UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF CALIFORNIA

PAR PHARMACEUTICALS, INC. AND HANDA PHARMACEUTICALS, LLC, Plaintiffs, v. TAKEDA PHARMACEUTICAL CO., LTD., TAKEDA PHARMACEUTICALS NORTH AMERICA, INC., TAKEDA PHARMACEUTICALS AMERICA, INC., AND TAKEDA PHARMACEUTICALS U.S.A., INC., Defendants.	Case No. 5:13-CV-1927 LHK (PSG) **DECLARATION OF MICHAEL MAYERSOHN, PH.D. IN SUPPORT OF DEFENDANTS' CLAIM CONSTRUCTION BRIEF** Date: June 12, 2014 Time: 1:30 p.m. Courtroom: 8, 4th Floor Judge: Hon. Lucy H. Koh
TAKEDA PHARMACEUTICAL CO., LTD., TAKEDA PHARMACEUTICALS U.S.A., INC., AND TAKEDA PHARMACEUTICALS AMERICA, INC., Plaintiffs, v. IMPAX LABORATORIES, INC., Defendant.	Case No. 5:13-CV-2416 LHK (PSG)
TAKEDA PHARMACEUTICAL CO., LTD., TAKEDA PHARMACEUTICALS U.S.A., INC., AND TAKEDA PHARMACEUTICALS AMERICA, INC., Plaintiffs, v. TWI PHARMACEUTICALS, INC., Defendant.	Case No. 5:13-CV-2420 LHK (PSG)

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I, Michael Mayersohn, Ph.D., declare as follows:

1. I submit this declaration in support of the claim construction brief submitted by defendants Impax Laboratories, Inc., Par Pharmaceutical, Inc., Handa Pharmaceuticals LLC, and TWi Pharmaceuticals, Inc. (collectively, "Defendants").

2. In particular, I submit this declaration to provide relevant background information regarding the technology at issue in U.S. Patent No. 8,173,158 (the "'158 patent"),[1] and to set forth my opinions regarding the meaning of the disputed claim terms from the perspective of a person of ordinary skill in the pertinent art at the relevant time.

I. QUALIFICATIONS

3. The following is a brief summary of my qualifications. My qualifications are more fully set forth in my curriculum vitae, attached as Exhibit B.

4. I was awarded the degree of Bachelor of Science in Pharmacy in 1966 from Columbia University College of Pharmaceutical Sciences and a Ph.D. in Pharmaceutics from the School of Pharmacy, State University of New York at Buffalo in 1971.

5. I was licensed by the State of New York to practice pharmacy in 1967 and practiced pharmacy in Buffalo, New York from that time until 1971.

6. Following receipt of my doctoral degree, I became an Assistant Professor in the Faculty of Pharmacy at the University of Toronto in Canada and became an Associate Professor there in 1975.

7. I have been a faculty member of the College of Pharmacy at the University of Arizona in Tucson since 1976, starting as an Associate Professor. I have been a full Professor since 1983.

[1] A copy of the '158 patent is attached as Exhibit A.

8. I have been a member of the Interdisciplinary Graduate Program in Pharmacology and Toxicology, the Center for Toxicology, and the Southwest Environmental Health Sciences Center, all of which are at the University of Arizona.

9. My research interests include the general area of pharmaceutical sciences with a specialty in pharmaceutics, biopharmaceutics and pharmacokinetics, including (a) the examination of the relationship between the physical and chemical characteristics of a drug and its dosage form and the fate and performance of that drug in the body, and (b) the development of rigorous mathematical models to quantitate the kinetic processes of drug absorption, distribution, excretion, metabolism, and clinical or pharmacological response.

10. I have maintained an active research program, which has been funded by national, state and private agencies. This program has involved numerous research projects and the supervision of many graduate students, post-doctoral fellows and technicians.

11. I have conducted research studies *in vitro* to characterize the physical and chemical properties of drugs and drug dosage forms including dissolution rates, stability and binding to other compounds. These studies have included an examination of the properties of a variety of drug dosage forms, including immediate and non-immediate release oral formulations.

12. I have also conducted *in vitro* and *in vivo* studies to characterize the plasma protein binding of drugs and their metabolic properties in the presence of varying enzymatic preparations.

13. I have conducted *in situ* and whole animal studies (in mice, rats, dogs and pigs) to characterize the pharmacokinetics and pharmacodynamics of drugs and their metabolites.

14. I have conducted clinical studies in human subjects to evaluate the pharmacokinetics of selected drugs and their metabolites. In all of the above studies, I developed selective, sensitive and reliable quantitative analytical methods.

15. In addition, I have performed "theoretical" or *in silico* experiments using simulation and other mathematical/computer techniques in order to answer specific questions concerning the disposition or interaction of drugs.

16. I am a member of several professional societies and organizations, including the American Association of Pharmaceutical Scientists, the American Society for Clinical Pharmacology and Therapeutics, and the American Society of Pharmacology and Experimental Therapeutics.

17. I have reviewed and continue to review publications for several peer-reviewed journals, including the Journal of Pharmaceutical Sciences and Pharmaceutical Research.

18. I have been a member of numerous national and state grant review agencies (National Institutes of Health, Veterans Administration, *etc.*) for which I reviewed research grant applications.

19. I have published over 160 original research publications, 18 book chapters and symposia, and 15 professional/educational publications. I have given more than 65 invited presentations and contributed to over 160 submitted presentations.

20. During the years 1995-1998, I was a member of the Food and Drug Administration ("FDA") Advisory Committee for Pharmaceutical Sciences (formerly, the Generic Drug Advisory Committee). This Committee advises the FDA in setting standards for bioavailability, bioequivalence, and in resolving matters of scientific interest to the agency.

21. I served one five-year term as a member of the Dissolution and Bioavailability Expert Committee of the United States Pharmacopoeia and a subsequent five-year term as Vice Chair of the same Committee, whose name was changed to the Biopharmaceutics Expert Committee. This Committee sets standards for dissolution testing and for drugs that are incorporated into individual monographs.

22. I am also the Course Director and Instructor of "Principles of Pharmacokinetics and Toxicokinetics for the Industrial Scientist," which is sponsored by the University of Arizona and given

to pharmaceutical scientists. This course has been successfully offered since 1994 and has enrolled well over 600 scientists. I am also a Course Director of similar on-site courses offered to the pharmaceutical industry and which have enrolled well over 1000 scientists.

23. I am being compensated for my work in this case at my standard rate of $800 per hour. My compensation is not affected by the outcome of this matter.

II. BACKGROUND

24. The '158 patent generally relates to methods of treating heartburn, acid reflux, or gastroesophageal reflux disease by administering a pharmaceutical composition containing small organic molecules called "proton pump inhibitors" ("PPIs"). In particular, the '158 patent relates to the use of a pharmaceutical composition comprising a specific PPI called dexlansoprazole. PPIs help to treat these conditions by shutting down proton pumps in the stomach that produce acid, thereby reducing the amount of acid in the stomach.

25. PPIs usually are administered orally, in the form of a tablet or a capsule containing granules that encapsulate the PPI. Because PPIs are chemically unstable in the acidic environment of the stomach, they must be protected from stomach acid. Drug manufacturers accomplish this by combining the PPI with various stabilizers and coatings, resulting in a drug formulation that has an outer layer (referred to as the "enteric coat") that protects the PPI from stomach acid. [2] The enteric coat allows the drug to pass through the stomach intact, ending up in the small intestine, where the PPI can be released and absorbed by the body.

26. The reason the enteric-coated drug formulation can pass through the stomach and protect the PPI from acid-degradation is because the enteric coat is sensitive to the pH of its environment. This pH-sensitivity allows the enteric coat to remain intact or undissolved in the highly

[2] A typical representation of such a layered formulation is shown in paragraph 53 of the Sinko declaration.

acidic environment of the stomach, but permits the coating to dissolve in the less acidic environment of the small intestine, thereby allowing the encapsulated PPI to be released from the drug formulation in the small intestine where it can then be absorbed.

27. Various PPIs are currently available on the market, with a number available in both branded and generic formulations. The first PPI that became commercially available, omeprazole, was sold under the brand name Prilosec® and has been on the market since 1989. Other PPIs, such as lansoprazole (which is sold under the brand name Prevacid®) and esomeprazole (a single enantiomeric form of the racemic drug omeprazole, sold under the brand name Nexium®) subsequently became available. Prevacid® (generically known as lansoprazole) is sold by Takeda, and lost its patent protection in 2009. Dexilant®, the drug at issue in this case, is a variant (*i.e.*, a single enantiomer) of lansoprazole and another member of the closely related PPI family of drugs. Dexilant® became commercially available in 2009, the same year Takeda lost its patent protection on its Prevacid® drug product.

28. The pharmaceutical composition disclosed in the '158 patent is made up of two types of enteric-coated particles comprising the PPI dexlansoprazole. ('158 Pat. Claim 1.) The first particle has an enteric coating that must release the PPI at a pH of about 5.0 to about 5.5. (*Id.*) The second particle has an enteric coating that must release the PPI at a pH of about 6.2 to about 6.8. (*Id.*) Moreover, the formulation must be therapeutically effective whether the dosage form is administered to a patient who is on an empty stomach (that is, under fasting conditions), or has eaten at various times (that is, under fed conditions). (*Id.*)

29. The '158 patent discloses three strengths of the pharmaceutical composition (30 mg, 60 mg, and 90 mg) in Example 1, and the use of one of those strengths, the 90 mg, in Example 2. While Tables 1, 2 and 3 purport to describe the compositions for each of these pharmaceutical formulations, they do not in fact provide any specific example of a particular formulations. Rather, Table 1 lists a

range of percentages of polymers that may be used in the enteric coatings of the granules, and Table 2 lists ranges of the various excipients, without even naming what the actual excipients should be. For example, Table 1, states that the "proportion of TAK-390 [dexlansoprazole] dose" in granule "LL" can be 15%-50% and in granule "H" can be between 50%-85% of the total dose. Similarly, Table 2 lists ranges for the ingredients in a composition for "Granules-LL," and Table 3 lists ranges for the ingredients in a composition for "Granules-H." The ranges for these ingredients are quite broad and the actual ingredient is not identified specifically, but only by function. For example, the amount of "diluent" can be between 5.0 and 30.0 percent, and no specific diluent is listed. Thus, Example 1 discloses various ranges for the types of ingredients used in the formulations, resulting in numerous possible compositions for each formulation, such that the exact composition of the formulation used in Example 2 cannot be ascertained from the information provided.

30. The '158 patent includes an example, Example 2, that discloses clinical studies performed on patients using the 90 mg strength of the pharmaceutical composition that includes these two types of enteric-coated particles comprising dexlansoprazole. ('158 Pat. at 23:36-27:17.) In particular, the pharmaceutical composition was administered to healthy adult subjects under fasting conditions (after an overnight fast), as well as under three fed conditions: 5 minutes before dosing, 30 minutes before dosing, and 30 minutes after dosing. ('158 Pat. at 24:1-6, Table 4.) Both the plasma concentrations of dexlansoprazole as a function of time, as well as the pHs of the stomach fluids of the subjects, were recorded. (*Id.* at 24:11-45, Tables 5-7.) Based on these collected data, various "pharmacokinetics" and "pharmacodynamics" parameters were then calculated and mathematically analyzed to determine the effect of food and the timing of food on the therapeutic effectiveness of the pharmaceutical formulation. (*Id.*)

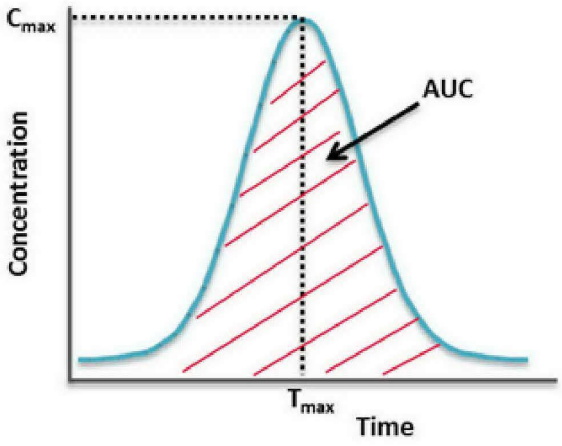
31. "Pharmacokinetics" (sometimes abbreviated as "PK") is a pharmaceutical science that deals with the determination of absorption, distribution, metabolism, and excretion of drugs

administered to the body. It is often described as examining the "effect of the body on the drug." This is in contrast to pharmacology, which is a qualitative examination of the "effect of the drug on the body." A more quantitative understanding of the relationship between pharmacokinetics and pharmacology is referred to as "pharmacodynamics" (sometimes abbreviated as "PD"), in which one examines the time-course of the effect of the drug on the body (*i.e.*, the pharmacological or clinical response) by quantitatively studying the time-course of the response and its relationship with the plasma concentration-time profile.

32. These two areas of study, PK and PD, are inextricably connected. The pharmacodynamic properties of a drug are often studied in combination with its pharmacokinetic properties to develop so-called pharmacokinetic/pharmacodynamic (PK/PD) models of the drug in individuals and populations of patients. The pharmacokinetic and pharmacodynamic events overlap. The driving force for the pharmacodynamic events following drug dosing is generally the concentration of drug in the blood (or plasma) or the rate at which those concentrations change. It is for this reason that there is interest in being able to describe the plasma concentration-time profile of a drug following its administration to a patient.

33. Following the administration of a drug, for example after oral ingestion, frequent blood samples are obtained for a time sufficient to characterize the entire plasma concentration-time profile. The blood samples or a fluid derived from blood (*e.g.*, plasma or serum) are treated and subjected 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 fluid. The resulting concentration-time profiles are then analyzed, either using a computer-based method to obtain a mathematical model that best describes the data, or by a model-independent method. In either approach, estimates of the values of the pharmacokinetic parameters of interest are obtained.

34. A stylized single-dose plasma concentration-time profile resulting from oral dosing is depicted below. As shown in the figure, the maximum concentration (C_{max}) achieved is at the peak of the curve, and the time corresponding to that maximum is referred to as T_{max}. Also shown in the figure is the total area under the curve (AUC), which is related to the extent of absorption or total exposure to the drug. The latter value is a measure related to the amount of drug that gets absorbed into the patient's blood.



35. The pharmacokinetic parameters C_{max}, T_{max}, and AUC are reported in Example 2 of the '158 patent for the fasted state as well as for the three fed states noted above. ('158 Pat. at 24:11-28; 24:62-25:12 and Tables 4, 5 and 6.) These parameters are then analyzed and compared to determine whether there are statistically significant differences between these parameters in the fasted and various fed states. (*Id.*) In addition, the '158 patent discloses the calculation of two pharmacodynamic parameters to determine the effect of food: "mean intragastric pH" and "% time pH>4 over 24 hours post dose." (*Id.* at 24:34-38; 25:13-27 and Table 7.) The "mean intragastric pH" parameter refers to the statistical mean determined from the pH measurement data. The "% time" parameter refers to the percentage of time that the pH of the stomach fluid is greater than pH 4, over a period of 24 hours after the patient is dosed.

III. OPINIONS AND BASES THEREFORE

A. Person of Ordinary Skill in the Art

36. For purposes of my analysis, I have considered how the terms of the '158 patent would have been understood from the viewpoint of a person of ordinary skill in the art. In my opinion, the art relevant to the claimed subject matter is pharmaceutical drug development and analysis, in particular, clinical pharmacokinetics and clinical pharmacodynamics. A person of ordinary skill in the art would have had a high level of education and skill, including an M.D., a Ph.D. or a Pharm.D. in pharmaceutical sciences, medicine, or a related field, and two years of work experience in the appropriate field, or alternatively, a Bachelor's or Master's Degree and a commensurately greater number of years of experience in the appropriate field.

37. I have been asked by counsel to read the claim terms from the perspective of a person of ordinary skill in the art in October 2007, which I understand is the date on which the earliest application that led to the '158 patent was filed. As of October 2007 and at all times since, I would have qualified as a person of at least ordinary skill in the art.

B. Construction of Disputed Claim Terms of the '158 Patent

38. I understand that Takeda has asserted claims 1-8 of the '158 patent against the Defendants in this case. Claims 1, 2, 3 and 4 are representative, and read as follows:

> 1. A method of treating heartburn, acid reflux or gastroesophageal reflux disease in a patient in need of treatment thereof, the method comprising the steps of: a) obtaining a pharmaceutical composition comprising dexlansoprazole from a group of pharmaceutical compositions comprising proton pump inhibitors; and b) administering to a patient suffering from heartburn, acid reflux or gastroesophageal reflux, **regardless of whether the patient is under fasted or fed conditions**, a therapeutically effective amount of the pharmaceutical composition obtained in step a), wherein the pharmaceutical composition comprises: (i) a first solid particle, wherein said first solid particle comprises dexlansoprazole and a first enteric coating, wherein the **first enteric coating releases the proton pump inhibitor from the solid particle at a pH of about 5.0 to about 5.5**; and (ii) a second solid particle, wherein said second solid particle comprises dexlansoprazole and a second enteric coating, wherein the **second enteric coating releases the proton pump inhibitor from the solid particle at a pH of about 6.2 to about 6.8**; wherein the first solid particle comprises from

about 15% to about 50% by weight of the pharmaceutical composition and the second solid particle comprises from about 50% to about 85% by weight of the pharmaceutical composition.

2. The method of claim 1, wherein the first **enteric coating has a pH of about 5.5**.

3. The method of claim 1, wherein the **second enteric coating has a pH of about 6.75**.

4. The method of claim 1, **wherein the changes in pharmacokinetics** after administration to the patient of a single dose of a therapeutically effective amount of the pharmaceutical composition comprising dexlansoprazole **under fasting or fed conditions does not produce statistically significant changes in intragastric pH**.

('158 patent, Claims 1-4 (disputed phrases bolded).)

1. "regardless of whether the patient is under fasted or fed conditions" (claim 1)

Defendants' Construction	Takeda's Construction
Regardless of whether the patient is dosed after an overnight fast, within 5 minutes before a meal, within 30 minutes before a meal, or within 30 minutes after a meal.	Without regard to food.

39. I understand that Defendants originally proposed a construction that defined "fasted or fed conditions" with respect to whether and when a patient has eaten a meal: "whereas the same therapeutic effect is achieved whether the patient has eaten a meal, will eat a meal, or is on an empty stomach." In my opinion, Defendants' original proposed definition was consistent with the specification of the '158 patent, which includes experimental results for several fasted and fed conditions, which vary depending on whether and when the patient has consumed a high-fat breakfast. ('158 Pat. at 23:36-27:17.) Specifically, the '158 patent includes results for testing conducted on patients "dosed under fasting conditions," "dosed 30 min after the start of a high-fat breakfast," "dosed 5 min before a high-fat breakfast," and "dosed 30 min before a high-fat breakfast." (*Id.* at Table 4.) Defendants' original proposed definition covered these various fasted and fed conditions, and further required that the administration of the pharmaceutical dosage form under these conditions should result in the same therapeutic effect.

40. I also understand that in an effort to construe claim terms appearing in different claims in the same way, Defendants have generally agreed to adopt Takeda's proposed construction for "fasting or fed conditions" in connection with its construction of that term in claim 4 of the '158 patent. While Takeda has proposed to define "fasted or fed conditions" in claim 1 to mean "without regard to food," Takeda has defined a nearly identical term – "fasting or fed conditions" – entirely differently in claim 4. (*Compare* Takeda Br. at 14 *with* Takeda Br. at 23.) Specifically, in connection with claim 4, Takeda defines "fasting conditions" to mean "dosing after an overnight fast," and "fed conditions" to mean "dosing within 30 minutes before or after a meal" (*id.* at 23), with the latter covering two of the three "fed" conditions disclosed in the '158 specification. (*Id.* at 24.) But the only difference between the "fast/fed" terms appearing in claims 1 and 4 is the replacement of "fast*ed*" with "fast*ing*" in claim 4. There is no reason why they should be different: the '158 patent treats these terms as identical, and persons of ordinary skill in the art would have understood them to be identical as well. ('158 Pat. at Fig. 1, Fig. 2, 4:1-4, 24:63-25:65.) Accordingly, the construction for "fasted or fed conditions" in claim 1 should be the same as that for "fasting or fed conditions" in claim 4.

41. I also understand that Defendants have slightly modified Takeda's construction for "fasting or fed conditions" to recite each of the three "fed" conditions disclosed in the '158 specification rather than lumping them together as in Takeda's proposal. Separately reciting each condition is appropriate in the context of claim 1, because the plain meaning of claim 1 requires a therapeutically effective amount of the PPI to be administered irrespective of whether the patient has been dosed under any of the fasted or fed conditions. (Exhibit C defines "regardless" as "without regard to, irrespective of.") In other words, the "regardless" term in claim 1 requires a therapeutic effect to be achieved *no matter which state the patient is in*: 30 minutes after eating, 5 minutes before eating, or 30 minutes before eating. ('158 Pat. at Table 4.)

42. Consistent with this requirement, Defendants' proposed definition separately identifies the fasted state, the fed state after the start of a meal, and the two fed states before the start of a meal, to indicate that the therapeutic results must be achieved no matter which of these states the patient is in when dosed with the drug. This construction is consistent with the specification, which defines "fasted" to mean "after an overnight fast ('158 Pat. at 23:63-24:4), and further defines three "fed" conditions: patient is dosed within 30 minutes after a meal, within 5 minutes before a meal, or within 30 minutes before a meal. ('158 Pat. at Table 4.) This construction is also consistent with the patent's statements distinguishing the invention from previously-available PPIs, which according to the patent should be taken shortly before eating a meal. ('158 Pat. at 2:4-15, 9:66-10:34.)

2. "enteric coating releases the proton pump inhibitor from the solid particle at a pH of" "about 5.0 to about 5.5" or "about 6.2 to about 6.8" (claim 1)

Defendants' Construction	Takeda's Construction
Enteric coating releases all of the proton pump inhibitor from the solid particle at a pH of [no less than 4.95 to a pH of no more than 5.55]/ [no less than 6.15 to a pH of no more than 6.85].	The target pH for dissolution of the enteric coating is approximately 5.0 to approximately 5.5 or approximately 6.2 to approximately 6.8.

43. Defendants' proposed construction has two parts: (1) the enteric coating must release all of the proton inhibitor, and (2) the pH at which the release takes place must be "about 5.0 to about 5.5" or "about 6.2 to about 6.8," where "about" is defined to mean 0.05 pH units. Once this definition of "about" is applied to the pH levels recited in the claims, the pH ranges become "no less than 4.95 to no more than 5.55" and "no less than 6.15 to no more than 6.85." In my opinion, Defendants' proposed construction is consistent with the intrinsic and extrinsic evidence.

a. "enteric coating releases the proton pump inhibitor . . at[3] a pH of"

44. Defendants' proposed construction requires that the enteric coating surrounding the PPI actually releases its PPI at or above a particular pH. This construction is consistent with the intrinsic evidence, in particular the claim language, which requires *release* of the PPI: "enteric coating *releases* the proton pump inhibitor . . . at a pH of . . . ." ('158 Pat. at Claim 1.) Defendants' construction is also consistent with the specification: "wherein the first enteric coating *releases* the active agent from the solid particle at a pH of about 5.0 to about 5.5," and "wherein the second enteric coating *releases* the active agent from the solid particle at a pH of about 6.2 to about 6.8," "[t]he second enteric coating surrounds the core and *releases* the active agent from the solid particle at a pH of about 6.2 to about 6.8." ('158 Pat. at 2:36-45; 12:24-36 (emphases added).)

45. In contrast, Takeda's proposed construction reads the "release" requirement entirely out of the claims while at the same time reading into the claims a new requirement, "target pH for dissolution." Instead of requiring, as the claim recites, that the PPI be released from the enteric coating at or above a particular pH, Takeda's construction only looks to see *what the enteric coat is made of*. If the enteric coat is made of a material that is designed to dissolve at a pH that corresponds to the claimed threshold pHs, then under Takeda's construction, the formulation falls within the scope of the claims. But enteric coats do not necessarily dissolve at the exact target pH at which they are supposed to dissolve. Rather, as discussed in detail in Dr. Sinko's declaration, the release of PPIs is affected by many more factors in addition to the pH, such as thickness and uniformity of the enteric coating, the nature of other excipients in the enteric coat, and the testing conditions. Thus, Takeda's proposed construction *entirely eliminates* the "release" requirement from the claims.

[3] I agree that the entirety of release need not occur "at" a particular pH. Defendants' proposed construction was intended to cover release "at or above" a particular pH, which as Takeda's expert, Dr. Sinko, also agrees, is the correct phraseology. (Sinko Decl. ¶¶ 50, 108, 119.) Thus, the phrase "at a pH of" as used in Defendants' proposed construction should be read to mean "at or above a pH of."

46. Defendants' construction also requires the release of *all* of the PPI contained within the enteric coating after the claimed threshold pH is reached, as modified by the word "about." Thus, under Defendants' proposed construction, the PPI must not begin to release below the recited threshold pHs. Accordingly, for the first pH term, the release must begin at a pH of no less than "about 5.0" and continue until completed, and for the second pH term, the release must begin at a pH of no less than "about 6.2" and continue until completed.

47. Without such a requirement, the bottom-end pH values recited in the claims become meaningless. As discussed above, the release of PPIs is affected by many more factors in addition to the pH, such as thickness and uniformity of the enteric coating, the nature of other excipients in the enteric coat, and the testing conditions. Thus, unless the claimed pH-dependent release is limited to require that the release begin only after the claimed threshold pH is reached, release at *any pH* would fall within the scope of the claims, if the other conditions are carefully manipulated. For example, the test conditions may be set in such a way that release occurs substantially below the claimed threshold pH, rendering the pH limitation meaningless.

48. Moreover, whether release below the "target" pH is covered by the claims is not relevant here, as the pH values in the claims are not the target pHs, as discussed above. The claims merely require that the drug begin releasing once a particular pH value is reached. Because the claims are not directed to the target pH, it is not necessary to further require that the claims cover release below the target pH. To the extent any release below the recited pH ranges is covered by the claims, it is that which is included in the expansion of the range by the term "about," as discussed in more detail below, i.e. ± 0.05. Otherwise, the recited pH values would be read out of the claims.

b. "about 5.0 to about 5.5" and "about 6.2 to about 6.8"

49. A construction of "about" to mean "approximately" as Takeda suggests, does nothing to illuminate the meaning of the term, and instead merely replaces one vague term for another. Even

Takeda seems to recognize this, as its expert Dr. Sinko offers an alternative definition for "about," to mean "0.2 pH units." (Sinko Decl. at p. 39, n. 8.) But Dr. Sinko's alternative construction is not supported by any scientific source, and in fact, one having ordinary skill in the art would have known at the time that pH values could be measured much more accurately than 0.2 pH units.

50. In particular, the United States Pharmacopeia (the "USP") supports Defendants' "+/- 0.05 pH units" construction. The long-established and well-regarded USP is "a book of public pharmacopeial standards," and "contains standards for chemical and biological drug substances, dosage forms, and compounded preparations, excipients, medical devices, and dietary supplements," and was and is routinely relied upon by persons of skill in the art in the relevant fields of the '158 patent, attached as Exhibit D. According to the USP's chapter on dissolution, the buffer stage dissolution medium for testing delayed-release dosage forms, a pH 6.8 phosphate buffer, is prepared by mixing and adjusting component chemicals "to a pH of 6.8 ± 0.05." (Exhibit E at DEX1668274.) The same chapter also describes the preparation of a dissolution medium for immediate release dosage forms as including the step of "adjust[ing] the solution so that its pH is within 0.05 unit of the specified pH". (*Id.* at DEX1668273; *see also* Exhibit F at PARDEX0001290.) Thus, the USP recognizes that the pH for release of an active agent from a dosage form should be measured to an accuracy of ± 0.05, and persons of ordinary skill in the art at the relevant time would have agreed with this accuracy level as well.

3. "enteric coating has a pH of" "about 5.5" or "about 6.75" (claims 2 and 3)

Defendants' Construction	Takeda's Construction
Enteric coating has a pH of [no less than 5.45 to no more than 5.55]/[no less than 6.70 to no more than 6.80].	The target pH for dissolution of the enteric coating is approximately 5.5 or approximately 6.75

51. Each of claims 2 and 3 is simply directed to an enteric coating that *has* a particular pH: claim 2 is directed to an enteric coating that "has a pH of about 5.5," and claim 3 is directed to an enteric coating that "has a pH of about 6.75." In my opinion, the requirement that a solid compound,

such as an enteric coating, "have" a pH, is nonsensical, as pH is defined as a measure of the acidity or basicity of an aqueous solution, not a solid compound. My best understanding of the plain meaning of a compound "having" a pH is that measuring the pH of a solution of the compound in water results in the particular pH value.

52. The idea that a solid material "has" or can exert a pH, can be understood in terms of the pH that that chemical creates when present in a saturated solution in water. Thus, for example, drug dissolution is often viewed as there being a saturated solution of drug surrounding the surface of the tablet or particle and which is referred to as the diffusion layer. This diffusion layer has a pH different from the bulk solution (*e.g.*, water of buffer solution) pH in that it consists only of the surface material present in that thin layer immediately surrounding the solid. In regard to the claims, it would represent the diffusion layer immediately surrounding the enteric-coated tablet and containing a saturated solution of the enteric coating material. The pH of that diffusion layer could be interpreted as being the pH as a result of the coating.

53. Here, the claim language requires that measuring the pH of an aqueous solution of the enteric coating material would result in a pH value of "about 5.5" or "about 6.75." Nothing about the claim language refers to the release of the drug at the recited pH's – to the contrary, the "release" requirement is expressly recited in claim 1, not claims 2 and 3, leading persons of ordinary skill in the art to believe that these different words have different meanings. While I agree that claims 2 and 3 are not artfully written, I understand that the claims should not be "corrected" during claim construction, but should be construed in view of the intrinsic evidence. Because a chemical "having" a pH plainly means that the pH of that chemical should be measured (as opposed to the pH at which the chemical dissolves), claims 2 and 3 plainly refer to the pH of the enteric coat itself.

4. "wherein the changes in pharmacokinetics . . . under fasting or fed conditions does not produce statistically significant changes in intragastric pH" (claim 4)

Defendants' Construction	Takeda's Construction
Wherein the changes in pharmacokinetics … when the patient is dosed after an overnight fast, within 5 minutes before a meal, within 30 minutes before a meal, or within 30 minutes after a meal does not produce any statistically significant differences in mean intragastric pH and percentage of time that gastric pH is greater than 4. The term 'statistically significant' means that the P value for the pairwise comparisons of the fed and fasted regimens is less than 0.05.	Wherein differences in pharmacokinetics . . . between fasting conditions, meaning dosing after an overnight fast, and fed conditions, meaning dosing within 30 minutes before or after a meal, do not produce statistically significant changes in mean intragastric pH over the 24-hour postdose interval. The term 'statistically significant' means that the P value for the pairwise comparison of the fed regimen with the fasted regimen is less than 0.05.

54. As discussed with respect to claim 1, above, I concur with Defendants' construction of "fasted or fed conditions" in the context of claim 1, and further agree that the construction for this term should be the same as the "fasting or fed conditions" portion of claim 4. However, as discussed above in the context of claim 1, Defendants have separately listed each of the "fed" conditions in their construction rather than grouping them together as in Takeda's construction. Similar to claim 1, the language in claim 4 states only that the pharmaceutical composition must be "therapeutically effective . . . under fasting or fed conditions" – that is, no matter which of the fasting or fed conditions the patient is in, the results must be therapeutically effective. Accordingly, it is again appropriate to separately recite the overnight fast, within 30 minutes after a meal, and within 5 minutes and 30 minutes before a meal, as in Defendants' proposed construction, in order to more accurately reflect the claim language and the specification.

55. I also agree with Defendants' adoption of Takeda's "statistically significant" definition, in that the pairwise comparisons should produce a P value less than 0.05. However, I disagree with Takeda's importation of the requirement that the pairwise comparisons be *only* between the fasted and fed regimens. Nothing about the plain meaning of the claim language restricts comparisons to only

those between the fasted and fed conditions, and there is no reason to limit the claims in this way. This is in contrast to claim 9, which specifically requires a comparison between the fed state and the fasted state and a statistical "bioequivalent" determination based on that comparison. ('158 Pat. at Claim 9.) Other comparisons are also possible and commonly made in pharmacodynamic analyses: for example, results for the fed condition 5 minutes before a meal could be compared to the results for the fed condition 30 minutes after a meal. While Takeda chose to include only some of the comparisons in the '158 specification, this in no way limits the plain meaning of the claim language, which makes no mention as to which comparisons are made for the purposes of statistical analysis. Thus, the term "statistically significant" means that the P value for the pairwise comparisons of the fed and fasted regimens is less than 0.05.

56. With regard to the meaning of "intragastric pH," Defendants' proposed construction again is consistent with the intrinsic evidence. The '158 patent includes an experiment in which the pH of the stomach fluid is measured using a pH recorder. ('158 Pat. at 24:30-33.) These measurements result in a large number of data points, which are used to calculate two pharmacodynamic ("PD") parameters to determine the effect of food: "mean intragastric pH" and "% time pH>4 over 24 hours post dose." (*Id.* at 24:34-38.) The "mean intragastric pH" parameter refers to the statistical mean determined from the pH measurement data. (*Id.*) The "% time" parameter refers to the percentage of time that the pH of the stomach fluids is over 4, for a period of 24 hours after the patient is dosed. (*Id.*)

57. Thus, the '158 patent discloses two parameters to determine the effect of food on intragastric pH: the mean intragastric pH, and the percentage of time the intragastric pH remains over 4. ('158 Pat. at 23:38-40, 23:56-60, 24:34-38, Table 7.) The results of studies conducted including *both* parameters are together referred to in the '158 patent as "the intragastric pH results," and the conclusions that are made with regard to the effect of fasting and fed conditions on intragastric pH are

made based on *both* parameters. ('158 Pat. at 25:15-27, 46-50, Table 7.) There is no reason to divorce these two parameters from each other, and doing so would be contrary to the specification.

58. I declare under the penalty of perjury under the laws of the United States that the foregoing is true and correct.

Executed on April 24 2014, in Tucson, Az

By: Michael Mayersohn
Michael Mayersohn, PH.D.