the Year	1989	College of Pharmacy, University of Arizona
Basic Science Educator of the Year	1996	College of Pharmacy, University of Arizona
Dean's Teaching Scholar	1997-1998	University of Arizona
Basic Science Educator of the Year	1998	College of Pharmacy, University of Arizona
Graduate Advisor of the Year	2000	Graduate and Professional Student Council, University
Basic Science Educator of the Year	2002	College of Pharmacy, University of Arizona of Arizona
Graduate Advisor of the Year	2002	Graduate and Professional Student Council, University of Arizona
Mortar Board Citation Award	2002	Mortar Board National Senior Honor Society, University of Arizona
Basic Science Educator of the Year	2005	College of Pharmacy, University of Arizona
Fellow, American College of Clinical Pharmacology	2005	American College of Clinical Pharmacology
Extraordinary Faculty Award	2008	The University of Arizona Alumni Association
Basic Science Educator of the Year	2009	College of Pharmacy, University of Arizona
Honorary Alumnus Award	2011	The University of Arizona, Alumni Association

PUBLICATIONS

Book Chapters

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3. M. Mayersohn, "Basic Concepts in Drug Disposition: Fundamental Principles of Pharmacokinetics," chapter 1 (pp. 3-28) in Drug Therapy for the Elderly, K.A. Conrad and R. Bressler, eds., C.V. Mosby, St. Louis, 1982.

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6. M. Mayersohn, "Principles of Drug Absorption," Chapter 2 (pp. 23-89), in Modern Pharmaceutics, 2nd ed., G.S. Banker and C.T. Rhodes (eds.), Marcel Dekker, New York, 1989.

7. M. Mayersohn, "Special Pharmacokinetic Considerations in Elderly," Chapter 9 (pp. 9-1-9-43) in Applied Pharmacokinetics: Principles of Therapeutic Drug Monitoring, 3rd ed., W.E. Evans, J.J. Schentag, and W.J. Jusko (eds.), Applied Therapeutics, Vancouver, Washington, 1992.

8. M. Mayersohn, "Principles of Drug Absorption," Chapter 2 (pp. 21-73), in Modern Pharmaceutics, 3rd ed., G.S. Banker and C.T. Rhodes (eds.), Marcel Dekker, New York, 1995.

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10. M. Mayersohn, "Principles of Drug Absorption," Chapter 2, in Modern Pharmaceutics, 4th ed.,G.S. Banker and C.T. Rhodes (eds.), Marcel Dekker, New York, 2002.

11. M. Mayersohn, “Principles and Applications of Pharmacokinetics”, Chapter 79 in: Medical Toxicology, 3rd ed., RC Dart (ed.), Lippincott, Williams and Wilkins, New York, 2004, pp. 282-337.

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Book Chapters: Symposia

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3. J.R. Woodworth, S.M. Owens and M. Mayersohn, "Phencyclidine Disposition Kinetics In Dogs: Preliminary Findings," in "Phencyclidine and Related Arylcyclohexylamines - Present and Future

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1. A.H. Goldberg, M. Gibaldi, J.L. Kanig and M. Mayersohn, "Increasing Dissolution Rates and Gastrointestinal Absorption of drugs *via* Solid Solutions and Eutectic Mixtures-IV," J. Pharm. Sci., 55, 581-583 (1966).

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3. M. Mayersohn, S. Feldman and M. Gibaldi, "Bile Salt Enhancement of Riboflavin and Flavin Mononucleotide Absorption in Man," J. Nutr., 98, 288-296 (1969).

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39. W. D. Hager, H. J. Pieniaszek, Jr., D. Perrier, M. Mayersohn and V. Goldberger, "Assessment of Beta Blockade with Propranolol," Clin. Pharmacol. Ther., 30, 283-290 (1981).

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41. S. Goldman, M. Olajos, H. Pieniaszek, D. Perrier, M. Mayersohn and E. Morkin,"Beta-Adrenergic Blockade with Propranolol in Conscious Euthyroid and Thyrotoxic Calves: Dosage Requirements and Effects on Heart Rate and Left Ventricular Performance," J. Pharmacol. Exp. Therap., 219, 394-399 (1981).

42. W.D. Hager, M. Mayersohn and P.E. Graves, "Digoxin Bioavailability During Quinidine Administration," Clin. Pharmacol. Ther., 30, 594-599 (1981).

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Professional/Educational Publications

1. M. Mayersohn and M. Gibaldi, "Mathematical Methods in Pharmacokinetics. I. Use of the Laplace Transform for Solving Differential Rate Equations," Amer. J. Pharm. Ed., 34, 608-614 (1970).

2. M. Mayersohn and M. Gibaldi, "Mathematical Methods in Pharmacokinetics. II. Solution of the Two Compartment Open Model," Ibid, 35, 19-28 (1971).

3. M. Mayersohn, "Physiological Factors Influencing the Gastrointestinal Absorption Efficiency of Oral Dosage Forms," Canad. Pharm.J., 104, 164-169 (1971).

4. M. Mayersohn, "Fundamental Principles in Efficient Drug Therapy. I. An Introduction to the Series and Some Basic Concepts," Bulletin of the Ontario College of Pharmacy, 20, 58-71 (1971).

5. M. Mayersohn, "Fundamental Principles in Efficient Drug Therapy. II. Pharmacokinetic Principles and Useful Analogies," Bulletin of the Ontario College of Pharmacy, 20, 124-130 (1971).

6. M. Mayersohn, "Dosage Regimen Calculation in Patients with Renal Insufficiency," Canad. J.Hosp.Pharm.,24, 215-221 (1971).

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8. M. Mayersohn, "Fundamental Principles in Efficient Drug Therapy. IV. Drug Distribution - Part II," Bulletin of the Ontario College of Pharmacy, 21, 53-61 (1972).

9. M. Mayersohn, "Drug Interactions - Some Therapeutically Useful Applications," Canad. J.Hosp. Pharm., 25, 105-107 (1972).

10. M. Mayersohn, "Formulation Aspects as they Affect Drug Availability," Bulletin of the Ontario College of Pharmacy, 21, 97-116 (1972).

11. M. Mayersohn, M.S.S. Chow, H.B. Kostenbauder and M. Rowland, "Aspirin Bioavailability," Monograph for the Bioavailability of Drugs Project of the American Pharmaceutical Association, J. Amer. Pharm. Assn., NS17, 107-112 (1977).

12. M. Mayersohn, "Clinical Pharmacokinetics: Applying Basic Principles to Therapy," Drug Therapy, 10, 79-83 (1980).

13. M. Mayersohn, "Designing a Dosage Regimen," Drug Therapy, 10, 99-102 (1980).

14. M. Mayersohn, "Drug Disposition in the Elderly," unit 2, module V In "Pharmacy Practice for the Geriatric Patient," B. Ameer, et al (eds.). Health Sciences Consortium, Carrboro, North Carolina, 1985.

15. M. Mayersohn and S. Tannenbaum, “On Reclaiming Data from the Literature: Literature Data “R and R” (Recovery and Reanalysis)” with a commentary by Dr. Gerhard Levy, “Using Other People’s Data in Publications”, Amer. J. Pharm. Ed., 62, 363-370 (1998).

PRESENTATIONS

Invited

1. "Drug Therapy in Patients with Renal Insufficiency," presented to the Medical Staff, Toronto General Hospital, Toronto, Ontario, April 19, 1971.

2. "Drug Interactions - Some Therapeutically Useful Applications," presented at the mid-year clinical meeting of the Canadian Society of Hospital Pharmacists," Toronto, Ontario, February 15, 1972.

3. "Formulation Aspects as they Affect Drug Availability," presented at the Ontario College of Pharmacy Seminar Series, Toronto, Ontario, May 7, 1972.

4. "Some Considerations in Evaluating Drug Products," presented at the Ontario Hospital Association Meeting, Toronto, Ontario, October 25, 1972.

5. "Pharmacokinetics and Its Clinical Implications," presented to the Drug Research Laboratories of the Health Protection Branch and the Department of Pharmacology, University of Ottawa, Ottawa, Ontario, October 27, 1972.

6. "Aspects of Drug Absorption," Faculty of Pharmacy, University of Alberta, Edmonton, Alberta, April 23, 1973.

7. "Psychotropics - Pharmacokinetic Consideration in Therapy" and a workshop on "Practical Kinetic Considerations of Psychoactive Agents," presented at the 5th Annual National Conference of Mental Health Pharmacists, Omaha, Nebraska, August 7-10, 1977.

8. "Pharmacokinetics in Clinical Problem Solving," Clinical Pharmacology Grand Rounds presented at the Veterans Administration Hospital (December 3, 1977) and at the Arizona Health Sciences Center (December 10, 1977).

9. "Drug Interactions with Digoxin," Clinical Pharmacology Rounds, presented at the Arizona Health Sciences Center, September 15, 1978, Tucson, Arizona.

10. "Literature Review in Pharmacokinetic Studies," Clinical Pharmacology Rounds, presented at the Arizona Health Sciences Center, October 31, 1978, Tucson, Arizona.

11. "Clinical Pharmacokinetics - General Principles and Clinical Applications," Clinical Pharmacology Grand Rounds, presented at the Arizona Health Sciences Center (November 1, 1978) and at the Veterans Administration Hospital (November 8, 1978), Tucson, Arizona.

12. "Pharmacokinetics of Procainamide," presented at the Cardiology Research Conference, College of Medicine, University of Arizona, Tucson, Arizona, November 27, 1978.

13. "Propranolol-Quinidine Interaction," Clinical Pharmacology Rounds, presented at the Arizona Health Sciences Center, March 27, 1979, Tucson, Arizona.

14. "Current Research Projects in Pharmacokinetics," Toxicology Seminar Series, to the Toxicology Program, University of Arizona, February 12, 1980, Tucson, Arizona.

15. "Current Research Projects in Pharmacokinetics," Toxicology Seminar Series, to the Toxicology Program, University of Arizona, February 12, 1980, Tucson, Arizona.

16. "Influence of Protein Binding on Drug Disposition," presented at the 2nd Annual Meeting of the American College of Clinical Pharmacy, Scottsdale, Arizona, June 26-28, 1981.

17. "The Xylose Test in the Elderly and Thiopental Disposition in the Elderly," Clinical Pharmacology Rounds, Arizona Health Sciences Center, Tucson, Arizona, February 8, 1982.

18. "Phencyclidine (PCP) Disposition Kinetics in Dogs," presented at the Joint French-U.S.A. Seminar on the Chemistry, Pharmacology, Present and Future of the Therapeutic Applications and Drug Abuse Aspects of Arylcyclohexylamines," Montpellier, France, September 20-24, 1982.

19. "Phencyclidine Disposition in Animals," presented at the Conference on the Pharmacokinetics of Psychoactive Drugs, Sponsored by the National Institute on Drug Abuse, Bethesda, Maryland, February 9-11, 1983.

20. "Rational Approaches to the Treatment of Drug Toxicity: Some Recent Considerations and the Application of Pharmacokinetic Principles," presented at the Conference on the Pharmacokinetics of Psychoactive Drugs, Sponsored by the National Institute on Drug Abuse, Bethesda, Maryland, February 9-11, 1983.

21. "Rational Approaches to the Treatment of Drug Toxicity: Some Recent Considerations and the Application of Pharmacokinetic Principles," presented to the Divisions of Preclinical and Clinical Research, National Institute on Drug Abuse, Bethesda, Maryland, February 24, 1983.

22. "Alteration of Drug Kinetics and Drug Absorption in the Elderly," presented at the 8th Annual Meeting, Associates of Clinical Pharmacology, Tucson, Arizona, February 29-March 2, 1984.

23. "Modulation of Phencyclidine (PCP) Pharmacokinetics with PCP-Specific Fab Fragments," presented at the National Institute on Drug Abuse Technical Review Meeting on Phencyclidine, Rockville, Maryland, May 7-9, 1985. (presented by S.M. Owens).

24. "Drug Absorption and Disposition in Aged Humans: General Considerations," presented at the 14th Annual Symposium of the Western Division, American Geriatrics Society, Sun City, Arizona, October 18, 1985.

25. Presentations made to the Pharmaceutical Research Department, F. Hoffmann- LaRoche Basel, Switzerland, July 1-December 30, 1986.
    "Comparison of Model-Dependent and Model-Independent Analysis in Pharmacokinetics"
    "The Influence of Plasma Protein Binding on Drug Disposition"
    "Statistical Moment Theory In Pharmacokinetics"
    "Drug Disposition in the Elderly"
    "Nonlinearity Processes in Drug Disposition"
    "Estimation of Hepatic Drug Metabolism"
    "Drug Interactions with Cimetidine"

26. "Drug Disposition in the Elderly," presented to the Metabolism Research Department, Upjohn Company, Kalamazoo, Michigan, March 16-17, 1987.

27. "The Influence of Age on Drug Disposition," presented to the Clinical Pharmacology Department, Carter-Wallace Laboratories, Cranbury, New Jersey, April 2, 1987.

28. "Biotechnology and Pharmacy: Implication for Education and Research-Pharmaceutics," presented to the National Advisory Board, College of Pharmacy, University of Arizona, Tucson, Arizona, November 4, 1988.

29. "Clinical Pharmacology, Clinical Pharmacokinetics and Therapeutic Drug Monitoring," Clinical Correlation Lecture, "Drug Disposition in the Elderly", Arkansas Medical Society Lecture Series, Department of Pharmacology, College of Medicine, University of Arkansas for Medical Sciences, Little Rock, Arkansas, January 23-24, 1989.

30. "Treatment of Drug Toxicity with Drug-Specific Antibodies," presented to the Department of Pharmaceutics, College of Pharmacy, University of Georgia, Athens, Georgia, February 10, 1989.

31. "Absorption and Disposition of Moclobemide in Patients with Risk Factors: Advanced Age, Reduced Liver or Kidney Function" (authored by: K. Stoeckel, J.P. Pfefen, M. Mayersohn, M.P. Schoerlin, C. Andreasen, E.E. Ohnhaus, F. Frey and T.W. Guentert). Invited participant, "Treatment of Depression in the 1990's - A Focus on Moclobemide", Lisbon, Portugal, March 9-12, 1989.

32. "Aging as a Variable in Pharmacokinetics", presented at the "Forum on Drug Development and Regulation-Drug Development and Aging Populations," Institute of Medicine, National Academy of Sciences, Washington, D.C., May 24-25, 1989.

33. Panel member and discussant, "McGill Consulting Conference on Bioequivalence," sponsored by the Health Protection Branch, Health and Welfare Canada, Montreal, Quebec, Canada, March 28-29, 1991.

34. "Bioavailability -- What Is It?" presented to the Ontario Pharmacists' Association, Toronto, Canada, May 4, 1991. Also presented three one-hour workshops.

35. "Clinical Pharmacology, Clinical Pharmacokinetics and Therapeutic Monitoring," presented to the Clinical Pharmacology Program, College of Medicine, University of Arizona, Tucson, Arizona, May 29, 1991.

36. "Residence Time Distributions," presented at the Pharmacokinetics Workshop I: Basic Concepts, American Society For Pharmacology and Experimental Therapeutics, San Diego, CA, August 18, 1991.

37. "Bioavailability of Ascorbic Acid," presented at the 1st International Congress on Vitamins and Biofactors in Life Sciences, Co-chairman of Symposium, "Bioavailability of Vitamins," Kobe, Japan, September 19, 1991.

38. "Pharmacokinetics: Basic Principles and Clinical Application," presented to the Department of Neurology, College of Medicine, University of Arizona, Tucson, AZ, January 7, 1992.

39. "Pharmacokinetics in the Elderly," presented at the symposium, "Pharmacokinetics: Defining Dosimetry for Risk Assessment," National Research Council, Board on Environmental Studies and Toxicology, National Academy of Sciences, March 4-5, 1992, Washington, DC.

40. "Physiological Factors Affecting Pharmacokinetics and Pharmacodynamics," Presentation as part of symposium, "Varaiability of Drug Response I: Influence of Physiological and Pharmaceutical Factors," 129th Annual Meeting, American Pharmaceutical Associaton, San Diego, CA, March 14, 1992.

41. "Estimation of Partition Coefficients and the Effect of Residual Blood in Tissues," presented at the 4th Annual Symposium on Frontiers of Pharmacokinetics and Pharmacoydnamics, Little Rock, AR, March 18-20, 1992.

42. "Drug Disposition in the Elderly," presented to the Division of Biopharmaceutics, Food and Drug Administration, Rockville, MD, July 23, 1992.

43. "Drug Disposition in the Elderly," presented to the Clinical Pharmacology Division, Eli Lilly Company, Indianapolis, IN; March 1, 1993.

44. "Drug Disposition in Women," presented to the Indianapolis-Cincinnati Discussion Group, American Association of Pharmaceutical Scientists, Indianapolis, IN; March 1, 1993.

45. "Drug Disposition and Aging in Humans," presented to the Clinical Research Division, Wyeth-Ayerst Company, Radnor, PA; May 24, 1993.

46. "Clinical Pharmacokinetic Considerations of PDA-641," presented to the Clinical Research Division, Wyeth-Ayerst Company, Radnor, PA, May 25, 1993.

47. "Relevant Issues in Pharmacokinetics", presented at the Modeling and Simulation of Biological Systems Workshop, Program on Medical and biological Engineering Workshops, University of Arizona, Tucson, AZ, April 16, 1994.

48. “Selected Recent Issues in the Pharmacokinetics and Toxicokinetics of Drugs of Abuse”, Presented at the Technical Review: “Metabolism, Pharmacokinetics and Pharmacodynamics of Drugs of Abuse”, National Institute on Drug Abuse Technical Review, San Diego, CA, November 4-5, 1994.

49. “Pharmacokinetic Aspects of Depot Drug Delivery Dosage Forms”, Presented to the Neuroscience Group, Hoechst-Roussel Company, Somerville, NJ, January 18, 1995.

50. "New Method for Plasma Protein Binding Quantitation for Highly Bound Molecules" and "Blood Sampling Device Permitting Simultaneous Response Measurement: Pharmacodynamic/Pharmacokinetic Model", Presented to the Animal Health Division, Central Research, Pfizer Pharmaceutical Company, Groton, CT, December 9, 1996.

51. "Aspects of the Pharmacokinetics and Pharmacodynamics of Cocaine and Its Interaction with Ethanol", Presented to the Center for Human Toxicology, University of Utah, Salt Lake City, UT, April 14, 1997

52. "Studies on the Pharmacokinetics and Pharmacodynamics of Cocaine", Presented at the 3rd Annual Science Fair, Southwest Environmental Health Sciences Center, University of Arizona, Tucson, AZ October 13, 1997.

53. "Relevant Aspects of Pharmacokinetics", Presented to the Radiology Discussion Group, College of Medicine, the University of Arizona, Tucson, AZ, October 12, 1999.

54. "Pharmacokinetic Principles", Presented at the Biomedical Engineering Research Seminar Series, College of Medicine, The University of Arizona, Tucson, AZ November 27, 2000.

55. "Pharmacokinetics and Special Populations: Geriatric Pharmacokinetics", Presented to the American College of Toxicology, 21st Annual Meeting, San Diego, CA, November 12-15, 2000.

56. "Pharmacokinetics in the Geriatric Population", Presented to the American Association of Pharmaceutical Scientists Annual Meeting, Denver, CO, October 21-25, 2001.

57. "Selected Principles of Pharmacokinetics as Applied to the Practice of Anesthesiology", Presented to the Faculty and Fellows of the Department of Anesthesiology, College of Medicine, The University of Arizona, Tucson, AZ, August 14 and 21, 2002.

58. "Porcine Models in Pharmacokinetics, Pharmacodynamics and Toxicology: A 'Pig in a Poke?", Introduction to the symposium, Chairman, Presented at the 11th North American International Society for the Study of Xenobiotics Meeting, Orlando, FL, October 27-31, 2002.

59. "Porcine Prediction of Pharmacokinetics Parameters in People", Presented at the 11th North American International Society for the Study of Xenobiotics Meeting, Orlando, FL, October 27-31, 2002.

60. "Insights and Handy Hints for Effective Teaching", Presented at the Physiological Sciences Teaching Round Table", College of Medicine, The University of Arizona, Tucson, AZ, December 6, 2002.

61. "Use of the Swine Model for the Prediction of Human Oral Bioavailability", Presented to the Celgene Company, San Diego, CA, September 29, 2003

62. "Herbal Medicine", Introduction to the symposium, Co-chairman, Presented at the 12th North American International Society for the Study of Xenobiotics Meeting, Providence, RI, October 12-16, 2003.

63. "Assessment of Bioavailability of Botanical Components in a Porcine Model: Illustrations with Curcumin and Ginger", Presented at the 12th North American International Society for the Study of Xenobiotics Meeting, Providence, RI, October 12-16, 2003.

64. "Comparison of Animal Models for the Prediction of Human Oral Bioavailability: Swine *vs*. Dog", Presented to Endo Pharmaceuticals, Inc., Chadds Ford, PA, January 15, 2004.

65. "An Evaluation of the Mini- (or Micro-) Swine for Assessing the Disposition and Bioavailability of Drugs in Humans", Presented to Syntonix, Inc., Waltham, MA, February 20, 2004.

66. "Selected Principles of Pharmacokinetics", Presented to Selectide, Inc., Tucson, AZ, Aug. 5, 19 and 26, 2004.

67. "Animal Models for the Assessment of Oral Drug Bioavailability in Humans: The Porcine Model", Presented to the AnorMed Corporation, Vancouver, British Columbia, Canada, May 29-30, 2006.

68. "Prediction of Drug Disposition Parameters in Humans from Interspecies (allometric) Scaling OR To Extrapolate is Human, To Be Correct Divine", Presented at the Gordon Conference on Drug Metabolism, Holderness School, Plymouth, NH, July 9-14, 2006

69. "A Tribute to Milo Gibaldi", Presented at the 11th Buffalo Pharmaceutics Symposium, Buffalo, NY, July 27-29, 2006.

70. "A Perspective on Allometry", Presented at the 11th Buffalo Pharmaceutics Symposium, Buffalo, NY, July 27-29, 2006.

71. "Animal Scale-Up Methods in Pharmacokinetics", Short Course Presented at the 14th North American Meeting of the International Society of Xenobiotics, Rio Grande, Puerto Rico, October 22-26, 2006.

72. "Pharmacokinetics – Some Principles and Applications to Forensic Toxicology: Everything (or at Least Some Things) you Wanted to Know but Were Afraid to Ask", California Association of Toxicologists and the American Association of Clinical Chemists, Phoenix, AZ, June 8-9, 2007.

73. "Strategies for Predicting Human Pharmacokinetics", American Course on Drug Development and Regulatory Sciences", Washington, DC, January 7-10, 2008.

Contributed

1. M. Mayersohn and M. Gibaldi, "Oxygen Requirements in the Transfer of Drugs Across the Everted Rat Intestine," presented to the Basic Pharmaceutics Section, American Pharmaceutical Association Academy of Pharmaceutical Sciences, 116th meeting, Montreal, Canada May 19, 1969.

2. M. Mayersohn and M. Gibaldi, "Drug Transport-III-The Influence of Sugars on the Passive Transfer of Several Drugs Across the Everted Rat Intestine," presented to the Basic Pharmaceutics Section, American Pharmaceutical Association, Academy of Pharmaceutical Sciences, 117th meeting, Washington, DC., April 14, 1970

3. M. Mayersohn, M. Gibaldi and B. Grundhofer, "Drug Transport V - Relationship Between Tissue Fluid Uptake, The K^+-Inhibition of Solute Transfer and the Permeability Characteristics of the Solute," presented to the Basic Pharmaceutics Section, American Pharmaceutical Association Academy of Pharmaceutical Sciences, 118th meeting, San Francisco, California, April 1, 1971.

4. M. Mayersohn, "Physiological Availability and Urinary Excretion Kinetics of Enteric Coated Acetylsalicylic Acid Tablets in Man," presented at the 18th Canadian Conference on Pharmaceutical Research, University of Manitoba, Winnipeg, Manitoba, August 14, 1971.

5. M. Mayersohn and L. Endrenyi, "Relative Bioavailability of Ampicillin Formulations in Man," presented at the 20th Canadian Conference on Pharmaceutical Research, Dalhousie University, Halifax, Nova Scotia, May 4, 1973.

6. J. Cobby, M. Mayersohn and M.E. Farlinger, "Studies on the Dissolution of Drug Particles" presented at the 20th Canadian Conference on Pharmaceutical Research, Dalhousie University, Halifax, Nova Scotia, May 4, 1973.

7. K. Suryasaputra and M. Mayersohn, "Drug Transfer Across the Isolated Intestinal Membrane" presented at the 20th Canadian Conference on Pharmaceutical Research, Dalhousie University, Halifax, Nova Scotia, May 4, 1973.

8. L.W. Hall and M. Mayersohn, "Computer Simulation by Continuous Biological Model Systems Using an IBM Application Program" presented at the 20th Canadian Conference on Pharmaceutical Research, Dalhousie University, Halifax, Nova Scotia, May 4, 1973.

9. J. Cobby, M. Mayersohn and S. Selliah,"Gas Chromatographic Assay for Diethyldithiocarbamate, A Metabolite of Disulfiram, in Biological Fluids," presented to the Pharmaceutical Analysis and Control Section, American

Pharmaceutical Association, Academy of Pharmaceutical Sciences, 21st National Meeting, Orlando, Florida, November 14-17, 1976.

10. J. Cobby, M. Mayersohn and S. Selliah, "The Disposition of Diethyldithio-carbamate, A Metabolite of Disulfiram, in the Dog," presented to the Basic Pharmaceutics Section, American Pharmaceutical Association, Academy of Pharmaceutical Sciences, 21st National Meeting, Orlando, Florida, November 14-17, 1976.

11. K.D. Gierke, D. Perrier, M. Mayersohn and F.I. Marcus, "Digoxin Disposition Kinetics in Normal and Azotemic Dogs" presented at the 50th Scientific Section, American Heart Association, Miami Beach, Florida, November 14-17, 1976.

12. B.M. Kapur, B. Danglay and M. Mayersohn,"In Situ TLC Quantitation of Amitriptyline and Nortriptyline Using HPTLC and Transferable Calibration Factors", presented at the 29th National meeting of the American Association of Clinical Chemists, Chicago, IL, July 17-23, 1977.

13. P. Walson, M. Mayersohn and D. Perrier, "Serum and Salivary Phenobarbital Levels on Chronic Oral Dosing Regimens," 7th International Congress of Pharmacology, Paris, France, July, 1978.

14. P. Walson, T. Mimaki, R. Curless, M. Mayersohn and D. Perrier, "Onc Daily Phenobarbital Dosage Regimens in Epileptic Children" 11th Epilepsy International Symposium, Florence, Italy, October, 1979.

15. D. Hager, P. Fenster, M. Mayersohn, D. Perrier, P. Graves, F. Marcus and S. Goldman, "Digoxin-Quinidine Interaction: Pharmacokinetic Evaluation," American Federation of Clinical Research, Washington, D.C., May, 1979.

16. P. Fenster, E-G.V. Giardina, J.T. Bigger, F.I. Marcus, M. Mayersohn and D. Perrier, "Efficacy and Kinetics of New Sustained-Release Procainamide Preparation," American Heart Association, 52nd Sci. Session, Anaheim, California, November 12-15, 1979.

17. P. Fenster, M. Mayersohn, D. Perrier and F.I. Marcus, "Pharmacokinetic Evaluation of a New Slow Release Procainamide Tablet," American Heart Association, 52nd Sci. Session, Anaheim, California, November 12-15, 1979.

18. S. Goldman, D. Perrier, M. Olajos, H. Pieniaszek, M. Mayersohn and E. Morkin, "Beta-Adrenergic Blockade (β) and Pharmacokinetics of Propranolol (P) in Thyrotoxicosis (T)," American Heart Association, 52nd Sci. Session, Anaheim, California, November 12-15, 1979.

19. W.D. Hager, H. Pieniaszek, D. Perrier, V. Goldberger and M. Mayersohn, "Assessment of Beta Blockade to Propranolol," American Federation of Clinical Research, May 1980.

20. S. Goldman, M. Olajos, D. Perrier, H. Pieniaszek, M. Mayersohn and E. Morkin, "In Vivo Titration of β-Adrenergic Receptors in Thyrotoxic Calf Heart," American Society for Clinical Investigation, July 1980.

21. S. Appelbaum, M. Mayersohn, D. Perrier and R.T. Dorr, "Allopurinol Kinetics and Bioavailability," Midyear Clinical Meeting, American Society of Hospital Pharmacy, December, 1980.

22. M. Mayersohn, "The 'Xylose Test' to Assess GI Absorption in the Elderly: A Literature Evaluation," American Association of Colleges of Pharmacy, 82nd Annual Meeting, Scottsdale, Arizona, June 28-July 1, 1981.

23. D. Jung, H.J. Pieniaszek, Jr., M. Mayersohn and D. Perrier, "Absolute Bioavailability (F) Determination by Simultaneous Nonlinear Regression FIT of Oral and Intravenous Data," presented to the Basic Pharmaceutics Section, Academy of Pharmaceutical Sciences, 129th Annual Meeting of the American Pharmaceutical Association, Las Vegas, Nevada, April 24-29, 1982.

24. J. Woodworth, S.M. Owens, M. Mayersohn and D. Perrier, "Phencyclidine Disposition Kinetics in Dogs," presented to the Basic Pharmaceutics Section, Academy of Pharmaceutical Sciences, 129th Annual Meeting of the American Pharmaceutical Association, Las Vegas, Nevada, April 24-29, 1982.

25. H.J. Pieniaszek, Jr., P. Graves, M. Mayersohn, F.I. Marcus and D. Perrier, "Pharmacokinetic Studies of Digitalis Glycosides," presented to the Basic Pharmaceutics Section, Academy of Pharmaceutical Sciences, 129th Annual Meeting of the American Pharmaceutical Association, Las Vegas, Nevada, April 24-29, 1982.

26. S.M. Owens, J. Woodworth, M. Mayersohn and D. Perrier, "Phencyclidine Analysis in Serum by Radioimmunoassay," presented to the Pharmaceutical Analysis and Control Section, Academy of Pharmaceutical Sciences, 129th Annual Meeting of the American Pharmaceutical Association, Las Vegas, Nevada, April 24-29, 1982.

27. D. Bikin, K. A. Conrad and M. Mayersohn, "Lack of Influence of Caffeine and Aspirin on Lithium Elimination," Clinical Research, 30, 249A (1982).

28. J. R. Woodworth, M. Mayersohn and S. M. Owens, "The Simultaneous Quantitative Analysis of Phencyclidine and Metabolites by Gas Chromatography," presented to the Pharmaceutical Analysis and Control Section, Academy of Pharmaceutical Sciences, 33rd National Meeting, San Diego, California, November 14-18, 1982.

29. S.M. Owens, M. Mayersohn and J.R. Woodworth, "Phencyclidine Blood Protein Binding: Influence of Protein, pH and Species," presented to the Pharmacology and Toxicology Section, Academy of Pharmaceutical Sciences, 33rd National Meeting, San Diego, California, November 14-18, 1982.

30. M. Mayersohn, K.A. Conrad and R. Achari, "Effect of a Cooked Meat Meal on Estimates of Creatinine Clearance," presented at the American Society for Clinical Pharmacology and Therapeutics Meeting, San Diego, California, March, 1983. Abstract: Clin. Pharmacol. Therap., 33, 264 (III-C), 1982.

31. S. Johnson and M. Mayersohn, "Gas Chromatographic Analysis of Xylose from Plasma and Urine," presented to the Pharmaceutical Analysis and Control Section, Academy of Pharmaceutical Sciences, 130th Annual Meeting of the American Pharmaceutical Association, New Orleans, Louisiana, April 11-14, 1983.

32. R. Achari and M. Mayersohn, "Gas Chromatographic Analysis of 4-methyl- pyrazole in Plasma," presented to the Pharmaceutical Analysis and Control Section, Academy of Pharmaceutical Sciences, 130th Annual Meeting of the American Pharmaceutical Association, New Orleans, Louisiana, April 11-14, 1983.

33. K. A. Conrad and M. Mayersohn, "Cimetidine Does Not Affect Single Dose Ibuprofen Kinetics in Volunteers," presented at the Second World Conference on Clinical Pharmacology and Therapeutics, Washington, D.C., July 31-August 5, 1983.

34. J.R. Woodworth, S.M. Owens and M. Mayersohn, "Phencyclidine Disposition in Dogs," presented to the Pharmacodynamics and Drug Disposition Section, Academy of Pharmaceutical Sciences, 34th National Meeting, Miami, Florida, November 13-17, 1983.

35. S.M. Owens and M. Mayersohn, "Anti-phencyclidine Fab as a Tool for Studying the Toxic Effects of Phencyclidine," presented at the N.I.H. Immunotoxicology Workshop, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina, October 17-18, 1983.

36. L.J. Schaaf, D.G. Perrier, M. Mayersohn and S. Campbell, "Influence of Smoking and Gender on the Pharmacokinetics of Metoprolol," presented at the 17th Annual Meeting of the Australasian Society of Clinical and Experimental Pharmacologists, University of Newcastle, New South Wales, December 12-14, 1983. Abstract: Clin. Exp. Pharmacol. Physiol., 8 (Suppl.), 40 (1984).

37. S.L. Johnson, M. Mayersohn and K.A. Conrad, "Gastrointestinal Absorption of Xylose in Man as a Function of Age," Clin. Res., 32, 243A (1984).

38. S.M. Owens and M. Mayersohn, "Anti-Phencyclidine (PCP) Fab Alters PCP Disposition," presented at the American Society of Pharmacology and Experimental Therapeutics Meeting, August 19-23, 1984, Indianapolis, Indiana. Abstract: Pharmacologist, 26, 236 (1984).

39. M. Mayersohn, "Gastrointestinal Absorption of Xylose as a Function of Age," presented at the 3rd Buffalo Pharmaceutics Symposium, July 25-28, 1984, Buffalo, New York.

40. P.E. Nolan, Jr., M. Mayersohn, P.E. Fenster and M. Bliss, "Single-dose Pharmacokinetics of Amiodarone," presented at the 6th Annual Meeting of the American College of Clinical Pharmacy, Orlando, Florida, July 7-10, 1985. Abstract: Drug Intell. Clin. Pharm., 19, 445 (1985).

41. W.N. Jones, K.B. Kern, J.P. Rindone, M. Mayersohn, M. Bliss and S. Goldman, "Digoxin-Diltiazem Interaction: A Pharmacokinetic Evaluation," presented at the 51st Annual Scientific Assembly of the American College of Chest Physicians, New Orleans, Louisiana, Oct. 28-Nov. 1, 1985.

42. M. Bliss, M. Mayersohn, T. Arnold, J. Logan, U.F. Michael and W. Jones, "Disposition Kinetics of Cefamandole During Continuous Ambulatory Peritoneal Dialysis," presented to the Pharmacodynamics and Drug Disposition Section, Academy of Pharmaceutical Sciences, 133rd Annual American Pharmaceutical Association Meeting, San Francisco, California, March 16-20, 1986. Abstract: 16, 128 (1986).

43. A. Lopez-Anaya, M. Mayersohn and K.A. Conrad, "Pharmacokinetics of Riboflavin as a Function of Age," presented to the Pharmacodynamics and Drug Disposition Section, Academy of Pharmaceutical Sciences, 133rd Annual American Pharmaceutical Association Meeting, San Francisco, California, March 6-10, 1986. Abstract: 16, 130 (1986).

44. P. Nolan, M. Mayersohn, P. Fenster, M. Bliss, and S. Quan, "Pharmacokinetic Comparison of Single Dose and Chronically Dosed Amiodarone in Healthy Volunteers," presented at the Third World Conference on Clinical Pharmacology and Therapeutics, Stockholm, Sweden, July 27 - August 1, 1986.

45. A. Lopez-Anaya and M. Mayersohn "Quantification of Ascorbic Acid in Biological Fluids by High Performance Liquid Chromatography with Fluorescence Detection," presented at the Western Regional Meeting of the American Association of Pharmaceutical Scientists, Reno, Nevada, February 8-10, 1986.

46. H.Y. Abdallah, M. Mayersohn and K.A. Conrad, "Influence of Age on Salicylate Kinetics in Man," presented at the Western Regional Meeting of the American Association of Pharmaceutical Scientists, Reno, Nevada, February 8-10, 1986.

47. S.P. Khor, S. Johnson and M. Mayersohn, "Noncompartmental Estimation of Initial Volume of Distribution V_1 Following an Intravenous Injection," presented at the Western Regional Meeting of the American Association of Pharmaceutical Scientists, Reno, Nevada, February 8-10, 1986.

48. R. D'Angio, M. Mayersohn, K.A. Conrad and M. Bliss, "Cimetidine Absorption in Humans During Sucralfate Coadministration," presented at the Western Regional Meeting of the American Association of Pharmaceutical Scientists, Reno, Nevada, February 8-10, 1986.

49. P.E. Nolan, F.I. Marcus, G. Hoyer, M. Bliss, M. Mayersohn and K. Gear, "Pharmacokinetic Interaction Between Amiodarone and Phenytoin," presented at the 36th Annual Scientific Session of the American College of Cardiology, New Orleans, Louisiana, March 8-12, 1987.

50. M.P. Schoerlin, M. Mayersohn, B. Hoevels and H. Eggers, "The Influence of Food on the Relative Bioavailability of Moclobemide, A New Monoamine Oxidase-A (MAO-A) Inhibitor," presented at the Third European Congress of Biopharmaceutics and Pharmacokinetics, Freiburg, Germany, April 21-24, 1987.

51. M.P. Schoerlin, M. Mayersohn, F. Horber, M. Dellenbach, J.P. Pfefen and F. Frey, "The Influence of Renal Insufficiency on the Absorption and Disposition of the Monoamine Oxidase-A Inhibitor Moclobemide," presented at the Third European Congress of Biopharmaceutics and Pharmacokinetics, Freiburg, Germany, April 21-24, 1987.

52. N. Egen, M. Bliss, M. Mayersohn and M. Bier, "Purification of Monoclonal Antibody from Murine Ascites Fluid by Preparation Scale Isoelectric Focusing by RIEF and ROTOFOR," presented at the Electrophoresis Americas Meeting, San Francisco, California, June 22-26, 1987.

53. S.P. Khor and M. Mayersohn, "Drug-Protein Binding and Hepatic Elimination: Theoretical and Mathematical Considerations," presented at the Japanese-United States Congress of Pharmaceutical Sciences, Honolulu, Hawaii, December 2-7, 1987.

54. H.P. Bozigian and M. Mayersohn, "Physiologic Based Model of Phencyclidine Kinetics in the Rat," presented at the Western Regional Meeting of the American Association of Pharmaceutical Scientists, Reno, Nevada, January 31-February 3, 1988.

55. M. Bliss, M. Mayersohn and N. Egen, "Evaluation of Polyethylne Glycols for the Purification of IgG from Ascites Fluid," presented at the Western Regional Meeting of the American Association of Pharmaceutical Scientists, Reno, Nevada, January 31-February 3, 1988.

56. S.P. Khor and M. Mayersohn, "Potential Error in the Measurement of Tissue to Blood Distribution Coefficients in Physiologically Based Pharmacokinetic Models. Theoretical Considerations," presented at the Western Regional Meeting of the American Association of Pharmaceutical Scientists, Reno, Nevada, January 31-February 3, 1988.

57. M.P. Schoerlin, M.Mayersohn, B. Hoevels and H. Eggers, "The Influence of Food on the Relative Bioavailability of Moclobemide, A New Monoamine Oxidase-A(MAO-A) Inhibitor," presented at the 16th CINP Congress, Munich, Federal Republic of Germany, August 15-19, 1988.

58. P.E. Nolan, S.G. Meeves, M. Bliss, M. Mayersohn and K. Reed, "Effect of the Menstrual Cycle on the Pharmacokinetics of Theophylline," presented at the 10th Annual Meeting of the American College of Clinical Pharmacy, Kansas City, Missouri, August 6-9, 1989.

59. H.J. Pieniaszek, Jr., M.P. Adams, D.M. Garner, M. Bliss, R.J. Reinhart and M. Mayersohn, "Moricizine Bioavailability after Simultaneous Administration of a Tablet and Solution Using Stable Isotopes and Quantitative Thermospray Liquid Chromatography/Mass Spectrometry (LC/MS)", presented at the 18th annual meeting of the American College of Clinical Pharmacology, Baltimore, Maryland, October 11-13, 1989.

60. S.P. Khor, H. Bozigian and M. Mayersohn, "Residual Capillary Blood in Tissues and Physiological Pharmacokinetic Modeling," presented at the 4th annual meeting of the American Association of Pharmaceutical Scientists, Atlanta, Georgia, October 22-26, 1989.

61. D. Campbell, R. Dart, and M. Mayersohn, "Pharmacokinetics of $^{121}_{I}$-radiolabeled Crotalus Atrox Venom," presented at the American Academy of Clinical Toxicology Meeting, Tucson, AZ, September 13-18, 1990.

62. H.P. Bozigian, M. Bliss, M. Mayersohn and N.J. Egen, "Isolation of Monochlonal Antibody to Phencyclidine from Murine Ascites Fluid Using Preparative Scale Recycling Isoelectric Focusing," presented at the 3rd North American International Society for the Study of Xenobiotics Meeting, San Diego, CA, October 21-25, 1990.

63. H. Abdallah and M. Mayersohn, "Pharmacokinetic Evaluation of a Tablet Dosage Form of Cyclosporine in Dogs," presented at the 5th Annual American Association of Pharmaceutical Scientists Meeting, Las Vegas, Nevada, November 4-9, 1990.

64. H. Abdallah and M. Mayersohn, "Measurement of Cyclosporine in Canine Blood by Monoclonal RIA and HPLC," presented at the 5th Annual American Association of Pharmaceutical Scientists Meeting, Las Vegas, Nevada, November 4-9, 1990.

65. S.P. Khor, M. Mayersohn, and G.A. Thompson, "Teicoplanin Plasma Protein Binding by Ultrafiltration and Equilibrium Dialysis," presented at the 5th Annual American Association of Pharmaceutical Scientists Meeting, Las Vegas, Nevada, November 4-9, 1990.

66. J.L. Burgess, R.C. Dart, and M. Mayersohn, "The Effect of Constriction Bands on Rattlesnake Venom Absorption: A Pharmacokinetic Study," presented to the Society of Academic Emergency Medicine, Washington, DC, May 12-15, 1991.

67. R.C. Dart, J.B. Sullivan, Jr., N.B. Egen, R. Garcia, M. Mayersohn and A.B. Sanders, "Effect of Anti-desipramine Fab on Desipramine Toxicity in the Rat," presented to the American Association of Clinical Toxicology, Toronto, Canada, October 1-4, 1991.

68. H.J. Pieniaszek, Jr., C.M. McEntegart, A.F. Davison, C-Y. Quon, R. Sampliner and M. Mayersohn, "Moricizine Pharmacokinetics in Patients with Hepatic Cirrhosis," presented at the 20th Annual Meeting of the American College of Clinical Pharmacology, Atlanta, Georgia, October 13-16, 1991.

69. A. Walters, H.H. Chow and M. Mayersohn, "Simultaneous Quantitation of the Enantiomers of Methanphetamine and Amphetamine by HPLC," presented at the 6th Annual Meeting of the American Association of Pharmaceutical Scientists, Washington, D.C., November 18-22, 1991.

70. H.C. Lee, S.P. Khor, H.H. Chow and M. Mayersohn, "Dialysis Method for Determining Binding and Estimating the Association Constant for Highly Bound Drugs," presented at the 6th Annual Meeting of the American Association of Pharmaceutical Scientists, Washington, D.C., November 18-22, 1991.

71. A. Hutchaleelaha, H.H. Chow and M. Mayersohn, "Inhibitory Effect of 4-methylpyrazole on Antipyrine Clearance in the Rat," presented at the 6th Annual Meeting of the American Association of Pharmaceutical Scientists, Washington, D.C., November 18-22, 1991.

72. Y. Cai, H.H. Chow and M. Mayersohn, "Disposition Kinetics of Amphotericin B in Rats," presented at the 6th Annual Meeting of the American Association of Pharmaceutical Scientists, Washington, D.C., November 18-22, 1991.

73. W. Zhang, S.M. Winter, M. Mayersohn and I.G. Sipes, "Pharmacokinetics of Salicylazosulfapyridine (SASP) in Male B6C3F Mice," presented at the 31st National Meeting of the Society of Toxicology, Seattle, Washington, February 23-27, 1992.

74. S.L. Johnson and M. Mayersohn, "Model-Independent Method for Determining the Central Volume from IV Bolus and Continuous Infusion Data," presented at the Western Regional Meeting of the American Association of Pharmaceutical Scientists, Reno, Nevada, March 2-3, 1992.

75. R.C. Dart, M.R. Maiorino, L. Boyer, K.M. Hurlbut, H.V. Aposhian, M. Mayersohn and J.B. Sullivan, "Dimercaptosuccinic Acid (DMSA): Efficacy, Safety, and Kinetics in Lead Poisoning," AAPCC/AACT/ABMT/CAPCC Annual Meeting, Tampa, Florida; September 19-22, 1992.

76. H.J. Pieniaszek, Jr., C.M. McEntegart, C.Y. Quon, U.F. Michael and M. Mayersohn, "Moricizine Pharmacokinetics in Patients with Renal Disease," American College of Clinical Pharmacology Annual Meeting, Washington, DC; September 18, 1992.

77. W. Zheng, M. Mayersohn, J.B. Bishop and I.G. Sipes, "Toxicokinetics of Salicylazosulfapyridine (SASP) and Its Metabolite, Sulfapyridine (SP) in Male B6C3F1 Mice," Society of Toxicology Meeting, New Orleans, Louisiana; March 14-18, 1992.

78. A. Walters, S. Perozhkow, J. Monteleone, H.H. Chow and M. Mayersohn, "Determination of Cocaine, Cocaethylene (CE) and Metabolites in Plasma by High Performance Liquid Chromatography," 7th Annual Meeting of the American Association of Pharmaceutical Scientists, San Antonio, Texas; November 16-19, 1992.

79. Y. Wu, H.H. Chow and M. Mayersohn, "Disposition Kinetics of Amphotericin B in Rats," 7th Annual Meeting of the American Association of Pharmaceutical Scientists, San Antonio, Texas; November 16-19, 1992.

80. J. Sukbuntherng, H.H. Chow and M. Mayersohn, "Quantitative Determination of the Enantiomers of Methamphetamine (MAP) Metabolites in Rat Urine by HPLC," 7th Annual Meeting of the American Association of Pharmaceutical Scientists, San Antonio, Texas; November 16-19, 1992.

81. R.A. Lal, H.H. Chow and M. Mayersohn, "d-Methamphetamine Blood Protein Binding: Influence of Drug Concentration, pH, and l-isomer," 7th Annual Meeting of the American Association of Pharmaceutical Scientists, San Antonio, Texas; November 16-19, 1992.

82. A. Hutchaleelaha, H.H. Chow and M. Mayersohn, "Pharmacokinetics of Methamphetamine (MAP) and Its Metabolites in the Rat," 7th Annual Meeting of the American Association of Pharmaceutical Scientists, San Antonio, Texas; November 16-19, 1992.

83. J. Monteleone, H.H. Chow and M. Mayersohn, "Pharmacokinetics of Cocaethylene in Male Rats Following Short-Term IV Infusion," 7th Annual Meeting of the American Association of Pharmaceutical Scientists, San Antonio, Texas; November 16-19, 1992.

84. S.R. Kim, H.H. Chow and M. Mayersohn, "*In Vivo* Studies of Cocaethylene Formation as a Result of Concurrent Administration of Cocaine and Ethanol in Rats," 7th Annual Meeting of the American Association of Pharmaceutical Scientists, San Antonio, Texas; November 16-19, 1992.

85. K.M. Hurlbut, R.C. Dart, R. M. Maiorino, M. Mayersohn, H.V. Aposhian, L.V. Boyer, "Pharmacokinetics of Dimercaptosuccinic Acid (DMSA) in Lead (Pb) Poisoned Patients and Normal Adults," presented at the 32nd Annual Meeting of the Society of Toxicology, New Orleans, Louisiana; March 14-18, 1993.

86. M. Mayersohn and R. Hamilton, "The Relationship Between the Terminal Disposition Half-Life and Mean Residence Time in Multicompartment Models," 5th North American Meeting of the International Society for the Study of Xenobiotics, Tucson, Arizona; October 17-21, 1993.

87. H.H. Chow, A. Hutchaleelaha and M. Mayersohn, "Comparative Pharmacokinetics and Interspecies Scaling of Amphotericin B in Several Mammalian Species," 5th North American Meeting of the International Society for the Study of Xenobiotics, Tucson, Arizona; October 17-21, 1993.

88. H.H. Chow, J. Sukbuntherng, A. Hutchaleelaha and M. Mayersohn, "Comparative Pharmacokinetics and Interspecies Scaling of Morphine in Several Mammalian Species," 5th North American Meeting of the International Society for the Study of Xenobiotics, Tucson, Arizona; October 17-21, 1993.

89. W. Zhang, M. Mayersohn, J.B. Bishop and I.G. Sipes, "Toxicokinetics of Salicylazosulfapyridine (SASP) and Its Metabolite Sulfapyridine (SP) in Male B6C3F1 Mice," 5th North American Meeting of the International Society for the Study of Xenobiotics, Tucson, Arizona; October 17-21, 1993.

90. S.R. Kim, H.H. Chow and M. Mayersohn, "Pharmacokinetic Aspects of Cocaine and Ethanol Interaction in Rats," 8th Annual Meeting of the American Association of Pharmaceutical Scientists, Orlando, Florida; November 14-18, 1993.

91. A. Hutchaleelaha, J. Sukbuntherng, H.H. Chow and M. Mayersohn, "Quantitative Determination of the Enantiomers of Methamphetamine (MAP) and Amphetamine (AP) in Rat Urine by HPLC," 8th Annual Meeting of the American Association of Pharmaceutical Scientists, Orlando, Florida; November 14-18, 1993.

92. A. Hutchaleelaha, J. Sukbuntherng, H.H. Chow and M. Mayersohn, "Pharmacokinetics of d- and 1-Amphetamine After Racemic Amphetamine Administration in Rats," 8th Annual Meeting of the American Association of Pharmaceutical Scientists, Orlando, Florida; November 14-18, 1993.

93. U.A. Pillai, T.L. Ziegler, D.X. Wang, R.L. Smith, D.C. Liebler, M. Mayersohn and I.G. Sipes, "3,3',3,3'-Tetra-chloroazobenzene (TCAB) Disposition and Pharmacokinetics in the Male F-344 Rats", 6th North American Meeting of the International Society for the Study of Xenobiotics, Raliegh, NC, October 23-27, 1994.

94. T.L. Ziegler, U.A. Pillai, M.J. Kattnig, D.X. Wang, D.S. Barber, M. Mayersohn and I.G. Sipes, "The Disposition and Elimination of 3,3',4,4'-Tetrachloroazoxybenzene (TCAOB) in the Male F-344 Rat", 6th North American Meeting of the International Society for the Study of Xenobiotics, Raliegh, NC, October 23-27, 1994 .

95. D. Van Wyck, R. Hakim, M. Mayersohn, D. Roe, T. Wiltbank, R. Wingard and L. Kirlin, "Iron Dextran Pharmacokinetics in Iron Deficient Hemodialysis Patients", Presented at the 27th Annual Meeting of the American Society of Nephrology, Orlando, FL, October 26-29, 1994.

96. J. Sukbuntherng, H.H. Chow and M. Mayersohn, "Quantitative Determination of cocaine (COC), Cocaethylene (CE) and Metabolites in Plasma and Urine by HPLC", 9th Annual Meeting of the American Association of Pharmaceutical Scientists, San Diego, CA, November 6-10, 1994.

97. A. Hutchaleelaha, H.H. Chow and M. Mayersohn, "The Influence of Activated Charcoal (AC) on the Disposition Kinetics of Intravenous Methamphetamine (MAP)", 9th Annual Meeting of the American Association of Pharmaceutical Scientists, San Diego, CA, November 6-10, 1994.

98. A. Hutchaleelaha, J. Sukbuntherng, H.H. Chow and M. Mayersohn, "Magnification of Stereoselective Differences in the Disposition Kinetics of Amphetamine (AP) Following Methamphetamine (MAP) Administration to Rats and Influence of Strain", 9th Annual Meeting of the American Association of Pharmaceutical Scientists, San Diego, CA, November 6-10, 1994.

99. V. Sinha and M. Mayersohn, "Interspecies Scaling of Half-Life for 2,3,7,8-Tetrachloro-p-Dibenzodioxin (TCDD) and 3,4,3',4'-Tetrachlorobiphenyl (TCB)", 9th Annual Meeting of the American Association of Pharmaceutical Scientists, San Diego, CA, November 6-10, 1994.

100. S.R.Kim, R. Hamilton and M. Mayrsohn,"Theoretical Model for Drug Deposition in Hair", 9th Annual Meeting of the American Association of Pharmaceutical Scientists, San Diego, CA, November 6-10, 1994.

101. S.R. Kim, H.H. Chow and M. Mayersohn, "Comparative Pharmacokinetics and Interspecies Scaling of Cocaine InSeveral Mammalian Species", 9th Annual Meeting of the American Association of Pharmaceutical Scientists, San Diego, CA, November 6-10, 1994.

102. D. Van Wyck, R. Hakim, M. Mayersohn, D. Roe, T. Wiltband, R. Wingard and L. Kirlin, "Pharmacokinetics of Iron Dextran in Iron Deficient Dialysis Patients: Evaluation and Comparison of Two Agents", 36th Annual Meeting of the American Society of Hematology, Nashville, TN, December 2-6, 1994.

103. T.L. Ziegler, D.S. Barber, U. Pillari, M. Mayersohn and I.G. Sipes, "The Disposition and Pharmacokinetic Parameters for 3,3',4,4'-Tetrachloroazobenzene (TCAB) and 3,3',4,4'-Tetrachloroazoxybenzene (TCAOB) in the Fischer-344 Male Rat", 34th Annual Society of Toxicology Meeting, Baltimore, MD, March 6-9, 1995.

104. V. Sihna, S. Tannenbaum and M. Mayersohn, "Potential Errors in the Estimation of Toxicokinetic Parameters from Body Burden Data", First Annual Science Fair, Center for Toxicology, Southwest Environmental Health Sciences Center, Tucson, AZ, May 26, 1995.

105. T. Kakkar, F. G. Walter and M. Mayersohn, "A Study of the Effectiveness of Chelex 100 as an Oral Iron Chelator in Reducing Iron Absorption in Rats", First Annual Science Fair, Center for Toxicology, Southwest Environmental Health Sciences Center, Tucson, AZ, May 26, 1995.

106. M.D.Karol, M. Mayersohn, C.J. Eason, J. Shi and J. Cavanaugh, "Evaluation of Interaction Potential Between Lansoprazole and Clarithromycin (Biaxin) in Normal Subjects", Presented at the American College of Gastroenterology Annual Scientific Meeting and Postgraduate Courses, New York, NY, October 13-18, 1995.

107. J. Valdez, T. Kakkar, D.K. Martin and M. Mayersohn, "Disposition Kinetics and Dermal Absorption of N,N-Diethyl-m-Toluamide (DEET)", Presented at the 35th Annual Society of Toxicology Meeting, Anaheim, CA, March 10-14, 1996.

108. T. Kakkar, F.G. Walter, D.K. Martin and M. Mayersohn, "A Study of the Effectiveness of Chelex 100 as an Oral Iron Chelator in Reducing Iron Absorption in Rats", Presented at the 35th Annual Society of Toxicology Meeting, Anaheim, CA, March 10-14, 1996.

109. D. K. Martin, V. Sinha and M. Mayersohn, "Cocaine and Cocaethylene Kinetics in the Isolated Rat Perfused Liver: Effect of Dose, Continuous Infusion and Ethanol", Presented at the 35th Annual Society of Toxicology Meeting, Anaheim, CA, March 10-14, 1996.

110. S. J. Tannenbaum, V. Sinha and M. Mayersohn, "Potential Errors in the Use of Body Burden Calculations for Estimation of Toxicokinetic Parameters", Presented at the 35th Annual Society of Toxicology Meeting, Anaheim, CA, March 10-14, 1996.

111. J. Sukbuntherng, D.K. Martin, Y. Pak and M. Mayersohn, "Characterization of the Properties of Cocaine in Blood: Clearance, Blood to Plasma Ratio and Plasma Protein Binding", Presented at the 35th Annual Society of Toxicology Meeting, Anaheim, CA, March 10-14, 1996.

112. J. A. Bourland, D.K. Martin and M. Mayersohn, "Ethanol and Drug Metabolism: A Broad Caategory of Metabolic Interaction *via* Carboxylesterase Transesterification", Presented at the 35th Annual Society of Toxicology Meeting, Anaheim, CA, March 10-14, 1996.

113. Y. Pak, J.A. Bourland, D.K. Martin and M. Mayersohn, "*In Vitro* Transesterification of Cocaethylene with Ethanol: Ethyl Ester Exchange", Presented at the 35th Annual Society of Toxicology Meeting, Anaheim, CA, March 10-14, 1996.

114. A. Hutchaleelaha and M. Mayersohn, "Pharmacokinetics and Metabolism of the Enantiomers of p-Hydroxymethamphetamine (OHMAP) in Rats", Presented at the 35th Annual Society of Toxicology Meeting, Anaheim, CA, March 10-14, 1996.

115. V. Sinha, R. Fisher, K. Brendel and M. Mayersohn, "Predicting the *In Vivo* Meabolic Clearance of Drugs from *In Vitro* Drug Metabolism Data", Presented at the 35th Annual Society of Toxicology Meeting, Anaheim, CA, March 10-14, 1996.

116. M. Mayersohn, V. Sinha and K. Brendel, "A Simplified Isolated Perfused Rat Liver Apparatus (IPRL): Extraction Ratio Estimation for Antipyrine", Presented at the 35th Annual Society of Toxicology Meeting, Anaheim, CA, March 10-14, 1996.

117. T.L. Ziegler, U.A. Pillai, M.J. Kattnig, T. McClure, D.C. Liebler, M. Mayersohn and I.G. Sipes, "The Absorption and Disposition Kinetics of 3,3',4,4'-Tetrachloroazoxybenzene (TCAOB) in the Male Rischer 344Rat", Presented at the 35th Annual Society of Toxicology Meeting, Anaheim, CA, March 10-14, 1996.

118. S.R. Kim and M. Mayersohn, "A Preliminary Physiologically Based Pharmacokinetic (PB-PK) Model of Cocaine (COC) in Humans", Presented at the 10th Annual Meeting of the American Association of Pharmaceutical Scientists, Seattle, Washington, October 27-31, 1996.

119. J.A. Bourland and M. Mayersohn, "In Vivo Alteration of Meperidine Pharmacokinetics in the Presence of Ethanol: Carboxylesterase-Mediated Ethyl Ester Exchange", Presented at the 10th Annual Meeting of the American Association of Pharmaceutical Scientists, Seattle, Washington, October 27-31, 1996.

120. S. Tannenbaum and M. Mayersohn, "Prediction of Pharmacokinetic Parameters in Humans on the Basis of Allometric Scaling Using a "Global" Slope", Presented at the 10th Annual Meeting of the American Association of Pharmaceutical Scientists, Seattle, Washington, October 27-31, 1996.

121. A. Hutchaleelaha, J. Sukbuntherng and M. Mayersohn, "Simple Apparatus for Serial Blood Sampling in Rodents Permitting Simultaneous Measurement of Locomotor Activity as Illustrated with Cocaine", Presented at the 10th Annual Meeting of the American Association of Pharmaceutical Scientists, Seattle, Washington, October 27-31, 1996.

122. J. Sukbuntherng, A. Hutchaleelaha, D.K. Martin and M. Mayersohn, "Pharmacokinetics of Cocaine in the Rat: The Effect of Dose and Route of Administration", Presented at the 10th Annual Meeting of the American Association of Pharmaceutical Scientists, Seattle, Washington, October 27-31, 1996.

123. A. Hutchaleelaha, J. Sukbuntherng, D.K. Martin and M. Mayersohn, "Pulmonary Clearance of Cocaine in the Rat Determined Following Intravenous and Intraarterial Dosing", Presented at the 10th Annual Meeting of the American Association of Pharmaceutical Scientists, Seattle, Washington, October 27-31, 1996.

124. V. Sinha, D.K. Martin, T.S. Kakkar, Y. Pak and M. Mayersohn, "Cocaine Kinetics in the Isolated Perfused Rat Liver (IPRL): Is Metabolite Inhibition Responsible for Non-Linear Kinetics?", Presented at the 10th Annual Meeting of the AmericanAssociation of Pharmaceutical Scientists, Seattle, Washington, October 27-31, 1996.

125. J-M. Sauer, R.L. Smith, J.W. Bao, M.J. Kattnig, R.K. Kuester, M.Mayersohn and I.G. Sipes, "The Metabolism and Elimination of trans-Methyl Styryl Ketone in the Male Fischer 344 Rat", Presented at the 36thAnnual Meeting of the Society of Toxicology, Cincinnati, OH, March 9-13, 1997.

126. T.S. Kakkar, D. K. Martin and M. Mayersohn, "Analysis of Methylsalicylate, Ethylsalicylate and Salicylic Acid from Biological Fluids Using a GC-MS Assay: Preliminary Pharmacokinetic Studies of Methylsalicylatein Rats", Presented at the 3rd Annual Science Fair, Southwest Environmental Health Sciences Center, University of Arizona, Tucson, AZ, October 13, 1997.

127. S. Tannenbaum, H. Boxenbaum and M. Mayersohn, "Allometric Analysis of Organ Extraction Ratios", Presented at the 3rd Annual Science Fair, Southwest Environmental Health Sciences Center, University of Arizona, Tucson, AZ, October 13, 1997.

128. J.S. Valdez, B. Parks, C. Porterfield and M. Mayersohn, "An Examination of Postmortem Redistribution of Selected Model Compounds", Presented at the 3rd Annual Science Fair, Southwest Environmental Health Sciences Center, University of Arizona, Tucson, AZ, October 13, 1997.

129. D. K. Martin and M. Mayersohn, "Development and Validation of an Analytical Method for the Quantitation of Ecgonine in Urine Using GC-MS", Presented at the 3rd Annual Science Fair, Southwest Environmental Health Sciences Center, University of Arizona, Tucson, AZ, October 13, 1997.

130. J. Sukbuntherng, D.K. Martin, Y. Pak and M. Mayersohn, "Characterization of the Properties of Cocaine in Human Blood: The Influence of Gender and Time of Menstrual Cycle", Presented at the 11th Annual Meeting of the American Association of Pharmaceutical Scientists, Boston, MA, November 2-6, 1997.

131. T. Kakkar, D.K. Martin and M. Mayersohn, "Analysis of Methylsalicylate, Ethylsalicylate and Salicylic Acid from biological Fluids", Presented at the 11th Annual Meeting of the American Association of Pharmaceutical Scientists, Boston, MA, November 2-6, 1997.

132. S. Tannenbaum, H. Boxenbaum and M. Mayersohn, "Allometric Analysis of Organ Extraction Ratios", Presented at the 11th Annual Meeting of the American Association of Pharmaceutical Scientists, Boston, MA, November 2-6, 1997.

133. J. Sukbuntherng and M. Mayersohn, "Allometric Relationship of the Metabolic Parameters of Ethanol", Presented at the 11th Annual Meeting of the American Association of Pharmaceutical Scientists, Boston, MA, November 2-6, 1997.

134. S. Tannenbaum and M. Mayersohn, "A Mathematical Approach to Predicting the Approximate Dose and Time of Drug Ingestion in Humans", Presented at the 12th Annual Meeting of the American Association of Pharmaceutical Scientists, San Francisco, CA, November 15-19, 1998.

135. J. Valdez, D.K. Martin and M. Mayersohn, "Analysis of Camphor, Menthol and Methylsalicylate from Human Plasma", Presented at the 12th Annual Meeting of the American Association of Pharmaceutical Scientists, San Francisco, CA, November 15-19, 1998.

136. T. Kakkar, Y. Pak, H.B. Boxenbaum and M. Mayersohn, "Estimation of K_i in a Competitive Enzyme-Inhibition Model: Comparisons Among Three Methods of Data Analysis", Presented at the 12th Annual Meeting of the American Association of Pharmaceutical Scientists, San Francisco, CA, November 15-19, 1998.

137. Y. Pak, T. Kakkar, H.B. Boxenbaum and M. Mayersohn, "Estimation of K_i in a Competitive Enzyme-Inhibition Model: Evaluation of a Minimal Experimental Design", Presented at the 12th Annual Meeting of the American Association of Pharmaceutical Scientists, San Francisco, CA, November 15-19, 1998.

138. S. Tannenbaum and M. Mayersohn, "A Mathematical Approach to Predicting the Approximate Dose and Time of Drug Ingestion in Humans", Presented at the Fourth Annual Biomedical Symposium, The Flinn Foundation, Tucson, AZ, December 11-12, 1998.

139. T. Kakkar, H. Boxenbaum and M. Mayersohn, "Estimation of K_i in a Competitive Enzyme-Inhibitioin Model: Comparisons Among Three Methods of Data Analysis", Presented at the 4th Annual Science Fair, Center for Toxicology, Southwest Environmental Health Sciences Center, Tucson, AZ May 27, 1999.

140. Y. Pak, T.Kakar, H. Boxenbaum and M.Mayersohn, "Estimation of K_i in a Competitive Enzyme Inhibition Model: Evaluation of a Minimal Experimental Design", Presented at the 4th Annual Science Fair, Center for Toxicology, Southwest Environmental Health Sciences Center, Tucson, AZ May 27, 1999.

141. D.Martin, J. Valdez and M.Mayersohn, "The Absorption of Menthol, Camphor and Methyl salicylate in Humans Following Application of Dermal Patches", Presented at the 4th Annual Science Fair, Center for Toxicology, Southwest Environmental Health Sciences Center, Tucson, AZ May 27, 1999.

142. D. Martin and M. Mayersohn, "Characterization of the blood protein binding of bisphenol A (BPA) in rats: influence of strain, gender and age", Presented at the 13th Annual Meeting of the American Association of Pharmaceutical Scientists, New Orleans, LA, November 14-18, 1999.

143. S.Tannenbaum and M. Mayersohn, "A pharmacokinetic/pharmacodynamic analysis of cocaine , cocaethylene (CE) and cocaine plus ethanol (C+E) in the dog: a literature evaluation", Presented at the 13th Annual Meeting of the American Association of Pharmaceutical Scientists, New Orleans, LA, November 14-18, 1999.

144. D. Martin, J. Valdez, J. Boren and M. Mayersohn, "The absorption of menthol, camphor and methyl salicylate in humans following application of dermal patches", Presented at the 13th Annual Meeting of the American Association of Pharmaceutical Scientists, New Orleans, LA, November 14-18, 1999.

145. Y.Pak, T.Kakkar and M.Mayersohn, "Distinguishing between enzyme inhibition mechanisms using simultaneous nonlinear regression (SNLR)", Presented at the 13th Annual Meeting of the American Association of Pharmaceutical Scientists, New Orleans, LA, November 14-18, 1999.

146. Y. Pak and M. Mayersohn, "Allometric Analysis of Morphine Pharmacokinetics", Presented at the Annual Meeting of the American Association of Pharmaceutical Scientists, Indianapolis, IN, October 29- November 2, 2000.

147. Y. Pak and M. Mayersohn, "Reanalysis of the Inhibition of Quinine Drug Metabolism: Determination of Enzyme Kinetic Parameters and Mechanism of Inhibition Using Simultaneous Nonlinear Regression", Presented at the Annual Meeting of the American Association of Pharmaceutical Scientists, Indianapolis, IN, October 29- November 2, 2000.

148. S. Tannenbaum and Michael Mayersohn, "Drugs That Undergo Michaelis-Menten Elimination Can Be Allometrically Scaled: Ethanol as a Prototype Drug", Presented at the Annual Meeting of the American Association of Pharmaceutical Scientists", Denver, CO, October 21-25, 2001.

149. S. Tannenbaum and Michael Mayersohn, "Estimation of the Fractional Conversion of Cocaine to Cocaethylene when Co-Administered with Ethanol", Presented at the 103rd Annual Meeting of the American Society of Clinical Pharmacology and Therapeutics, Atlanta, GA, March 24-27, 2002

150. Y.Pak and M. Mayersohn, "Sensitive and Rapid Isocratic HPLC Method for the Quantitation of Curcumin in Plasma", Presented at the Annual Meeting of the American Association of Pharmaceutical Scientists, Toronto, Ontario, Canada, November 11-15, 2002.

151. Y. Pak, K. Stollberg and M. Mayersohn, "An Animal Model for Fixed Drug Eruptions in Humans: A Case of Antipyrine in the Yucatan Micropig", Presented at the Annual Meeting of the American Association of Pharmaceutical Scientists" Toronto, Ontario, Canada, November 11-15, 2002.

152. Y. Pak, D.K. Martin, K. Stollberg, S. Cannon and M. Mayersohn, "Use of a Porcine Model to Predict Oral Drug Absorption and Disposition in Humans: Antipyrine as a Test Compound", Presented at the Annual Meeting of the American Association of Pharmaceutical Scientists, Toronto, Ontario, Canada, November 11-15, 2002.

153. D.K.Martin, Y. Cai, Y. Pak and M. Mayersohn, "Absolute Oral Bioavailability of Green Tea Components in the Yucatan Micropig", Presented at the Annual Meeting of the American Association of Pharmaceutical Scientists, Toronto, Ontario, Canada, November 11-15, 2002.

154. H. Tang, Y. Pak and M. Mayersohn, "Distribution Pattern of P-glycoprotein (pgp) mRNA expression Along the Small Intestine of the Yucatan Micropig", Presented at the Annual Meeting of the American Association of Pharmaceutical Scientists, Toronto, Ontario, Canada, November 11-15, 2002.

155. T.Sanghvi, N.Ni, M.Mayersohn and S.H. Yalkowsky, "Prediction of Absorption Efficiency", Presented at the Annual Meeting of the American Association of Pharmaceutical Scientists, Toronto, Ontario, Canada, November 11-15, 2002.

156. Y. Pak, R. Patek, D. Zhang, S. Cannon, K. Spiker and M. Mayersohn, "An Examination of the Disposition Kinetics and Bioavailability of Curcumin, A Component of Turmeric, in the Porcine Model", Presented at the Annual Meeting of the American Association of Pharmaceutical Scientists, Salt Lake City, UT, October 27-30, 2003.

157. Y. Pak, R. Patek and M. Mayersohn, " Quantitative HPLC Analysis of Gingerols from Plasma", Presented at the Annual Meeting of the American Association of Pharmaceutical Scientists, Salt Lake City, UT, October 27-30, 2003.

158. Y. Pak, R. Patek and M. Mayersohn, "Determination of *in vitro* Stability of Curcumin in Buffer and in Porcine Blood and Plasma", Presented at the Annual Meeting of the American Association of Pharmaceutical Scientists, Salt Lake City, UT, October 27-30, 2003.

159. Y. Pak, R. Patek and M. Mayersohn, "Characterization of Selected Cytochrome P450 Enzymes Along the Porcine Small Intestine", Presented at the Annual Meeting of the American Association of Pharmaceutical Scientists, Salt Lake City, UT, October 27-30, 2003.

160. H. Tang and M. Mayersohn, "Evaluation of a Swine Model for Assessment of Absolute Oral Drug Bioavailability in Humans: Evaluation of the Literature", Presented at the Annual Meeting of the American Association of Pharmaceutical Scientists, Salt Lake City, UT, October 27-30, 2003.

161. H. Tang, I. Mahmood, H. Boxenbaum and M. Mayersohn, "A New Model for Prediction of Human Clearance by Allometric Scaling", Presented at the Annual Meeting of the American Association of Pharmaceutical Scientists, Salt Lake City, UT, October 27-30, 2003.

162. H. Tang and M. Mayersohn, "A Global Examination of Allometric Scaling and the Prediction of Vertical Allometry for Human Clearance", Presented at the Annual Meeting of the American Association of Pharmaceutical Scientists, Salt Lake City, UT, October 27-30, 2003.

163. H. Tang and M. Mayersohn, "Prediction of Fraction of Drug Removed from the Body During Hemodialysis in Humans Using Unbound Volume of Distribution (Vu)", Presented at the Annual Meeting of the American Association of Pharmaceutical Scientists, Salt Lake City, UT, October 27-30, 2003.

164. H.Tang and M. Mayersohn, "Accuracy of Allometrically-Predicted Pharmacokinetic Prameters in Humans – Role of Species Selection", Presented at the Annual Meeting of the American Association of Pharmaceutical Scientists, Baltimore, MD, November 7-10, 2004.

165. H.Tang and M. Mayersohn, "A Pharmacokinetic Model to Predict Drug Diposition and Concentration-Time Profiles in Hair", Presented at the Annual Meeting of the American Association of Pharmaceutical Scientists, Baltimore, MD, November 7-10, 2004.

166. H. Tang and M. Mayersohn, "Validation of A Simple Pharmacokinetic-Based Model for Predicting the Efficiency of Drug Removal by Hemodialysis", Presented at the Annual Meeting of the American Association of Pharmaceutical Scientists, Baltimore, MD, November 7-10, 2004.

167. Y. Pak, R. Patek, S. Cannon, K. Spiker and M. Mayersohn, "Disposition and Oral Bioavailability of ginger Phytochemical Components in the Yucatan Micropig", Presented at the Annual Meeting of the American Association of Pharmaceutical Scientists, Baltimore, MD, November 7-10, 2004.

168. D. Zhang, Y. Pak, R. Patek and M. Mayersohn, "*In Vitro* Kinetic Study of Gingerols and Shoagol in Aqueous Solution and Body Fluids", Presented at the Annual Meeting of the American Association of Pharmaceutical Scientists, Baltimore, MD, November 7-10, 2004.

169. H. Tang and M. Mayersohn, “A Mathematical Description of the Functionality of Correction Factors Used in Allometry for Predicting Human Drug Clearance”, Presented at the Annual Meeting of the American Association of Pharmaceutical Scientists, Memphis, TN, November 6-10, 2005.

170. H. Tang, A. Hussain, M. Leal, M. Mayersohn and E. Fluhler, “Interspecies Prediction of Human Drug Clearance Based on Scaling Data from One or Two Animal Species”, Presented at the Annual Meeting of the American Association of Pharmaceutical Scientists, San Diego, CA, November 11-15, 2007.

Continuing Education

1. "Principles of Drug Action-Drug Interactions and the Influence of Disease States and Physiological Disorders on Drug Disposition in Man," Twelve Continuing Education Lectures presented to pharmacists, Toronto, Ontario, Canada, November 1971-February 1972.

2. "Influence of Dosage Form on Drug Availability and Response," presented to the Ottawa Pharmacists Association, Ottawa General Hospital, Ottawa, Ontario, October 27, 1972.

3. "Clinical Equivalency of Drugs," presented to Pharmacy Apprenices and Interns, Toronto General Hospital, August 15, 1973.

4. "Role of the Clinical Pharmacokinetics Laboratory in Drug Therapy," presented at the 12th Annual Homecoming Seminar on Pharmacotherapeutics, College of Pharmacy, The University of Arizona, Tucson, Arizona, November 6, 1976.

5. "Physiological Factors Affecting Therapeutic Response," Continuing Education Lecture presented to Pharmacists, Phoenix, Arizona (April 11, 1978) and Tucson, Arizona (April 13, 1978).

6. "Pharmacokinetics," presented at the 25th Annual Conference of Arizona State Society for Medical Technology, Phoenix, Arizona (April 18, 1978).

7. "Pharmacokinetics," Continuing Medical Education Lecture, Phoenix, Arizona, December 9, 1978.

8. "Basic Principles of Pharmacokinetics," presented to the Optometrists Association through the Continuing Education Program of the College of Pharmacy, University of Arizona, Tucson, Arizona, March 3, 1979.

9. "Changes in Drug Disposition with Age and Disease," one hour presentation, the University of Arizona College of Medicine Clinical Seminar Series, "Therapeutics and Pharmacology," December 5, 1981, Tucson, Arizona.

10. "Influence of Age, Hepatic Dysfunction and Renal Disease on Drug Disposition," presented at the 17th Annual Southwestern Clinical Pharmacy Seminar, Tucson, Arizona, February 17-19, 1984.

11. "Geriatric Therapeutics - Changes in Drug Disposition," presented at the 18th Annual Southwestern Clinical Pharmacy Seminar, Tucson, Arizona, February 22-24, 1985.

12. "Aging and Drug Disposition," presented to the Geriatrics Faculty and Staff, University Medical Center, July 6, 1989.

13. "Drug Development and Disposition in Women," 26th Annual Southwestern Clinical Pharmacy Seminar, Tucson, Arizona; February 19-20, 1993.

Current:

Course Director and Instructor, "Principles of Pharmacokinetics and Toxicokinetics for the Industrial Scientist", University of Arizona.

Course Director and Instructor, "Development of Biotechnology Products – Biopharmaceutical and Pharmacokinetic Considerations", University of Arizona.

Course Director and Instructor, "Pharmacokinetics and Pharmacodynamics (PK/PD): Principles and Applications in Non-Clinical Drug Development", American Chemical Society.

Previous:

Member and secretary of the Review Committee to examine the research activities of the Pharmaceutical Chemistry Division of the Health Protection Branch, Health and Welfare Canada, April 17-19, 1974.

Member of the Pharmaceutical Research Committee of the Association of Faculties of Pharmacy of Canada, 1974-1975; 1975-1976.

Examiner, Pharmacy Examining Board of Canada, 1975-1976.

Consultant ("Expert on Drugs") to the Biopharmaceutics Section, Division of Drugs, Food and Drug Administration, Department of Health and Human Services, 1978-1983.

Ad Hoc member, Initial Review Group (Study Section), Drug Abuse Biomedical Research Review Committee, National Institute on Drug Abuse, Department of Health and Human Services, June 22-26, 1981, Washington, D.C.

Member, Special Review Committee and Site Visiting Team of the Alcohol, Drug Abuse and Mental Health Administration, Department of Health and Human Services, University of Southern California, April 22-23, 1982.

Member of the reaction panel, "Collaborative Teaching and Research Between Basic and Applied Sciences: Exploration of the Barriers to Collaboration and and Suggested Approaches to Achieve Collaboration," Subcommittee of the Section of Teachers of Clinical Instruction, American Association of Colleges of Pharmacy, 1982.

Chairman, Volwiler Award Peer Review Panel on Pharmaceutics-Biopharmaceutics, American Association of Colleges of Pharmacy, 1982.

Member, Initial Review Group (Study Section), Drug Abuse Biomedical Research Review Committee, National Institute on Drug Abuse, Department of Health and Human Services:

October 25-27, 1982
February 22-25, 1983
June 21-23, 1983
October 25-28, 1983
February 21-23, 1984
June 26-28, 1984
October 22-25, 1984
February 19-21, 1985
June 18-21, 1985
October 15-17, 1985
February 18-20, 1986
June 22-26, 1986

Member, Contract Review Committee, National Institute on Drug Abuse, Department of Health and Human Services, May 7-8, 1984.

Member, Site Visiting Team, National Institute on Aging, Department of Health and Human Services, Boston University School of Medicine, October 4-5, 1984.

Member, Site Visiting Team, Pharmacological Sciences Review Committee, National Institutes of Health, Department of Health and Human Services, Northwestern University School of Medicine, November 19-21, 1984.

Member, Veterans Administration Medical Service Merit Review Board for Alcoholism and Drug Dependence (Clinical Pharmacology):

November 1, 1985
May 5, 1986
November 10, 1986
April 1, 1987
October 1, 1987
April 6, 1988
September 27, 1988
April 26, 1989

Member, Special Review Committee and Site Visiting Team, National Institute on Drug Abuse, Department of Health and Human Services, Yale University, School of Medicine, November 4-6, 1985.

Member, Special Review Committee, Drug Abuse Biomedical Research Review Committee, National Institute on Drug Abuse, Department of Health and Human Services, June 3, 1987.

Member, Special Review Committee and Site Visiting Team, National Institute on Drug Abuse, Department of Health and Human Services, University of California at San Francisco, School of Medicine, July 22-July 24, 1987.

Member, Special Review Committee, Alcohol, Drug Abuse, and Mental Health Administration Small Business Innovation Research Program, Department of Health and Human Services, November 17, 1987.

Member, Special Review Committee and Site Visiting Team, National Institute on Drug Abuse, Department of Health and Human Services, University of California at San Francisco, School of Medicine, March 21-23, 1988.

Member, Special Review Committee, Alcohol, Drug Abuse and Mental Health Adminstration Small Business Innovation Research Program, Department of Health and Human Services, April 13, 1988.

Secretary, Biotechnology Section, American Association of Pharmaceutical Scientists (1987-88).
Member, Special Review Committee, National Institute on Drug Abuse, Department of Health and Human Services, June 13-14, 1989.

Member, Special Review Committee, Pharmacology Study Section, General Medical Sciences, National Institute of Health, August 1-2, 1990.
Member, Dale E. Wurster Research Award Nominations Committee, American Association of Pharmaceutical Scientists, 1990.

BIOTECH Section representative to the Publications Committee, American Association of Pharmaceutical Scientists, 1990-1991; 1991-1992.

Member, Fellows Selection Committee, American Association of Pharmaceutical Scientsists, Chicago, IL, August 16, 1990.

Member, Discipline Advisory Board for Fulbright Scholar Awards in Life Sciences, Council for the International Exchange of Scholars, Washington, DC.

September 26, 1990
August 9, 1991
October 3, 1991
October 2, 1992

Member, Initial Review Group, National Institute on Drug Abuse, Department of Health and Human Services, October 16-18, 1990.

Member, the McGill International Task Force on Bioequivalence, McGill University, Montreal, Quebec, Canada March 29-30, 1991.

Member, Initial Review Group, National Institute on Drug Abuse, Department of Health and Human Services, June 12-14, 1991.

Member, Special Review Committee (SRCD-10), National Institute on Drug Abuse, Department of Health and Human Services, July 30-31, 1991.

Member, Special Review Committee (SRCD-9), National Institute on Drug Abuse, Department of Health and Human Services, August 1-2, 1991.

Member, Special Review Committee, Site Visiting Team, General Clinical Research Center, Northwestern Hospital and University, National Institutes of Health, Chicago, IL, December 17-18, 1991.

Member, Special Review Committee, Site Visiting Team, Center Grant, Rockefeller University, National Institute on Drug Abuse, Department of Health and Human Services, Rockville, Maryland, July 9-10, 1992.

Member, Fellows Selection Committee, American Association of Pharmaceutical Scientists, Alexandria, Virginia, July 11, 1992.

Member, Special Review Committee, Site Visiting Team, Center Grant, University of California, San Francisco, National Institute on Drug Abuse, Department of Health and Human Services, Rockville, Maryland, August 13-14, 1992.

Member, Concept Review Committee, National Institute on Drug Abuse, National Institutes of Health, Rockville, Maryland; June 30, 1993.

Member, Biochemistry Research Subcommittee Initial Review Group, National Institute on Drug Abuse, National Institutes of Health, Pentagon City, Virginia; October 18-20, 1993.

Member, Special Review Committee (SRCDE), National Institute on Drug Abuse, National Institutes of Health, Pentagon City, Virginia; October 20, 1993.

Faculty Member, Pharmaceutical Manufacturers Association Education and Research Institute Course on Pharmacokinetics, Washington, DC, September 29-30, 1993.

Member, Editorial Advisory Board, Journal of Pharmaceutical Sciences (1994 – 2001)

Course Director and Instructor, “Principles of Pharmacokinetics and Toxicokinetics for the Industrial Scientist" and “Selected Topics in Pharmacokinetics and Toxicokinetics”

1994
April 30- May 5, Tucson, AZ
October 10-14, Somerset, NJ
1995
May 7-11, Tucson, AZ
October 16-20, Somerset, NJ
1996
May 5-9, Tucson, AZ
1997
May 18-22, Tucson, AZ
June 9-13, Presented to GlaxoWellcome, Research Triangle Park, NC
1998
March 2-3, Presented to Roche Biosciences, South San Francisco, CA
March 23-25, Presented to Pfizer, Groton, CT
May 18-22, Tucson, AZ
July 6-8, Presented to Dupont Merck Pharmaceutical Co., Newark, DE

October 12-15, Iselin, NJ
1999
March 16-18, Presented to Pfizer, Groton, CT
May 3-7, Tucson, AZ
July 27-29, Presented to Parke-Davis, Ann Arbor, MI
2000
March 13-15, Presented to Pfizer, Groton, CT
April 10-13, Presented to Schering-Ploug Research Institute, Kenilworth, NJ
May 1-5, Tucson, AZ
June 12-14, DuPont Pharmaceutical Company, Newark, DE
October 16-18, Presented to Pfizer, Groton, CT
Decemer 18-20, Presented to Novartis Pharmaceutical Corporation
2001
March 28-29, Presented to Eisai Inc., Teaneck, NJ
April 23-27, Tucson, AZ
June 18-21, Presented to DuPont Pharmaceutical Company, Newark, DE
July 24-26, Presented to Pfizer, Groton, CT
November 5-9, Tucson, AZ
November 15-16, Presented to Aventis Pharmaceuticals, Bridgewater, NJ
2002
March 14-15, Presented to Pfizer, Groton, CT
March 26-28, Presented to Teva Pharmaceuticals USA, North Wales, PA
April 29- May 3, Tucson, AZ
May 13-15, Presented to Pfizer LaJolla, LaJolla, CA
June 24-28, Presented to Pfizer Ann Arbor, Ann Arbor, MI
November 18-22, Tucson, AZ
2003
April 28- May 2, Tucson, AZ
May 27-29, Presented to Millennium Pharmaceuticals, Cambridge, MA
July 28-30, Presented to Pfizer, Groton, CT
November 17-21, Tucson, AZ
2004
January 19-23, Presented to Pfizer Ann Arbor
May 3-7, Tucson, AZ
July 22-23, Presented to Aventis Pharmaceutical Company
September 30-October 1, 2004, Presented to Pfizer, Groton, CT
2005
April 18-22, Tucson, AZ
May 4-6, Presented to Pfizer, Ann Arbor, MI
June 3-4, Presented to Quest Pharmaceutical Services, Newark, DE
November 7-11, Tucson, AZ
2006
March 13-15, Presented to Novartis, Cambridge, MA
April 17-18, Presented to Encysive, Houston, TX
April 24-26, Presented to Abbott Biotechnology Corporation, Worchester, MA
May 1-5, Tucson, AZ
May 22-24, Centocor, Radnor, PA
September 18-19, Novartis Pharmaceuticals, East Hanover,NJ
2007
March 20-22, Pfizer, Ann Arbor, Michigan
April 23-27, Tucson, AZ
August 14-15, Charles River Laboratories, Sparks, NV
2008
April 28-May 2, Tucson, AZ
2009
April 27-May, Tucson, AZ
August 17-18, Takeda, San Diego, CA
2010
May 2-7, 2010, Tucson, AZ
May 17-21, Amgen, Thousand Oaks, CA

2011
May 2-6, Tucson, AZ
2012
April 30-May 4, Tucson, AZ
July 25-26, Boehringer-Ingelheim, Ridgefield, CT
October 5, GlaxoSmithKline, King of Prussia, PA
2013
November 14-15, Dart Neuroscience, San Diego, CA
2014
June 23-25, Cubist Pharmaceutical Co., Lexington, MA
2015
February 16-17, Eli Lilly, Indianapolis, IN

Member, Initial Review Group, National Institute on Drug Abuse, National Institutes of Health, Health and Human Services, Bethesda, MD, February 13-15, 1995.

Member, Initial Review Group, National Institute on Drug Abuse, National Institutes of Health, Health and Human Services, Rockville, MD, March 20, 1995.

Member, Special Review Committee, National Institute on Drug Abuse, National Institutes of Health, Health and Human Services, Rockville, MD, July 12, 1995.

Member, Advisory Committee for Pharmaceutical Science, (formerly, Generic Drug Advisory Committee) Food and Drug Administration, Department of Health and Human Services, 1995-1998.
September 6-7, 1995
August 15-16, 1996
October 4, 1996 (member of *ad hoc* committee to discuss a specific drug approval problem)
January 27, 1997 (member of *ad hoc* committee on Food Effects and Bioavailability)
December 11-12, 1997
October 22-23, 1998

Member, Committee on Dissolution and Bioavailability, United States Pharmacopeial Convention, 1995-2000.
June 12, 1995
September 18, 1995
September 8-9, 1997
January 21, 1998
May 12-13, 1999

Vice Chair, Biopharmaceutics Committee, United States Pharmacopeial Convention, 2000-2005
August 30-31, 2000
May 15-16, 2001
February 27-28, 2002
September 19, 2002
August 20-21, 2003

Course Director and Instructor, "Bioavailability and Bioequivalence for the Industrial Scientist: Principles, Assessment, Practical and Regulatory Issues", Aspen, CO, August 13-17, 1995.

Member, Special Review Committee, National Institute on Drug Abuse, National Institutes of Health, Health and Human Services, Reston, VA, October 31, 1995.

Member, Special Review Committee, National Institute on Drug Abuse, National Institutes of Health, Health and Human Services, Rockville, MD, November 28-30, 1995.

Member, USP Fellowship Program Review Panel, May 1996.

Member, Special Review Committee, National Institute on Drug Abuse, National Institutes of Health, Health and Human Services, Rockville, MD, June 11, 1996.

Member, Special Review Committee, National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Health and Human Services, Bethesda, MD, June 17-18, 1996.

Member, Special Review Committee, National Institute on Drug Abuse, National Institutes of Health, Health and Human Services, Rockville, MD, November 18-19, 1996.

Expert Scientist, "Expert Meeting on Food-Effect Bioavailability and Bioequivalence Studies", Food and Drug Administration, Health and Human Services, Rockville, MD, January 27, 1997

Member, Initial Review Group, National Institute on Drug Abuse, National Institutes of Health, Health and Human Services, Pentagon City, VA, February 10-12, 1998.

Chairman, Special Emphasis Panel, National Cancer Institute, National Institutes of Health, Health and Human Services, Rockville, MD, May 20-21, 1999.

Member, Initial Review Group, National Institute on Drug Abuse, National Institutes of Health, Health and Human Services, Bethesda, MD, March 1-2, 2000

Member, Contract Review Group, National Institute on Drug Abuse, National Institutes of Health, Health and Human Services, Rockville, MD, October 4, 2002.

Development of Biotechnology Products – Biopharmaceutic and Pharmacokinetic Considerations", San Diego, CA, August 8-10, 2005

"Pharmacokinetics and Pharmacodynamics (PK/PD): Principles and Applications in Non-Clinical Drug Development", American Chemical Society
2006
March 28-29, Atlanta, GA
September 13-14, San Francisco, CA

Member, Special Review Committee, National Institute on Drug Abuse, National Institutes of Health, Health and Human Services, Rockville, MD, December 2, 2008.

Member, National Institutes of Health, National Institute on Drug Abuse, Clinical Research Loan Repayment Program Review

Member, Nominating Committee for the Council of Experts, United States Pharmacopeial Convention, Rockville, MD, 2009

Member, Electorate Nominating Committee, Section on Pharmaceutical Sciences, American Association for the Advancement of Science, February 2010-February 2013.

OTHER PROFESSIONAL ACTIVITIES

Consultant

Novopharm Pharmaceutical Company, Scarborough, Ontario (1972-1976)

Sands Pharmaceutical Company, Toronto, Ontario (1974-1975)

Clinical Institute, Addiction Research Foundation, Toronto, Ontario (1974-1976)

Clinical Pharmacology Department, Medical Products Division, E.I. Du Pont De Nemours (1987-1988)

Environ Corporation, Arlington, Virginia (1992)

Luitpold Pharmaceutical Company (1993-1996)

R. W. Johnson Pharmaceutical Research Institute (1994)

Wyeth-Ayerst Pharmaceutical Company (1994)

Hoechst-Roussel Pharmaceutical Company (1995)

ClinTrials (1995-1997)

Biogen (1996-1997)

T Cell Sciences (1996-1997)
CoCensys (1997)
RJ Reynolds (1997)
Pfizer (1997-1998)
Targacept and Rhone-Poulanc-Rorer (1999))
AnorMed (2000- 2006)
Celgene (2003)
Endo (2003-2004)
Konec (2003-2004)
MDS Capital (2003)
Syntonix (2004)
Salix (2005)
Targacept (2005)

Scientific Reviewer for the Following Journals

Journal of Pharmaceutical Sciences
Journal of Pharmacokinetics and Biopharmaceutics
Life Sciences
Journal of Pharmacology and Experimental Therapeutics
International Journal of Pharmaceutics
Biopharmaceutics and Drug Disposition
Canadian Journal of Pharmaceutical Sciences
The Medical Letter
American Journal of Pharmaceutical Education
Science
Clinical Chemistry
Pharmaceutical Research
Toxicology and Applied Pharmacology
Alcohol
Pharmaceutical Research
Journal of Clinical Psychiatry
Journal of Pharmacy and Pharmacology
Journal of Biochemical and Biophysics Methods

Membership in Professional and Scientific Associations

Rho Chi Pharmaceutical Honor Society
American Association of Pharmaceutical Scientists
American Association of Colleges of Pharmacy
American Association for the Advancement of Science
American Society for Clinical Pharmacology and Therapeutics
American Society of Pharmacology and Experimental Therapeutics

ATTACHMENT B

ATTACHMENT B

Exhibit No.	Description
1001	U.S. Patent No. 9,393,208, *Method for Delivering a Pharmaceutical Composition to Patient in need thereof* (filed Dec. 28, 2015) (issued Jul. 19, 2016)
1004	U.S. Patent No. 6,926,907, *Pharmaceutical Compositions for the Coordinated Delivery of NSAIDS* (filed May 31, 2002) (issued Aug. 9, 2005)
1005	U.S. Patent No. 8,557,285, *Pharmaceutical Compositions for the Coordinated Delivery of NSAIDS* (filed Aug. 23, 2011) (issued Oct. 15, 2013)
1006	Howden, *Review Article: Immediate-Release Proton-Pump Inhibitor Therapy – Potential Advantages*, 22 (Suppl. 3) ALIMENT. PHARMACOL. THER. 25 (2005)
1007	U.S. Patent No. 5,877,192, *Method for the Treatment of Gastric Acid-Related Diseases and Production of Medication using (-) Enantiomer of Omeprazole* (filed Apr. 11, 1997) (issued Mar. 2, 1999)
1009	EC-Naprosyn prescribing information (Jan. 2007)
1010	Zegerid approval letter and prescribing information (2004)
1011	Goldstein et al., 116 *A Single Tablet Multilayer Formulation of Enteric-Coated Naproxen Coupled with Non-Enteric Coated OMEPRAZOLE is Associated with a Significantly Reduced Incidence of Gastric ulcers vs. Enteric-Coated Naproxen: A Prospective, Randomized, Double-Blind Study*, 134(4) GASTROENTEROLOGY A19 (2008)

Exhibit No.	Description
1012	Hochberg et al., *A Novel, Single-Tablet Formulation that Delivers Immediate-Release Omeprazole Followed by Enteric-Coated (EC) Naproxen Significantly Reduces the Incidence of Gastric Ulcers Compared with EC Naproxen Alone: Results of a Prospective, Randomised, Double-Blind, 6-Month Study including Patients with OA and RA*, EULAR (2008)
1013	U.S. Patent No. 9,220,698 Prosecution History Excerpt: Amendment C and Response to Final Office Action (Jan. 30, 2013)
1014	Wolfe et al., *Acid Suppression: Optimizing Therapy for Gastroduodenal Ulcer Healing, Gastroesophageal Reflux Disease, and Stress-Related Erosive Syndrome*, 118 GASTROENTEROLOGY S9 (2000)
1015	Bell et al., *Appropriate Acid Suppression for the Management of Gastro-Oesophageal Reflux Disease*, 51(suppl. 1) DIGESTION 59 (1992)
1016	Hassan-Alin et al., *Lack of Pharmacokinetic Interaction between Esomeprazole and the Nonsteroidal Anti-Inflammatory Drugs Naproxen and Rofecoxib in Healthy Subjects*, 25(11) CLIN. DRUG INVEST. 731 (2006)
1017	Khosravan et al., *Pharmacokinetic Interactions of Concomitant Administration of Febuxostat and NSAIDs*, 46 J. CLIN. PHARMA. 855 (2006)
1018	Jung et al., *Steady-State Pharmacokinetics of Enteric-Coated Naproxen Tablets Compared with Standard Naproxen Tablets*, 16(6) CLIN. THER. 923 (1994)
1019	Davies et al., *Clinical Pharmacokinetics of Naproxen*, 32(4) CLIN. PHARMACOKINET. 268 (1997)
1021	Dan M. Roden, *Principles of Clinical Pharmacology, in* HARRISON'S PRINCIPLES OF INTERNAL MEDICINE 13 (Dennis L. Kasper et al. eds., 16th ed. 2005)

Exhibit No.	Description
1022	Malcolm Rowland & Thomas N. Tozer, CLINICAL PHARMACOKINETICS (3d ed. 1995)
1023	Clissold et al., *Omeprazole A Preliminary Review of its Pharmacodynamic and Pharmacokinetic Properties, and Therapeutic Potential in Peptic Ulcer Disease and Zollinger-Ellison Syndrome*, 32 DRUGS 15 (1986)
1024	U.S. Patent No. 7,411,070, *Form of S-Omeprazole* (filed Sept. 25, 2003) (issued Aug. 12, 2008)
1025	U.S. Patent No. 5,714,504, *Compositions* (filed Jan. 23, 1995) (issued Feb. 3, 1998)
1026	Michael Mayersohn, *Principles of Drug Absorption, in* MODERN PHARMACEUTICS 21 (3d ed. 1996)
1027	Howden, *Clinical Pharmacology of Omeprazole*, 20(1) CLIN. PHARMACOKINET. 38 (1991)
1028	Lind et al., *Esomeprazole Provides Improved Acid Control vs. Omeprazole in Patients with Symptoms of Gastro-Oesophageal Reflux Disease*, 14 ALIMENT. PHARMACOL. THER. 861 (2000)
1029	Regårdh et al., *Pharmacokinetics and Metabolism of Omeprazole in Animals and Man – An Overview*, 20(suppl. 108) SCAND. J. GASTROENTEROL 79 (1985)
1030	Vimovo prescribing information (Dec. 2014)
1031	*Target*, WEBSTER'S NEW WORLD COLLEGE DICTIONARY (4th ed. 2005)
1032	*Target*, THE AMERICAN HERITAGE DICTIONARY OF THE ENGLISH LANGUAGE (4th ed. 2006)
1033	*Target*, MERRIAM-WEBSTER'S CONCISE DICTIONARY (Large print ed. 2006)

Exhibit No.	Description
1042	Goldlust et al., *Nighttime Dosing of Omeprazole Immediate-Release Oral Suspension Rapidly Decreases Nocturnal Gastric Acidity*, 99(10) AM. J. GASTROENTEROLOGY S39 (2004)
1043	Nexium Prescribing Information (Feb. 2001), available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2001/21153lbl.pdf (last visited Nov. 22, 2017)
1044	Prilosec Prescribing Information (June 2002), available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2002/19810s074lbl.pdf (last visited Nov. 22, 2017)
1045	Opinion & Order, *Horizon Pharma, Inc. v. Dr. Reddy's Labs., Inc.*, No. 15-cv-3324-SRC-CLW (consolidated) (D.N.J. Nov. 14, 2017), ECF No. 82
1046	U.S. Patent No. 9,393,208 Prosecution History Excerpts