Inter Partes Review 2014-00360
U.S. Patent No. 8,329,216

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AMNEAL PHARMACEUTICALS, LLC,
Petitioner,

v.

Patent of ENDO PHARMACEUTICALS INC.,
Patent Owner

Case 2014-00360
U.S. Patent No. 8,329,216

DECLARATION OF PROF. DIANE J. BURGESS, PH.D.

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Patent Trial and Appeal Board
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

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Filed by:

Joseph A. Mahoney (Lead Counsel)
Registration No. 38,956
MAYER BROWN LLP
71 South Wacker Drive
Chicago, IL 60606
Telephone: (312) 701-8979
Facsimile: (312) 706-8530

711136759

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Amneal v. Endo
IPR2014-00360

Email: jmahoney@mayerbrown.com

Erick J. Palmer (Back-Up Counsel)
Registration No. 64,456
MAYER BROWN LLP
71 South Wacker Drive
Chicago, IL 60606
Telephone: (312) 701-8352
Facsimile: (312) 706-9316
Email: ejpalmer@mayerbrown.com

Counsel for Patent Owner, Endo Pharmaceuticals Inc.

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I, Diane J. Burgess, Ph.D., hereby declare:

I. SUMMARY OF MY OPINIONS

1. In my opinion, claims 1, 2, 6, and 12 are patentable over Maloney (Exhibit 1006). ***First***, the multiple peaks limitations of claims 1, 2, 6, and 12 of U.S. Patent No. 8,329,216 (the "'216 patent") are not inherent properties of any oxymorphone composition, regardless of formulation. The clinical evidence I have considered demonstrates that some oxymorphone compositions, including an oral oxymorphone solution and immediate release oxymorphone tablets, do not exhibit multiple plasma concentration peaks of oxymorphone within about 12 hours of administration. ***Second***, the prior art teaches away from the claimed controlled release oxymorphone formulations, and a person of ordinary skill in the art would not have had a reasonable expectation of achieving a controlled release oxymorphone formulation having a therapeutic effect over a period of at least 12 hours from the teachings of Maloney.

2. In my opinion, claims 1, 2, 6, and 12 are also patentable over the combination of Oshlack (Exhibit 1007) and the Handbook of Dissolution Testing (Exhibit 1008) for the very same reasons.

3. In my opinion, claims 13, 14, 17, 21-43, 45-51, and 54-71 are patentable over the combination of Oshlack and the Handbook of Dissolution Testing. ***First***, neither of these prior art references teaches the claimed dissolution

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ranges. A person of ordinary skill in the art would have understood that there is no general correlation between the dissolution profile obtained using Paddle Method at 50 rpm, as recited in the claims of the '216 patent, and one obtained using the Basket Method at 100 rpm, as disclosed in Oshlack. A person of ordinary skill in the art would have also understood that the Handbook of Dissolution Testing's statement to the contrary is wrong and is contradicted by numerous scientific publications available at the time of the invention. ***Second***, the prior art teaches away from the claimed controlled release oxymorphone formulations, and a skilled artisan would not have reasonably expected to achieve a controlled release oxymorphone composition having a therapeutic efficacy over a period of at least 12 hours from the combined teachings of Oshlack and the Handbook of Dissolution testing. Oxymorphone is known to undergo substantial first-pass metabolism in the liver and is converted primarily to a metabolite that is inactive toward treating pain. However, the prior art teaches away from formulating extended release compositions containing drugs that are substantially metabolized before systemic circulation.

4. In my opinion, claims 31, 32, 35, 36, 38-41, 49-51, and 56 are patentable for an additional reason. The food effect limitations of these claims are not inherent properties of any oxymorphone composition, regardless of formulation. The evidence I have considered demonstrates that when immediate

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release oxymorphone compositions are administered with food, the claimed effects on C_{max} and $AUC_{(0\text{-}inf)}$ are not achieved.

5. In my opinion, certain secondary considerations, including the commercial success of Patent Owner's Opana® ER covered by the '216 patent, unexpected results, and the satisfaction of a long-felt but unmet need, support the nonobviousness of the challenged claims.

II. MATERIALS CONSIDERED

6. In forming my opinions in this declaration, I considered the following documents:

- Amneal's Petition and Exhibits 1001-1024
- The '216 patent and it prosecution history, including the various declarations submitted to the PTO during prosecution of the '216 patent
- The deposition testimony of both Dr. Palmieri and Ms. Gray in this proceeding
- The exhibits I specifically reference in this declaration

7. Additionally, I reviewed general texts and publications in the scientific and regulatory literature commonly used by pharmaceutical scientists as resources for information and considered the common knowledge that would have been available to a person of ordinary skill in the art at the time of the invention.

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In forming my opinions in this declaration, I also conducted searches of the scientific literature.

III. EXPERIENCE AND QUALIFICATIONS

8. A copy of my current curriculum vitae is attached at Exhibit 2011. A summary of my relevant experience and qualifications are provided below.

9. In 1979, I received a Bachelors of Science degree in Pharmacy from the University of Strathclyde, Glasgow, UK. In 1984, I received a doctorate in Pharmaceutics from the University of London, UK. I joined the faculty at the University of Connecticut in 1993 and was promoted to Full Professor of Pharmaceutics in 1999. I am currently a Distinguished Professor at the University of Connecticut (appointed in 2009) and hold positions as the Pharmaceutics Discipline Coordinator, and the Chair of the School of Pharmacy Study Abroad Committee.

10. I have served as an executive of several professional organizations focused on the field of pharmaceutics and drug development. For example, I was the 2002 President of the American Association of Pharmaceutical Scientists ("AAPS"), which is the largest professional organization globally representing scientists in pharmaceutics, biopharmaceutics, and related disciplines. From 2009 until 2010, I was president of the Controlled Release Society ("CRS"), which is a

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professional organization focused on developments in controlled release technologies.

11. I have served on the Editorial Advisory Boards of nine international journals. I currently serve on the board of THE AAPS JOURNAL, AAPSPHARMSCITECH, THE INTERNATIONAL JOURNAL OF PHARMACEUTICS, the JOURNAL OF MICROENCAPSULATION, THE JOURNAL OF PHARMACY AND PHARMACOLOGY, CURRENT DRUG DISCOVERY, CRITICAL REVIEWERS IN THERAPEUTIC DRUG CARRIER SYSTEMS, THE JOURNAL OF DRUG DELIVERY & TRANSFORMATIONAL RESEARCH, and the JOURNAL OF DIABETES SCIENCE & TECHNOLOGY.

12. I am also currently an editor of THE INTERNATIONAL JOURNAL OF PHARMACEUTICS. From 2003 until 2012, I was an editor for the JOURNAL OF DRUG DELIVERY SCIENCE AND TECHNOLOGY. From 1999 until 2004, I was an editor for the AMERICAN ASSOCIATION OF PHARMACEUTICAL SCIENCE JOURNAL. I also serve as referee for 19 journals, including the JOURNAL OF CONTROLLED RELEASE, CRITICAL REVIEWERS IN THERAPEUTIC DRUG CARRIER SYSTEMS, PHARMACEUTICAL RESEARCH, NATURE, INTERNATIONAL JOURNAL OF PHARMACEUTICS, and the JOURNAL OF PHARMACY AND PHARMACOLOGY, to name a few. In my roles as editor and referee, I routinely analyze the scientific methodologies, data, descriptions, and analyses provided in submissions to confirm that such

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methodologies, data, descriptions, and analyses are scientifically rigorous and correctly support any conclusions and hypotheses drawn there from. In cases where the data does not conclusively support a proposition set forth in the article, I may suggest additional experiments for the author(s) to conduct to confirm such proposition or may suggest rejection of the manuscript from publication.

13. My research group has studied controlled release formulations for more than thirty years. I have authored or co-authored 178 refereed scientific articles, most of which have been published in high-impact scientific journals. I have also authored two pharmaceutical books relating to drug delivery and authored chapters related to drug delivery and drug release in 34 other books. In addition, my research has been presented 487 times at major international scientific meetings, and I have been invited to present on more than 240 occasions, including giving 20 keynote and plenary addresses.

14. At the University of Connecticut, I direct an active research group of assistant research professors, post-doctoral fellows, graduate students, professional students, and undergraduate students. My research interests relate to microsphere, liposome, emulsion and hydrogel preparation and characterization for application as targeted and controlled release delivery systems for drugs, genes, vaccines and other systems, including fundamental colloid and surface chemistry, investigation of mechanisms of formation, formulation, development of novel technologies,

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stability assessment and prediction, transport and mathematical modeling of transport, IVIVC testing of drug release, surface and interfacial phenomena related to biological systems and drug delivery, and interfacial rheology and tension. As part of our research, my research group routinely performs dissolution testing of various pharmaceutical formulations. Indeed, in 2009, the Board of Trustees of the University of Connecticut renamed one of my laboratories as the SOTAX Dissolution and Release Testing Laboratory (SOTAX is a manufacturer of apparatus uses for the dissolution testing of pharmaceuticals).

15. My research is funded by extramural grants from companies and funding agencies. More than 22 graduate students working under my direction have obtained their doctorate. Also, as part of my academic career, I have taught courses in Controlled Drug Delivery, Foundations of Pharmaceutics, Drug Discovery and Development, Advanced Biopharmaceutics, and Interfacial and Colloid Chemistry.

16. I have received various honors and awards throughout my career. In 2014, I am the recipient of the AAPS Research Achievement Award in Formulation Design and Development, the AAPS Outstanding Educator Award, and the CRS's Distinguished Service Award. In 2013, I was awarded the AAPS IPEC Ralph Shangraw Memorial Award for outstanding research in the area of pharmaceutical excipients. In 2011, I received the APSTJ Nagai International

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Woman Scientist Award from the Japanese Pharmaceutical Science Association. I was the first recipient of the CRSI Fellowship for outstanding contributions in the area of drug delivery in 2010. In 2007, I received the Outstanding Manuscript Award from the AAPS Journal. I was elected Pharmacy School Teacher of the Year in 2005. And in 1991, I was awarded the Outstanding Teacher of the Year Award.

17. I am a named inventor of two issued U.S. patents and three U.S. patent applications, none of which are at issue in this proceeding.

18. Based on my academic credentials and research over the past thirty plus years, I am an expert in pharmaceutical drug development, controlled release technologies, dissolution testing of pharmaceutical formulations, and assessment of *in vivo* clinical data, to name a few.

19. I am being compensated at my standard rate of $600 for providing my opinions and analysis in this proceeding. My compensation is not contingent in any way on the substance of my opinions.

IV. SUMMARY OF THE '216 PATENT

20. Severe pain is one of the most frequently treated complaints confronting today's clinicians. It is a well-known fact that pain is both under-treated and inappropriately managed. One paramount goal of pain management involves providing continuous relief of chronic pain, which can be recurring or

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otherwise last for an extended duration. (Ex. 1001 at 1:39-42). Patients suffering from this level of pain typically include those with advanced-stage cancer, back problems, and other serious diseases. A class of compounds called opioids is frequently used for analgesia. Opioids that have been used for pain include oxycodone, fentanyl, hydromorphone, hydrocodone, and oxymorphone.

21. These compounds have traditionally been available as immediate release ("IR") formulations, which means that the entire dose of the active ingredient is released quickly. As such, IR opioid formulations have multiple drawbacks. Opioids that rapidly metabolize (like oxymorphone as discussed below) require frequent dosing because of the short duration during which analgesia is achieved. (Ex. 1001 at 1:50-54). If frequent dosing is not maintained, the patient may experience recurring pain as the drug loses effect in the body, leaving the patient without relief. In order to maintain continuous relief, IR opioids must therefore be taken according to a rigid schedule to provide effective management of chronic pain. Typically, patients take the IR medications every 4 to 6 hours in order to maintain pain relief. (*Id.*).

22. Opioid-containing controlled release ("CR") formulations, also called extended release ("ER") formulations, can have a profound effect on the quality of life of the patient and directly affect the success of the treatment regimen. ER dosage forms have been shown to provide therapeutic benefits beyond simply

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reducing the number of daily doses required. The inventors were the first to discover an *in vitro* dissolution profile that achieved a safe and effective treatment for relieving pain over a 12 hour period. (Ex. 1001 at Figures 1-4). The '216 patent pertains to methods of relieving pain over a period of 12 to 24 hours by administering controlled release oxymorphone tablets.

23. Oxymorphone is a semisynthetic opioid agonist with a significantly higher parenteral analgesic potency compared to parenteral morphine. Oxymorphone was first approved by the Food and Drug Administration ("FDA") (NDA No. 11-737) in 1959 and marketed in June of that year. Immediate release oral oxymorphone was originally marketed in the early 1960s, but was voluntarily removed from the market for commercial reasons. 2 mg and 5 mg tablets were commercially available for about 7 years, and 10 mg tablets were commercially available for about 11 years.

24. The '216 patent pertains to a method of relieving pain over a period of at least 12 hours by administering a controlled release oxymorphone tablet. The inventors were the first to discover an in vitro dissolution profile that unexpectedly achieved therapeutic efficacy for the treatment of pain over at least a 12 hour period. (Ex. 1001 at Figures 1-4).

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V. THE LEVEL OF ORDINARY SKILL IN THE ART

25. In my opinion, a person of ordinary skill in the art at the time of the claimed invention would possess at least a Master's degree in the field of pharmaceutical sciences or a related discipline and have several years of experience in formulation of various dosage forms, including immediate release and extended release, and the testing of such dosage forms for regulatory approval. A person of ordinary skill in the art could be a person with a lower level of formal education if such a person has a higher degree of experience. I have considered this level of ordinary skill in the art in forming my opinions in this declaration.

26. I not only met but exceeded these qualifications in the relevant 2001 timeframe.

VI. MULTIPLE PEAKS IN THE OXYMORPHONE PLASMA CONCENTRATION IS NOT AN INHERENT PROPERTY OF ALL OXYMORPHONE COMPOSITIONS

27. I have been asked to provide my opinion on whether Amneal's Petition sufficiently demonstrates by a preponderance of the evidence (*i.e.*, more likely than not) that the claimed multiple peaks feature of the oxymorphone plasma concentration in claims 1, 2, 6, and 12 is an inherent property of any oxymorphone composition, regardless of formulation. In my opinion, Amneal's Petition does not.

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28. In forming my opinions, I considered the following statements regarding the legal standard for determining a claimed feature is an inherent property of a prior art composition:

- Inherency requires that the feature be "necessarily present" in the prior art reference.
- Inherency may not be established by probabilities or possibilities.
- A claimed feature is inherent in a prior art reference if it is the natural result flowing from the explicit disclosure of the reference.

A. Multiple Plasma Concentration Peaks Within 12 Hours of Administration Is Not an Inherent Property of All Oxymorphone Compositions

29. Claim 1 is an independent claim. One of its limitations is that "the blood plasma levels of oxymorphone exhibit two or three peaks within about 12 hours after administration. . . ." Claims 2, 6, and 12 all depend from claim 1 and therefore also contain this limitation.

30. I understand that Dr. Palmieri believes that multiple peaks in the plasma concentration of oxymorphone within 12 hours of administration "is an inherent property of all oxymorphone compositions." (Palmieri Decl., Ex. 1003 at ¶ 95). Dr. Palmieri's opinion is based on Figures 6 and 7 of the '216 patent. (*Id.*). Figure 6 plots the plasma concentration of oxymorphone as a function of time for Treatments 2A (controlled release oxymorphone tablet), 2B (controlled release

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oxymorphone tablet), and 2C (oral solution of oxymorphone). ('216 patent, Ex. 1001 at 13:58-14:56). Figure 7 plots the plasma concentration of oxymorphone as a function of time for Treatments 3A (controlled release oxymorphone tablet under fasted conditions), 3B (controlled release oxymorphone tablet under fed conditions), 3C (oral solution of oxymorphone under fasted conditions), and 3D (oral solution of oxymorphone under fed conditions). (*Id.* at 15:42-16:35). Dr. Palmieri relies on the small shoulders at around 12 hours in the oral solutions to conclude that all oxymorphone compositions necessarily exhibit multiple peaks after administration.

31. However, Dr. Palmieri's deposition testimony confirmed that the claimed multiple peaks are not inherent properties of all oxymorphone compositions. I understand that Dr. Palmieri was asked whether he considered any scientific publications outside of the '216 patent to determine whether those formulations exhibited multiple peaks within 12 hours of administration. (Palmieri Tr., Ex. 2012 at 170:16-20). Dr. Palmieri responded that some oxymorphone compositions exhibit multiple peaks while others do not:

> A Do I recall reading the documents that I cite? ***Sometimes they're there, and sometimes they weren't there. But again, you have to wonder about the validity of the data.*** With clinical studies there's always variation.

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(*Id.* at 170:21-171:3 (emphasis added)).[1]

32. I agree with Dr. Palmieri on this point: some oxymorphone compositions exhibit multiple peaks in the plasma concentration of oxymorphone within about 12 hours of administration, and some oxymorphone compositions do not. In reaching my conclusion, I have considered two clinical studies not disclosed in the '216 patent. The first is a clinical study [redacted]. The second is a clinical study in which immediate release oxymorphone tablets were administered to subjects. Based on my review of the clinical results of these studies, it is my opinion that multiple peaks in the oxymorphone plasma concentration within about 12 hours of administration are ***not*** inherent to all oxymorphone compositions because sometimes the unclaimed oral solution and immediate release tablets clearly do not exhibit multiple peaks.

1. Study A

33. [redacted]

[1] I understand that Dr. Palmieri later testified that multiple peaks are exhibited by all oxymorphone compositions. (Palmieri Tr., Ex. 2012 at 205:9-206:1). However, this testimony came only after Dr. Palmieri conferred with Amneal's counsel. (*Id.* at 210:19-212:1).

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36. It is therefore my opinion that multiple plasma concentration peaks of oxymorphone are ***not*** necessarily exhibited by all oxymorphone compositions, regardless of formulation, and there is no evidence that they naturally flow from the compositions disclosed in Maloney or Oshlack.

2. Study B

37. Exhibit 2014 is an article entitled *Single- and Multiple-Dose Pharmacokinetic and Dose-Proportionality Study of Oxymorphone Immediate-Release Tablets*, which was published in the scientific journal DRUGS R D in 2005. This article describes a clinical study examining the pharmacokinetics and dose proportionality of an immediate-release tablet formulation containing oxymorphone following single and multiple-dose administration in healthy subjects. (Ex. 2014 at 91). The study included 24 participants (male and female) and employed a randomized, three-way crossover design. (*Id.*). Single doses of 5 mg, 10 mg, and 20 mg of immediate release oxymorphone tablets were co-administered with the opioid antagonist naltrexone. (*Id.*). Subjects were fasted from 10 p.m. the day before and were administered a single dose on Day 1. (*Id.* at 93). Subjects were fed four hours after administration of the oxymorphone. (*Id.*).

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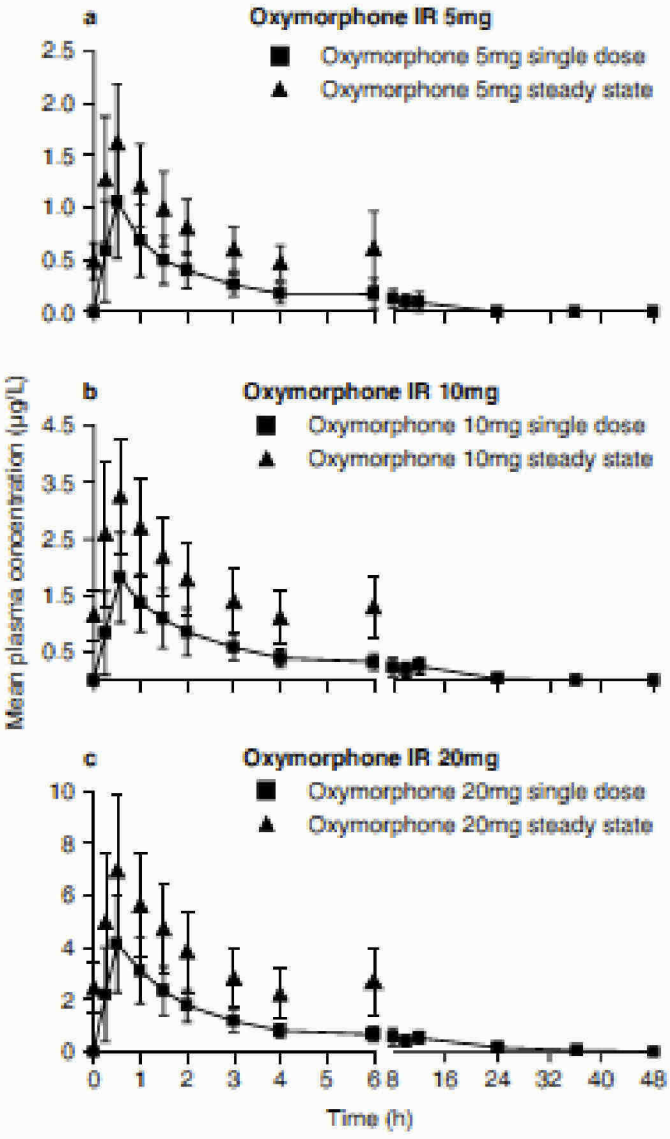
A 7-day washout period was used prior to administration of the next randomized oxymorphone formulation. (*Id.*).

38. The mean single-dose and steady-state plasma concentrations of 5 mg, 10 mg and 20 mg immediate release oxymorphone are shown in Figure 1 of Exhibit 2014, which is excerpted as follows:



(*Id.* at 97).

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39. The above graphs illustrate that the mean plasma concentrations following administration of a single dose of the 5 mg, 10 mg, and 20 mg immediate-release oxymorphone tablets exhibited only a single plasma concentration peak between 0 and 12 hours.[2] These results are consistent with the results of the clinical study described above in Ex. 2013.

40. This is further proof that not ***all*** oxymorphone compositions ***necessarily*** exhibit multiple plasma concentration peaks of oxymorphone within about 12 hours of administration.

B. Any Differences in the Protocols of These Clinical Studies Do Not Account for Differences in the Peak Plasma Properties

41. The studies described in Exhibits 2013 and 2014 demonstrate that some oxymorphone compositions exhibit multiple plasma concentration peaks within about 12 hours of administration of oxymorphone whereas others do not. In the studies described in Exhibits 2013 and 2014, a plasma concentration peak at about 12 hours is absent.

42. In accounting for this difference in the observed peak plasma concentration behavior of the oxymorphone compositions used in the clinical

[2] Peak plasma concentrations in the '216 patent are determined after administration of a single dose of oxymorphone. (*See*, *e.g.*, Ex. 1001 at 13:59-62, 15:60-16:9, 24:20-35). This is consistent with FDA guidances. (*See* Ex. 2015 at 8 ("[T]his guidance generally recommends single-dose pharmacokinetic studies for both immediate- and modified-release drug products to demonstrate [bioequivalence] because they are *generally* more sensitive in assessing release of the drug substance from the drug product into the systemic circulation. . . .")).

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studies described in Exhibits 2013 and 2014 and those in the '216 patent, I have considered the clinical study protocols for each study. For example, the clinical studies in Exhibits 2013 and 2014 administered the oxymorphone formulations (i) with naltrexone and (ii) under fasted conditions. The clinical study described as "Study 2" in the '216 patent did not. (See '216 Patent, Ex. 1001 at 13:52-14:4). In my opinion, however, neither of these conditions would affect the presence or absence of the plasma concentration peak at about 12 hours. Accordingly, had the oral oxymorphone solution and immediate release oxymorphone tablets used in Exhibits 2013 and 2014 been administered without naltrexone and/or under fed conditions, a plot of the plasma concentration of oxymorphone versus time would have yielded a single peak within about 12 hours of administration.

1. Naltrexone has no effect on the pharmacokinetics of oxymorphone

43. In clinical studies involving healthy volunteers (as opposed to patients), the opioid antagonist naltrexone is generally co-administered with oxymorphone to reduce adverse effects of the oxymorphone. Patent Owner has conducted clinical studies demonstrating that the co-administration of naltrexone does not affect the shape of the mean plasma concentration curve of oxymorphone.

44. [redacted]

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45. This is consistent with the scientific literature. For example, Exhibit 2017 is an article entitled *Pharmacokinetics and Dose-Proportionality of Oxymorphone Extended Release and Its Metabolites: Results of a Randomized Crossover Study*. This article was published in the journal PHARMACOTHERAPY in 2004. The authors expressly maintain that "[p]revious studies have shown that

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naltrexone does not significantly affect the pharmacokinetics of oxymorphone and its metabolites." (Ex. 2017 at 470). Additionally, Exhibit 2018 is an article entitled *Bioequivalence of Oxymorphone Extended Release and Crush-Resistant Oxymorphone Extended Release*, published in the journal DRUG DESIGN, DEVELOPMENT AND THERAPY in 2011. This article also demonstrates that naltrexone does not affect the number of peaks in the plasma concentration within about 12 hours of co-administration with oxymorphone. (Ex. 2018 at 458-59). Significantly, in both articles, the controlled release oxymorphone compositions, when co-administered with naltrexone, exhibit multiple peaks, including the peak at 12 hours observed for the compositions disclosed in the '216 patent. (Ex. 2017 at 470, 472; Ex. 2018 at 458-59). These studies provide further evidence that naltrexone does not affect the pharmacokinetic profile of oxymorphone.

46. Moreover, although the '216 patent is silent as to whether any of its clinical studies co-administered naltrexone with oxymorphone, [redacted]

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47. Accordingly, it is my opinion that the co-administration of naltrexone with oxymorphone does not explain the absence of a plasma concentration peak of oxymorphone at 12 hours in the clinical studies described in Exhibits 2013 and 2014.

2. Administering Oxymorphone Under Fasted Conditions Would Not Affect the General Shape of the Mean Plasma Concentration Profile

48. Administering oxymorphone in a fasted state, as described in Exhibits 2013 and 2014, also does not explain the absence of a plasma concentration peak at 12 hours in those clinical studies. According to Dr. Palmieri, "Study 3" and "Study 5" disclosed in the '216 patent demonstrate that when controlled release

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and immediate release oxymorphone formulations are administered under fed and fasted conditions, plasma concentration peaks are exhibited at 12 hours by those formulations under both fed and fasted conditions. (Ex. 1003 at ¶ 94). Thus, the alleged peaks observed at 12 hours for the oxymorphone compositions in the '216 patent are independent of whether the oxymorphone is administered with or without food.

C. The Peak Limitations of Claim 70 Are Not Inherent to All Oxymorphone Compositions

49. I understand that Dr. Palmieri opines that the multiple peak limitation of claim 70—*i.e.*, a first oxymorphone plasma concentration peak at about 3 hours and a second at about 6-7 hours—is an inherent property of all oxymorphone compositions. (*See, e.g.*, Palmieri Decl., Ex. 1003 at ¶ 119). I disagree.

50. During his deposition, Dr. Palmieri expressly admitted that these peak plasma concentration properties are not exhibited by all oxymorphone formulations. For example, relying on Table 9 of the '216 patent, Dr. Palmieri admitted that the oral oxymorphone solution used in Treatment 2C of "Study 2" exhibits peaks at 0.75 and 12 hours. (Palmieri Tr., Ex. 2012 at 164:21-165:4). As shown in Table 13 of the '216 patent, the oral solution of oxymorphone exhibits peaks at (i) 0.75 and 12 hours under fasted conditions (Treatment 3C) and (ii) 1 and 12 hours under fed conditions (Treatment 3D). (*Id.* at 165:5-166:3).

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51. Accordingly, the claimed peak plasma concentration profile of claim 70 is not an inherent property of all oxymorphone compositions.

VII. THE COMBINATION OF OSHLACK AND THE HANDBOOK OF DISSOLUTION TESTING DOES NOT RENDER OBVIOUS ANY OF THE CHALLENGED CLAIMS

52. I understand that the Board has instituted review of claims 13, 14, 17, 21-43, 45-51, and 54-71 of the '216 patent in view of the combination of Oshlack (Ex. 1007) and the Handbook of Dissolution Testing (Ex. 1008). Oshlack is a patent that discloses a certain formulation approach for controlled release formulations containing a long list of actives, including opioids. (Ex. 1007 at 6:50-7:39). The patent describes examples of these formulations with several opioids, but no oxymorphone formulations are described or tested. Certain desired dissolution profiles that are measured using the USP Paddle or Basket Methods, both at 100 rpm, are disclosed, in each instance for opioids other than oxymorphone. (*See* Ex. 1007 at 11:61-12:12, Examples 1-28). The challenged claims of the '216 patent, however, require specific dissolution profiles as measured using the USP Paddle Method at 50 rpm. Nowhere does Oshlack discuss how results from the USP Paddle or Basket Methods at 100 rpm would be expected to relate to each other, or to the USP Paddle Method at 50 rpm, or what dissolution rates would provide for a controlled release formulation of

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oxymorphone with at least 12 hours of analgesic effectiveness, as claimed in the '216 patent.

53. I understand that Amneal contends that the claimed dissolution profiles would have been obvious in view of those disclosed in Oshlack combined with the following statement from the Handbook of Dissolution Testing:

> As specified in individual monographs—but for general purposes when not otherwise specified—rates of 50 rpm for the paddle and 100 rpm for the basket are recommended ***and have proved to be roughly equivalent to one another in producing dissolution***.

(Ex. 1008 at 35 (emphasis added)). I disagree. As detailed below, there is no evidence in the prior art or Amneal's Petition demonstrating that the dissolution profiles disclosed in Oshlack are actually "roughly equivalent" to those claimed. Moreover, a person of ordinary skill in the art could not have reasonably predicted what the rates reported in Oshlack would have been if determined with the Paddle Method at 50 rpm as claimed in the '216 patent.

54. In forming my opinions, I considered the following statements regarding the legal standard for determining whether a patent claim is obvious:

- As the Petitioner, Amneal has the burden of proving that the challenged claims would have been obvious to a person of ordinary skill in the art at the time of the invention by a preponderance of the evidence (*i.e.*, more likely than not).

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- Obviousness requires assessing (1) the level of ordinary skill in the pertinent art, (2) the scope and content of the prior art, (3) the differences between the prior art and the claims at issue, and (4) secondary considerations of non-obviousness such as commercial success, long-felt but unsolved needs, unexpected results, and failure of others, etc.
- A party alleging unpatentability due to obviousness must show that a POSA would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the POSA would have had a reasonable expectation of success in doing so.
- A reference that "teaches away" from a given combination may negate a motivation to modify the prior art to meet the claimed invention.
- A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the inventors.

A. The USP Paddle Method at 50 rpm and Basket Method at 100 rpm Are Useful Not Because They Provide Equivalent Dissolution, But Because They Provide a Reproducible, Discriminatory Quality-Control Test

55. In assessing whether the Paddle Method at 50 rpm is "roughly equivalent" to—or would have been obvious over—the Basket Method at 100 rpm,

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it is important to appreciate the purposes of a dissolution test as well as the reasons underlying the common selection of these two agitation rates.

56. One of the purposes of *in vitro* dissolution tests is to distinguish between manufactured batches of the pharmaceutical formulation that are suitable and unsuitable for human consumption. Thus, the goal of any such *in vitro* dissolution test is to be discriminatory for quality-control purposes. In this sense, "discriminatory" means that the *in vitro* dissolution test distinguishes between a batch that will be safe and effective at treating the relevant condition and a batch that will not be safe and effective due to some problem during manufacturing. From a quality-control perspective, the agitation rates of 50 rpm for the Paddle Method and 100 rpm for the Basket Method generally provide discriminatory test conditions. From an efficacy standpoint, these low agitation rates are thought to better imitate the *in vivo* agitation that pharmaceutical tablets experience in the digestive tract, which assists in correlating *in vitro* dissolution data to *in vivo* clinical data. (*See* Ex. 2020 at 148 ("In choosing the dissolution method, one must consider the appropriate dissolution medium and use a slow dissolution stirring rate so that *in vivo* dissolution is approximated.")).

57. In addition, from an analytical perspective, these agitation rates in the respective apparatuses generally provide reproducible dissolution profiles having acceptable variances. Exhibit 2021 is a true and correct copy of an excerpt of a

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book entitled *Dissolution Theory, Methodology, and Testing*. I note that this book was edited by Dr. Palmieri. According to this book:

> The rotating basket method is routinely used for capsule formulations at an agitation speed of 50-100 rpm. Rates outside a range of 50-150 rpm are generally unacceptable because of irreproducibility associated with the hydrodynamics below 50 rpm and turbulence above 150 rpm. High turbulence in the vessel leads to a loss of discriminatory power associated with the dissolution method.

(Ex. 2021 at 35).

> The rotating paddle method is routinely used at an agitation speed of 25 to 75 rpm. Rates outside a range of 25 to 75 rpm are generally unacceptable because of irreproducibility of the hydrodynamic effects below 25 rpm and turbulence above 100 rpm. High turbulence in the vessel leads to a loss of discriminatory power associated with the method.

(*Id.* at 38-39). Although Exhibit 2021 was published in 2007, the information provided in the specific passages above was common knowledge to those in the field at the time of the invention.

58. Given the benefits of these agitation rates, it should come as no surprise that they fall within the recommendations of the FDA. Exhibit 2022 is a true and correct copy of a Guidance for Industry published by the FDA in August

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1997 entitled *Dissolution Testing of Immediate Release Solid Oral Dosage Forms*. In Appendix A of this Guidance, the FDA provides the following dissolution testing conditions for immediate release solid oral dosage forms:

> In general, mild agitation conditions should be maintained during dissolution testing to allow maximum discriminating power and to detect products with poor in vivo performance. Using the basket method, the common agitation (or stirring speed) is 50-100 rpm; with the paddle method, it is 50-75 rpm (Shah et al., 1992).

(Ex. 2022 at A-2).

59. Accordingly, the Paddle Method at 50 rpm and the Basket Method at 100 rpm are commonly used in the pharmaceutical industry not because they provide "roughly equivalent" dissolution. They are commonly used because these agitation rates generally provide reproducible dissolution data from which quality-control measures can be taken. This is illustrated in Exhibit 2023, which is an article co-authored by Ms. Gray entitled *Intrinsic Dissolution Performance Testing of the USP Dissolution Apparatus 2 (Rotating Paddle) Using Modified Salicylic Acid Calibrator Tablets: Proof of Principle*. As shown in the excerpted Figures below, the paddle apparatus at 50 rpm as compared to the same apparatus at 100 rpm exhibits tighter dissolution rates at each time point for the salicylic acid tablets studied:

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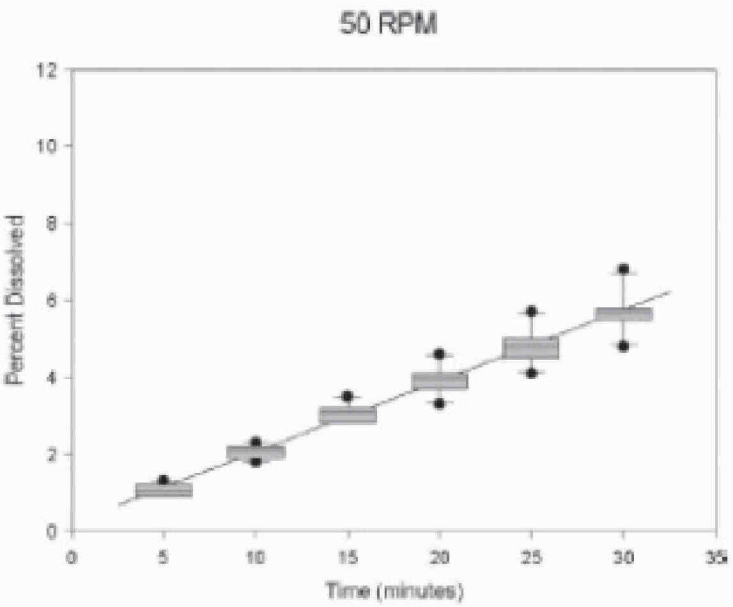

Figure 6. Box Plot of paddle apparatus at 50 rpm

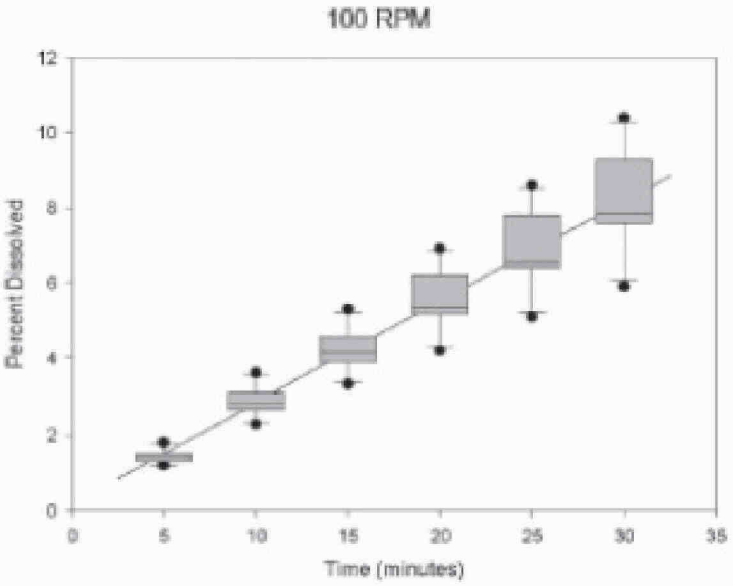

Figure 7. Box plot of paddle apparatus at 100 rpm

(Ex. 2023 at 11, Figures 6, 7). Also notable from this figures is the fact that within the paddle apparatus, the elevated stirring rate provides faster dissolution (i.e., a

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higher dissolution rate). This was commonly known for both basket and paddles at the time of the invention of the '216 patent.

60. Accordingly, the Paddle Method at 50 rpm and the Basket Method at 100 rpm are commonly used not because they provide "roughly equivalent dissolution." They are commonly used because they provide reproducible *in vitro* data from which *in vivo* pharmacokinetic data may be correlated.

B. There Is No Evidence Demonstrating That the USP Paddle Method at 50 rpm and Basket Method at 100 rpm Are "Roughly Equivalent" for Any Oxymorphone Composition

61. I understand that the Handbook of Dissolution Testing states as follows:

> As specified in individual monographs—but for general purposes when not otherwise specified—rates of 50 rpm for the paddle and 100 rpm for the basket are recommended ***and have proved to be roughly equivalent to one another in producing dissolution***.

(Ex. 1008 at 35 (emphasis added)). When I first read this statement, I was immediately suspicious of the broad interpretation that Ms. Gray ascribed to it for a number of reasons.

62. First, this statement is overly generalized, and the Handbook of Dissolution Testing does not provide any information on what is meant by the phrase "have proved to be roughly equivalent to one another in producing

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dissolution." It also does not identify which pharmaceutical formulations or active pharmaceutical ingredients have been shown to exhibit "roughly equivalent" dissolution under the two methods—and certainly does not identify any oxymorphone compositions. It also does not provide any numerical bounds on what it means for the dissolution to be roughly equivalent. Nor does it identify any time period over which the "roughly equivalent" dissolution is measured. Accordingly, it provides no guidance to a person of ordinary skill in the art as to whether these two methods provide "roughly equivalent" dissolution at each time point or only at certain time points (*e.g.*, at 30 min, 1 hr, 2 hr, etc.).

63. Second, based on all my years of experience in pharmaceutical dissolution testing, I am not aware of any fundamental scientific principle that would result in these two methods having "roughly equivalent" dissolution profiles under any circumstance, much less "for general purposes." My experience is confirmed by scientific literature that was available at the time of the invention.

64. Exhibit 2024, for instance, is an article entitled *Comparison of Operational Characteristics of Different Dissolution Testing Systems* that was published in 1978 in the JOURNAL OF PHARMACEUTICAL SCIENCES. According to the authors:

> When relative merits of dissolution apparatus design are discussed, ***there often are no data available to compare results directly with other apparatus*** in the same

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> laboratory. Thus, ***differences in*** parameters such as the dissolution medium or ***relative levels of agitation***, recognized as having profound influence on dissolution results (1), ***often make direct comparison impossible***.

(Ex. 2024 at 1732 (emphasis added)). Thus, in contrast to the Handbook of Dissolution Testing, this article teaches a person of ordinary skill in the art that without data, comparing the paddle and basket methods at different agitation rates is "often . . . impossible."

65. This principle persisted in the field up to the time of the invention and is still generally accepted today. Exhibit 2020 is an excerpt from a book entitled *Applied Biopharmaceutics & Pharmacokinetics, 4th Edition* ("*Applied Biopharmaceutics*"), which was published in 1999 and was available to a person of ordinary skill in the art at the time of the invention. According to this book:

> The use of various testing methods makes it even more difficult to interpret dissolution results because ***there is no simple correlation among dissolution results obtained with various methods***.

(Ex. 2020 at 145 (emphasis added)). *Applied Biopharmaceutics* notes that "[d]issolution results at 50 rpm with the paddle method ***may be*** equivalent to the dissolution at 100 rpm with the basket method" but, relying on data from several scientific studies, concludes ***"[n]o simple correlation can be made for dissolution results obtained with different methods***." (*Id.* (emphasis added)). In other words,

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it acknowledges that, in select cases, the Paddle Method at 50 rpm and the Basket Method at 100 rpm may result in equivalent dissolution. However, it makes clear that, as a general principle, dissolution cannot be correlated between the two methods. This is consistent with my understanding.

66. Unlike the statements in *Applied Biopharmaceutics*, I note that the statement in the Handbook of Dissolution Testing regarding the alleged equivalence of the Paddle Method at 50 rpm and the Basket Method at 100 rpm is not supported by a citation to the scientific literature. During his deposition, Dr. Palmieri testified that if he wanted to verify the truthfulness of a statement that is not supported by a specific citation, he would go to other scientific publications for verification. (Palmieri Tr., Ex. 2012 at 108:2-6). I agree.

67. I have analyzed the scientific literature for information relating to the alleged "rough equivalence" of the Paddle Method at 50 rpm and the Basket Method at 100 rpm. What I found confirms my initial suspicions. As I detail below, some pharmaceutical formulations have faster dissolution rates under the Basket Method at 100 rpm, other pharmaceutical formulations have faster dissolution rates under the Paddle Method at 50 rpm, and still other pharmaceutical formulations have similar dissolution rates under both methods. In other words, there is no general correlation between the two methods. Whether a pharmaceutical formulation will exhibit similar or different dissolution rates under

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the Paddle Method at 50 rpm and the Basket Method at 100 rpm is not reasonably predictable given (i) the complicated hydrodynamic effects on dissolution caused by the different apparatuses and agitation rates and (ii) the large number of formulation-based factors that affects dissolution rates. I address these hydrodynamic and formulation factors as well as relevant examples from the scientific literature in turn below.

1. The Paddle Method at 50 rpm and the Basket Method at 100 rpm generate different hydrodynamics in the dissolution vessel

a) The type of stirrer and agitation level will change the hydrodynamics of the dissolution vessel

68. One of the most critical factors impacting an observed dissolution profile is the hydrodynamics (*i.e.*, the study of liquids in motion) of the dissolution medium in the dissolution vessel. I note that Ms. Gray agrees with me. Exhibit 2025 is a chapter authored by Ms. Gray excerpted from a book entitled *Pharmaceutical Dissolution Testing*. In this chapter, Ms. Gray states:

> During the dissolution test, the hydrodynamic aspects of the fluid flow in the vessel have a major influence on the dissolution rate (1).

(Ex. 2025 at 39). Two of the most important variables affecting the hydrodynamics in a dissolution vessel are (i) the agitation rate and (ii) the shape and design of the stirrer (*i.e.*, paddle or basket).

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69. Exhibit 2026 is an excerpt from a textbook entitled *Remington: The Science and Practice of Pharmacy, 20th Edition* ("Remington"). Remington was published in 2000 and, at that time, was commonly used in graduate-level and professional pharmaceutical sciences classes. Remington, which is unquestionably a more reliable source than the Handbook of Dissolution Testing, contradicts the statement in the Handbook of Dissolution Testing. According to Remington:

> ***The relationship between intensity of agitation and the rate of dissolution varies considerably according to the type of agitation used***, degree of laminar and turbulent flow in the system, ***shape and design of the stirrer***, and physicochemical properties of the solid.

(*Id.* at 662 (emphasis added)). It also states that experimental studies have established an empirical relationship between the rate of dissolution and the intensity of agitation,

$$K = a(N)^b \quad (1)$$

wherein K is the dissolution rate, N is the speed of agitation, and *a* and *b* are constants. (*Id.*). Equation 1 has been known in the field of dissolution for more than fifty years and was reported by Wurster and Taylor as early as 1965 in an article entitled *Dissolution Rates* published in the JOURNAL OF PHARMACEUTICAL SCIENCES. (Ex. 2027 at 170-71). The empirical relationship described in Equation 1 is based on scientific data. (*Id.*).

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70. According to Remington as well as Wurster and Taylor, the value of *b* depends on the rate controlling mechanism(s) at play. (Ex. 2026 at 662; Ex. 2027 at 170-71). Bulk dissolution of a solid can be thought of as a two step process: (1) dissolution of the solid into a thin layer of solution forming a layer around the solid (what is commonly referred to as the "stagnant diffusion layer") between the solid particle and the bulk solution, followed by (2) diffusion from the stagnant layer into the bulk solution. If the dissolution rate is controlled solely by diffusion (*i.e.*, Step 2), then *b* is 1 or close to 1, such that the dissolution rate is effectively the product of *a* and the agitation rate. (*Id.*). If the dissolution rate is controlled by an interfacial reaction (*i.e.*, Step 1), then *b* approaches zero and the dissolution rate is independent of the agitation rate and is equal to the constant *a*. (*Id.*). When both of these processes affect the dissolution rate, *b* will vary between zero and 1. (*Id.*). Dissolution of pharmaceutical formulations is generally affected by the stagnant diffusion layer.

71. Other variables influence the dissolution rate, "including the degree of laminar and turbulent flow, the density of the solid phase, the size and characteristics of the solid, ***the stirrer***, and the dissolution vessel," as well as the heat of solution of the solute. (Ex. 2027 at 171 (emphasis added)). Accordingly, all of these factors, including whether a paddle or basket is being used as the

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stirrer, will affect the constants a and b, as determined from a plot of dissolution rate versus agitation rate.

72. Thus, assuming that the dissolution rates for the Paddle Method at 50 rpm and the Basket Method at 100 rpm are equivalent as Amneal contends, Equation 1 can be written as follows:

$$a_{P50}(50)^{b_{P50}} = a_{B100}(100)^{b_{B100}} \quad (2)$$

For Equation 2 to hold true, however, the four variables a_{P50}, b_{P50}, a_{B100}, and b_{B100} must perfectly align such that the dissolution rates on each side of the equation are equivalent. Given that each of these four variable themselves depend on a number of method- and formulation-specific factors, there is no general correlation between the Paddle Method at 50 rpm and the Basket Method at 100 rpm—much less one that makes them "roughly equivalent" in producing dissolution. Although there may be some pharmaceutical formulations for which the relationship described in Equation 2 may be true, there are certainly many others for which it is not true. This is confirmed by *Applied Biopharmaceutics* as well as other scientific literature discussed in more detail below.

b) The Paddle Method at 50 rpm creates a "dead zone" of fluid flow where the dissolving formulation is located

73. My opinion is also based on a known hydrodynamic problem associated with the Paddle Method at 50 rpm. At this low agitation rate, a "dead zone" of fluid flow directly underneath the paddle is created. As Ms. Gray

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describes it in a recent publication, this "dead zone" has "slow shear and limited agitation." (Ex. 2028 at 1296). During a dissolution test employing a paddle at 50 rpm, the dosage form being tested is located in this "dead zone." (*Id.* at 1296-97). In contrast, during a dissolution test employing a basket at 100 rpm, the dosage form is placed inside the basket and is therefore not located in a "dead zone." (*Id.*). This difference will be expected to affect the dissolution rate.

74. As I noted above, the dissolution process occurs in two steps: (1) dissolution of the solid into the stagnant diffusion layer and (2) diffusion of the dissolved component from the stagnant diffusion layer into the bulk solution. The thickness of the stagnant diffusion layer is inversely proportional to the agitation. Thus, the greater the agitation, the thinner the stagnant diffusion layer, the faster the dissolution.

75. This has an important implication when comparing the dissolution rate of the Paddle Method at 50 rpm and the Basket Method at 100 rpm: the stagnant diffusion layer in the basket method would be expected to be smaller than in the paddle method. Indeed, because the dosage form sits in a "dead zone" with "slow shear and limited agitation," the stagnant diffusion layer in the paddle method will be thicker, which will require more time for the dissolved matter to diffuse from the interface of the solid particle to the bulk solution. This, in turn, will decrease the dissolution rate.

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76. Thus, from a hydrodynamic standpoint, a person of ordinary skill in the art would expect that, in general, the Basket Method at 100 rpm would provide faster dissolution compared to the Paddle Method at 50 rpm, not that the two methods would be "roughly equivalent."

2. Due to factors unique to each formulation, hydrodynamics often cause different dissolution profiles for the two methods

77. It is fundamental that formulation and manufacturing factors may influence the dissolution rate of a pharmaceutical composition. Because these formulation and manufacturing factors interact differently with the different hydrodynamic environments created under the Paddle Method at 50 rpm and the Basket Method at 100 rpm, different dissolution profiles for the same pharmaceutical formulation are often observed. Thus, a universal correlation between these two methods does not exist, contrary to Ms. Gray's opinion.

78. According to Remington:

> The physicochemical properties of the drug substance play a ***prime role*** in controlling its dissolution from the dosage form.

(Ex. 2026 at 656 (emphasis added)). For example, the solubility of a drug substance affects its dissolution rate. (*Id.*) In addition, a drug's particle size, crystalline state, state of hydration, solvation, and complexation changes a drug's rate of dissolution. (*Id.*). Further, "physical properties such as density, viscosity,

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and wettability contribute to the general dissolution problems of flocculation, flotation, and agglomeration." (*Id.*).

79. "Adsorption characteristics of the drug also have been found to have significant effect on the dissolution of certain drugs." (*Id.*) For example, polar groups on the drug may form weak bonds through van der Waals forces, dipole and induced-dipole interactions with the formulation, similar to the interactions used to separate compounds in adsorption chromatography. (*Id.* at 598).

80. Also, the dissolution rate of a drug will vary according to its surface area per particle size. (*Id.* at 656). "[H]igher dissolution rates may be achieved through reduction of the particle size" because the surface area increases with decreasing particle size. (*Id.*). Indeed, micronization "increases the surface areas exposed to the dissolution medium and hence improves the rate of dissolution" for even sparingly soluble drugs. (*Id.*). However, merely increasing the surface area of the drug "does not always guarantee an equivalent increase in the dissolution rate." (*Id.*). Rather, the increased surface area must be in contact with the dissolution medium to increase the dissolution rate. (*Id.*).

81. Solid phase characteristics of drugs also play a role in the dissolution rate. (*Id.*). These solid phase characteristics include "amorphicity, crystallinity, state of hydration, and polymorphic structure." (*Id.*) As commonly known and

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described in Remington, an amorphous form of a drug had a higher dissolution rate than the crystalline form. (*Id.*).

82. Remington also notes that even the manufacturing can have substantial effects on the dissolution rate:

> The effect of ***various formulations and manufacturing processing factors on the rate of dissolution and bioavailabilty*** of the active ingredients from tablets and capsules have been well documented by several investigators since the early 1960s . . . . ***[T]he magnitude and significance of these effects must be determined individually for each tablet or capsule product.***

(*Id.* at 657). In particular, "the dissolution rate of a pure drug can be altered significantly when mixed with various excipients during the manufacturing process." (*Id.*). These excipients comprise diluents, fillers, dyes, binding agents, disintegrants, and lubricants. (*Id.*). For example, in one formulation a 5-20 % increase in a diluent, starch, resulted in a dramatic increase in dissolution, almost three fold. (*Id.*).

83. Lubricants also affect the dissolution rate. In a study with salicylic acid tablets, it was found a hydrophobic lubricant, magnesium stearate, slowed the dissolution of salicylic acid. (*Id.* at 658). In the same study, sodium lauryl sulfate, a water-soluble lubricant, "enhanced the dissolution rate significantly." (*Id.*).

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However, another water-soluble lubricant, sodium stearate, retarded dissolution. (*Id.*)

84. In addition to formulation factors, processing factors can also cause the dissolution rate to vary. (*Id.*). For example, wet granulation generally improves the dissolution rates of poorly soluble drugs. (*Id.*). This is because wet granulation with "fillers and diluents such as starch, spray-dried lactose, and microcrystalline cellulose, tend to increase the hydrophilicity of the active ingredients." (*Id.*).

85. Further, the amount of force used to compress the tablet can greatly influence dissolution. (*Id.*). According to Remington:

> There is always a competing relationship between the enhancing effect due to the increase in surface area through the crushing effect and the inhibiting effect due to the increase in particle bonding that causes an increase in density and hardness and, consequently, a decrease in solvent penetrability.

(*Id.* at 658-59). In addition, high compression inhibits wettability of the tablet due to the formation of a sealing layer created by a lubricant during compression. (*Id.* at 659).

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86. Given the complex interplay between hydrodynamic, formulation, and process factors, all of which influence the ultimate dissolution rate observed, a person of ordinary skill in the art would not have reasonably expected that the Paddle Method at 50 rpm would provide "roughly equivalent" dissolution to the Basket Method at 100 rpm "for general purposes." Instead, a person of ordinary skill in the art would have understood that to determine whether the Paddle Method at 50 rpm was "roughly equivalent" to the Basket Method at 100 rpm, comparative dissolution testing using both methods would be required on a product-by-product basis. This is consistent with the deposition testimony of Ms. Gray:

> Q. And so, in some circumstances, depending on the drug, or the size, structure, et cetera, the results of the dissolution tests based on the basket method or paddle method may be different?
>
> A. You know, ***it is case by case***.

(Gray Tr., Ex. 2029 at 72:8-16 (emphasis added)).

3. The scientific literature confirms that the statement in the Handbook of Dissolution Testing is not generally applicable

87. Consistent with the fundamental pharmaceutical dissolution principles discussed above, the scientific literature demonstrates that "for general purposes," the Paddle Method at 50 rpm and the Basket Method at 100 rpm ***do not*** provide "roughly equivalent" dissolution. As summarized below, in many cases, the Basket Method at 100 rpm actually provides a faster dissolution rate than the

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Paddle Method at 50 rpm, which is consistent with what a person of ordinary skill in the art would expect. In some cases, the Paddle Method at 50 rpm produces faster dissolution than the Basket Method at 100 rpm. In other cases, the two methods produce similar dissolution.

a) Exhibit 2030 – Ozkan, et al. (Acetaminophen)

88. The influence of the apparatus, agitation speed, and formulation differences on dissolution rate is illustrated in Exhibit 2030. Exhibit 2030 is an article entitled *Comparative Dissolution Testing of Paracetamol Commercial Tablet Dosage Forms* published in 2000 in the scientific journal ACTA POLONIAC PHARMACEUTICA ("Ozkan"). Accordingly, Ozkan would have been available to a person of ordinary skill in the art at the time of the invention.

89. Ozkan presents comparative dissolution testing of nine commercial pharmaceutical tablets containing acetaminophen produced by different drug companies. (*Id.* at 34). The dissolution testing was carried out using, *inter alia*, the Paddle Method at 50 rpm and the Basket Method at 100 rpm at various pH values. (*Id.* at 35-36). The dissolution data reported in Ozkan for each commercial tablet are the average of twenty tablets. (*Id.* at 34). Accordingly, the dissolution method employed in this study was robust.

90. The acetaminophen tablets were immediate release, and therefore most of the drug was dissolved within 15 minutes. (*Id.* at Figures 1-4). However,

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at a pH of 1.2 and a mixing time of 5 min, the percentage of dissolved acetaminophen for each of the nine tablets can readily be estimated from Figure 1a (Paddle Method at 50 rpm) and Figure 3b (Basket Method at 100 rpm). This data is summarized in Table 1 below.

Table 1. Comparison of dissolution of commercial acetaminophen tablets using the Paddle Method at 50 rpm and the Basket Method at 100 rpm. (The FFKO tablets are not included in this comparison because the % dissolved could not be determined from Figure 3b.)

Dosage Form	% Dissolved (5 min) (Paddle Method at 50 rpm and pH 1.2)[a]	% Dissolved (5 min) (Basket Method at 100 rpm and pH 1.2)[b]	% Difference[c]
FRCH	~25	~50	+100
FPMD	~40	~95	+138
FWYT	~50	~70	+40
FOIF	~70	~30	-57
FNOB	~75	~60	-20
FIEU	~85	~100	+18
FSNV	~100	~90	-10
FDIF	~90	~85	-6

[a] Approximated from Figure 1a of Exhibit 2030.

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[b] Approximated from Figure 3b of Exhibit 2030.

[c] $\frac{(Basket-Paddle)}{(Paddle)} x\ 100$.

91. This data shows that for four of the commercial tablets (highlighted in yellow), the Basket Method at 100 rpm produced faster dissolution than the Paddle Method at 50 rpm. The dissolution of two of these products—FRCH and FPMD—were substantially faster using the Basket Method at 100, with an increase of more than 100%. For the other four commercial tablets (highlighted in purple), the Paddle Method at 50 rpm produced faster dissolution.

92. Based on these results, a person of ordinary skill in the art at the time of the invention would not believe that the statement in the Handbook of Dissolution Testing is generally applicable to the commercial acetaminophen tablets studied and would, in fact, reach the opposite conclusion. In half of the cases, the acetaminophen tablets exhibited faster dissolution under the Basket Method at 100 rpm. And in the other half, the acetaminophen tablets exhibited faster dissolution under the Paddle Method at 50 rpm. This study demonstrates there is no general correlation between the dissolution obtained under the Paddle Method at 50 rpm and the Basket Method at 100 rpm and, in fact, these methods often lead to significantly different dissolution rates.

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93. Thus, the Handbook of Dissolution Testing's statement that these two methods "have proved to be roughly equivalent to one another in producing dissolution" does not hold true in practice. (Ex. 1008 at 35).

b) Exhibit 2031 – DeHaan (Theophylline)

94. Exhibit 2031 is an article entitled *Studies on different dissolution models IV. Erosion of tablets* ("DeHaan"). DeHaan was published in 1982 in the journal PHARMACEUTISCH WEEKBLAD SCIENTIFIC EDITION and was therefore available to a person of ordinary skill in the art at the time of the invention.

95. DeHaan reports comparative dissolution testing of theophylline monohydrate tablets. (Ex. 2031 at 191). Theophylline is a Class 1 drug with a high solubility. In preparing the pharmaceutical compositions, "hard" tablets having a porosity of 1.4% were prepared by applying a compression force of 20±1 kN, and "soft" tablets having a porosity of 28.4% were prepared by applying a compression force of 850±30 N. (*Id.*). The paddle and basket methods disclosed in DeHaan both employed an agitation rate of 100 rpm. (*Id.*). Despite theophylline's high solubility, Figures 2 and 3 of DeHaan demonstrate that the dissolution profile is significantly slower under the Paddle Method at 100 rpm than under the Basket Method at 100 rpm. (*Id.* at 193, Figures 2, 3). For example, at 1 hour, about 58% of the theophylline in the hard tablets is dissolved using the Paddle Method at 100 rpm, whereas about 72% of the theophylline is dissolved

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using the Basket Method at 100 rpm. The difference between these methods is even more pronounced in the soft tablets. (*Id.* at 193, Figure 2). At 1 hour, again about 58% of the theophylline in the soft tablets is dissolved using the Paddle Method at 100 rpm, but about 93% is dissolved using the Basket Method at 100 rpm. (Id.).

96. Although the paddle method disclosed in DeHaan was carried out at 100 rpm, the dissolution rate would be expected to decrease when the agitation rate is decreased from 100 rpm (as disclosed in DeHaan) to 50 rpm (as claimed in the '216 patent). (*See*, *e.g.*, Ex. 2023 at Figures 6, 7 (showing faster dissolution for the paddle method at 100 rpm than at 50 rpm)). Thus, DeHaan teaches that, for both its hard and soft theophylline monohydrate tablets, the Paddle Method at 50 rpm and the Basket Method at 100 rpm result in significantly different dissolution profiles and release rates.

97. The results reported in DeHaan are consistent with a study published in 2004 using theophylline tablets. Exhibit 2032 is an article entitled *Effect of Hydrodynamic Environment on Tablet Dissolution Rate* published in the journal PHARMACEUTICAL DEVELOPMENT & TECHNOLOGY by Wu and co-workers ("Wu"). Similar to the tablets tested in DeHaan, these theophylline tablets exhibited much slower dissolution rates under the Paddle Method at 50 rpm than the Basket Method at 100 rpm. (Ex. 2032 at 27, Figures 3-4). For example, using the Basket

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Method at 100 rpm provided complete dissolution after 10 minutes. (*Id*. at 28, Table 1). Under the Paddle Method at 50 rpm, complete dissolution took 45 minutes. (*Id*.). The dissolution data are summarized in the following chart:

Time (min)	Paddle 50 rpm	Basket 100 rpm
5	20	95
10	41	100
15	75	99
30	96	100
45	99	100
60	100	100

98. The substantial differences in the dissolution rates observed between the two methods in the Wu study therefore holds despite the high solubility of theophylline. Accordingly, the fact that an active pharmaceutical ingredient is highly soluble does not mandate that the Paddle Method at 50 rpm and the Basket Method at 100 rpm produce "roughly equivalent" dissolution.

c) Exhibit 2033 – Cappola (ranitidine)

99. Exhibit 2033 is an article entitled *A Better Dissolution Method for Ranitidine Tablets USP* authored by Michael L. Cappola ("Cappola"). This article

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was published in the first issue of the journal PHARMACEUTICAL DEVELOPMENT AND TECHNOLOGY in 2001 and was therefore publicly available to a person of ordinary skill in the art at the time of the invention. I note that Cappola was previously disclosed during the prosecution of the '216 patent, but neither Dr. Palmieri nor Ms. Gray discussed this article in their declarations in this proceeding.

100. Figure 1 of Cappola demonstrates that for 150 mg and 300 mg dosages forms of ranitidine sold by Boehringer Ingelheim Pharmaceuticals Inc., the dissolution rate under the Basket Method at 50 rpm is substantially higher than the dissolution rate under the Paddle Method at 50 rpm. (Ex. 2033 at 12-13, Figure 1). For example, using the Basket Method at 50 rpm, almost all of the ranitidine in the 150 mg tablets had dissolved by 15 minutes. (*Id.* at 13, Figure 1). Using the Paddle Method at 50 rpm, only about 60% had dissolved by 15 minutes, and 90% of the ranitidine had dissolved at 60 minutes. Similar results were observed for the 300 mg tablet. (*Id.*). Given that increased agitation rate generally increases dissolution, if the Basket Method had been performed at 100 rpm (as disclosed in Oshlack), a person of ordinary skill in the art would have expected the 150 mg ranitidine tablet to have a significantly faster dissolution rate using the Basket Method at 100 rpm versus the Paddle Method at 50 rpm. Similar results would be expected for the 300 mg rantidine tablet. (*Id.*).

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101. Additionally, like theophylline, ranitidine is a Class I drug with a high solubility. This is further support for the conclusion that highly soluble drugs may also exhibit substantially different dissolution profiles when employing the Paddle Method at 50 rpm versus the Basket Method at 100 rpm.

4. The Statement in the Handbook of Dissolution Testing Is Not Generally Applicable to Controlled Release Formulations

102. All of the studies I have described above in Paragraphs 87-101 involved the dissolution of immediate release formulations. The claims of the '216 patent are directed to controlled release formulations. This difference does not change my opinions.

103. The Handbook of Dissolution Testing itself does not distinguish between immediate release and controlled release formulations. Instead, it makes a blanket assertion that for general purposes, the Paddle Method at 50 rpm and the Basket Method at 100 rpm produce "roughly equivalent" dissolution. As noted above, the statement is not generally applicable to immediate release formulations, and there is nothing to suggest that it is generally applicable to extended release formulations. This is consistent with *Applied Biopharmaceutics*, which relied on several studies involving controlled release pharmaceutical formulations in concluding that there is no correlation between different dissolution methods. (*See* Ex. 2020 at 145).

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104. My opinion is also supported by other scientific literature. Exhibit 2034 is an article entitled *Release characterization of dimenhydrinate from an eroding and swelling matrix: selection of appropriate dissolution apparatus* authored by Missaghi and Fassihi. This article was published in the INTERNATIONAL JOURNAL OF PHARMACEUTICS in 2005. Although this study was not available to a person of ordinary skill in the art at the time of the invention, it confirms the generally accepted principle that there is no correlation between the dissolution data obtained using the Paddle Method at 50 rpm and the Basket Method at 100 rpm.

105. In this study, the authors conducted dissolution testing on a controlled release formulation containing dimenhydrinate, hydroxypropyl methyl cellulose ("HPMC"), and polyethylene oxide. (Ex. 2034 at Abstract). I note that Oshlack discloses the use of dimenhydrinate, an antihistamine, as the very first suitable therapeutically active agent, and HPMC as a matrix ingredient. (Ex. 1007 at 6:51-55, 8:62-65). Oshlack also discloses that its sustained-release matrix may contain other pharmaceutically acceptable carriers and excipients conventionally used in the pharmaceutical art. (*Id.* at 9:46-56). As of the filing date of Oshlack, polyethylene oxide was used in pharmaceutical formulations and had its own Monograph in USP23/NF18. (Ex. 2035 at 2285-86). Thus, the pharmaceutical formulation described in Exhibit 2034 contains several ingredients expressly

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disclosed in Oshlack (although it does not employ Oshlack's extrusion process for forming multi-particulate extrudates and therefore falls outside of Oshlack's disclosure). Dissolution testing using the Paddle Method at 50 rpm resulted in a significantly different release profile than the Basket method at 100 rpm. (Ex. 2034 at 40-41, Tables 2-4).

106. Figure 4 of Exhibit 2034 compares the dissolution profile of the pharmaceutical formulation at various time points and demonstrates that the Paddle Method at 50 rpm provides significantly different dissolution than the Basket Method at 100 rpm. (*Id.* at 39, Figure 4). For example, at 1 hour, about 23% of the dimenhydrinate had dissolved under the Paddle Method at 50 rpm. (*Id.*). In contrast, at 1 hour, less than 10% had dissolved using the Basket Method at 100 rpm. (*Id.*). This is greater than a 100% difference and is certainly not "roughly equivalent."

107. Several conclusions can be drawn from this study. First, a formulation that falls within the structural characterization of the formulations disclosed in Oshlack exhibits substantially different dissolution behavior under the Paddle Method at 50 rpm and the Basket Method at 100 rpm—directly contradicting the Handbook of Dissolution Testing. Second, the Paddle Method at 50 rpm gives a faster dissolution rate than the Basket Method at 100 rpm, which again demonstrates that there is no general correlation between these two methods.

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108. I also want to note Figure 2 in Exhibit 2034. During her deposition, Ms. Gray testified that for extended release formulations, agitation rate has very little effect on the observed dissolution. (Gray Tr., Ex. 2029 at 86:11-88:3). I disagree for the reasons already provided above: increasing agitation rate generally increases dissolution. (*See*, *supra*, ¶¶ 59, 68-70, 74-75). This is confirmed by Figure 2 of Exhibit 2034, which demonstrates that the controlled release formulation exhibits substantially faster dissolution using the Paddle Method at 100 rpm than the Paddle Method at 50 rpm.

5. The skilled artisan could not have reasonably predicted what Oshlack's dissolution rates would have been using the Paddle Method at 50 rpm

109. During her deposition, Ms. Gray confirmed that the Handbook of Dissolution Testing did not provide any citation to support its statement relating to the alleged equivalence of the Paddle Method at 50 rpm to the Basket Method at 100 rpm. (Gray Tr., Ex. 2029 at 197:3-19). When asked whether she conducted a search of the scientific literature relating to this issue, Ms. Gray confirmed that she searched her own internal files but could not find any studies to support the general applicability of the statement in the Handbook of Dissolution Testing. (*Id.* at 198:21-199:13). Ms. Gray, however, alleged that the "rough equivalence" of the two methods was "common knowledge among dissolution analysts." (*Id.* at 201:2-11). I am not only a "dissolution analyst" but am a dissolution expert with over

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thirty years of experience. As I stated above, Ms. Gray's overly broad interpretation of the statement in the Handbook of Dissolution Testing is not common knowledge, is not supported by any scientific principles underlying the dissolution phenomenon, and is actually contradicted by the peer-reviewed scientific literature.

110. Notably, Ms. Gray's assertion that the statement in the Handbook of Dissolution Testing is common knowledge is based on her review of non-public, confidential development reports she personally obtained from her clients. (*See id.* at 198:21-199:17, 201:2-17). This information would not have been publicly accessible to a person of ordinary skill in the art as Ms. Gray herself admitted none of these development reports have ever been published. They therefore cannot form the basis for any alleged "common knowledge" in the field.

111. When the prior art is considered as a whole, including the scientific publications I have discussed above, a person of ordinary skill in the art could not have reasonably predicted what the dissolution ranges disclosed in Oshlack, as measured by the Basket Method at 100 rpm, would have been using the Paddle Method at 50 rpm as claimed in the '216 patent. The scientific literature above demonstrates that sometimes the Basket Method at 100 rpm produces a substantially faster dissolution; sometimes the Paddle Method at 50 rpm produces a substantially faster dissolution; and sometimes both methods give similar

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dissolution profiles. Given the complex, multi-faceted, and sheer number of variables that influence the dissolution rate, there was no scientific basis at the time of the invention—nor is there even one today—that would have permitted a person of ordinary skill in the art to reasonably predict the effect of changing the apparatus and agitation rate on the dissolution of a controlled release formulation disclosed in Oshlack.

112. Consequently, it is my opinion that the dissolution profile claimed in the '216 patent would not have been obvious at the time of the invention in view of the combination of Oshlack and the Handbook of Dissolution Testing. First, Amneal has failed to provide any evidence actually showing that Oshlack discloses the claimed dissolution profile. The prior art demonstrates that dissolution would not be expected to be equivalent using the Paddle Method at 50 rpm and the Basket Method at 100 rpm. Second, there was no general correlation between the two dissolution methods that would have allowed a person or ordinary skill in the art to reasonably predict what Oshlack's dissolution would have been using the claimed dissolution test method.

113. Put simply, a person of ordinary skill in the art would have had to test the formulations of Oshlack using the claimed dissolution method to determine their dissolution profiles at those parameters. Noticeably absent from Amneal's

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Petition is any evidence of such testing, despite its dissolution testing relating to the Maloney reference.

114. Additionally, were Amneal to rely on Oshlack's alternative disclosure of dissolution using the Paddle Method at 100 rpm, these values would also fail to teach the claimed dissolution. As indicated above, the dissolution rate would be expected to increase when the agitation rate is increased from 50 rpm to 100 rpm, but the extent of this increase is not reasonably predictable. (*See*, *e.g.*, Ex. 2023 at 11, Figures 6, 7 (showing faster dissolution for the paddle method at 100 rpm than at 50 rpm); Ex. 2020 at 145 (noting that increased agitation rates result in increased dissolution)).

VIII. THE PRIOR ART TEACHES AWAY FROM A CONTROLLED RELEASE OXYMORPHONE COMPOSITION

115. There is no clinical data disclosed in Maloney or Oshlack—or any other prior art reference raised in Amneal's Petition—demonstrating either (i) the *in vivo* pharmacokinetic data of a controlled release oxymorphone formulation or (ii) the *in vitro* dissolution profile needed to achieve these *in vivo* pharmacokinetic characteristics. In fact, Maloney and Oshlack do not even provide any specific examples of any controlled release oxymorphone compositions. Oxymorphone, along with all of the other known opioids, is merely disclosed in a laundry list of allegedly suitable active pharmaceutical ingredients.

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116. Without knowing the *in vivo* pharmacokinetic characteristics required to provide analgesia over at least a twelve hour period, a person of ordinary skill in the art would not have been able to assess whether the alleged oxymorphone formulations disclosed in Maloney and Oshlack would achieve therapeutic efficacy. As noted in *Applied Biopharmaceutics*:

> The interpretation of dissolution data is probably the most difficult job for the pharmacist. In the absence of in vivo data, it is generally ***impossible*** to make valid conclusions about bioavailability from the dissolution data alone.

(Ex. 2020 at 145 (emphasis added)). Exhibit 2040 (discussed in more detail below) echoes this point:

> Unless it can be demonstrated that the in vitro release behavior reflects the in vivo performance in humans, ***the data can be of no relevant value in predicting or judging the clinical effectiveness*** of a drug product.

(Ex. 2040 at 476 (emphasis added)).

117. Given that Maloney and Oshlack completely fail to provide any pharmacokinetic data with respect to any oxymorphone composition, the prior art as a whole teaches away from a controlled release oxymorphone formulation—and certainly does not provide a person of ordinary skill in the art with a reasonable

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expectation of successfully formulating an oxymorphone composition that alleviates pain over at least a 12 hour period.

A. The Prior Art Taught Away From Using Low Bioavailable Drugs in Controlled Release Formulations

118. The amount of the drug from an oral composition that is available systemically throughout the body (*i.e.*, the blood plasma level) is referred to as the oral bioavailability of the drug formulation. Oxymorphone has a low oral bioavailability, which is confirmed by Patent Owner's clinical studies. For example, in the clinical study described in Exhibit 2013, the blood plasma concentrations of oxymorphone and its two metabolites, 6-hydroxyoxymorphone and oxymorphone-3-glucuronide, were measured for three immediate release oxymorphone compositions. C_{max} and AUC for the inactive metabolite oxymorphone-3-glucuronide were orders of magnitude larger than those for oxymorphone and its active metabolite 6-hydroxyoxymorphone for each of the formulations. (Ex. 2013 at 20, Table 4).

119. The lower the bioavailability of a drug formulation, the smaller the fraction of the administered dose that actually enters the blood plasma and is thereby available at the drug's site of action to deliver the desired effect. If its oral bioavailability is low enough, a drug may only be effective for a minimal amount of time, if at all. The effect of low bioavailability is more significant and problematic for a controlled release formulation because its slow release from the

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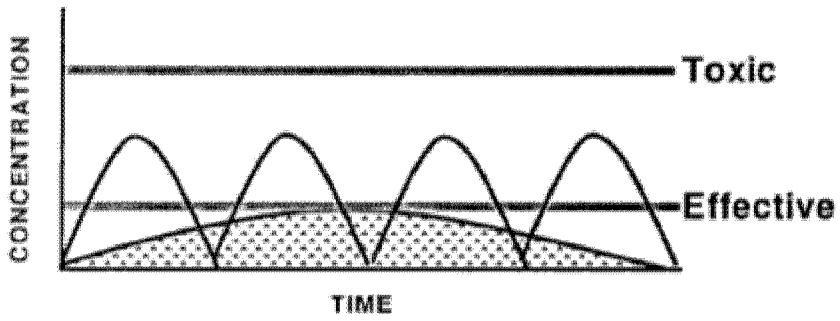
tablet into the digestive tract may result in nearly complete metabolism and thereby no effective concentration of drug in the bloodstream.

120. Exhibit 2037 is a chapter authored by J. Mordenti & R. L. Williams entitled *Controlled Release Drug Delivery: Pharmacodynamic Consequences*, *in* the book Oral Sustained Release Formulations: Design and Evaluation ("Mordenti Chapter"). The Mordenti Chapter explains:

> A poorly available or inadequately dosed controlled release product may produce no effective concentrations throughout a dosing interval, whereas an immediate release product with the same degree of bioavailability or dosing limitation may still produce intermittently effective concentrations (Figure 1, middle panel)."

(Ex. 2037 at 196). A copy of Figure 1, middle panel, of the Mordenti Chapter is reproduced below:



(*Id.* at 197, Figure 1(II)). The stippled region in the Figure shows how a controlled release drug with a low bioavailability may never reach the minimum effective plasma concentration. In order to maintain therapeutically effective blood levels of

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such a poorly bioavailable drug, a higher dose of the drug is needed. However, the elevated dose of drug can lead to significant and potentially prohibitive challenges in drug formulation, as I discuss in more detail below.

121. There are several factors that affect the oral bioavailability of a drug, including the ability of the drug to be absorbed in the gastrointestinal ("G.I.") tract and the rate the drug is metabolized and or extracted in the G.I. tract and the liver. The latter plays a key role in the bioavailability of oral formulations, because orally absorbed drugs are first absorbed from the G.I. tract and then transported to the liver by the hepatic portal vein. If the given drug is metabolized (or extracted and excreted) by the liver, less of the drug will reach the bloodstream unchanged, thus resulting in a lower bioavailability. This is commonly known as "first-pass metabolism" or the "first-pass effect."

122. As a result of their diverse physical and chemical properties, individual drugs react differently to the liver's enzymes. Some drugs experience little to no first-pass metabolism. Oxycodone is an example of such a drug, as reflected by its relatively high bioavailability. (*See* Ex. 2038 at 2537 (noting that "[a]bout 60 to 87% of an oral dose of oxycodone reaches the central compartment in comparison to a parenteral dose. This high oral bioavailability is due to low pre-systemic and/or first-pass metabolism.")). In contrast, other drugs, such as

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oxymorphone, undergo extensive first-pass metabolism in the liver. (*See* Ex. 2039 at 1036 ("Oxymorphone undergoes extensive hepatic metabolism in humans.")).

123. Moreover, the rate at which a drug is metabolized in the liver is not uniform, but can depend on the concentration of the drug in the liver. This is because the liver's metabolic enzymes have a limited capacity, which may become saturated (used up) in some situations. Accordingly, if the drug concentration in the liver is below saturation, the drug may be subject to substantial metabolism and, consequently, have low bioavailability in the bloodstream. With higher drug concentrations, the liver's enzymes can become saturated—i.e., overwhelmed—and unable to metabolize the drug present in the liver. When more drug is present than the enzymes can metabolize, a greater proportion of drug passes into the systemic circulation. In other words, at higher concentrations, such as occurs with immediate release dosing, more of the drug will be available systemically in a disproportionate amount as compared to if only smaller concentrations are introduced to the liver over an extended period of time as occurs with extended release dosing.

124. The concentration of drug present in the liver is a function of both the dose and the rate at which the drug is released from the formulation. With an immediate release formulation, substantially all of the drug is released at once, thus potentially saturating hepatic enzyme metabolic capacity more thoroughly, which

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in turn allows a potentially greater amount of free, unbound drug to escape first-pass metabolism. (See Ex. 2037 at 208 ("Nonlinear disposition may be prominent after oral administration because of the relatively high concentrations of drug entering the hepatic portal system and reaching hepatic sites of biotransformation. These concentrations may be particularly high after oral administration of a solution or immediate release dose.")). In contrast, with a controlled formulation, the drug is being released from the dosage form at a slower rate, which allows enzyme complexes more time to recover and thus free up to bind and to metabolize new molecules of drug. (See id. at 208-09 ("Controlled release formulations have less of a tendency to produce saturable first pass metabolism because of their slower rate of drug input and consequently lower intrahepatic drug concentration.")). This will reduce the amount of the drug that is available systemically and thus decrease the bioavailability of an controlled release versus an immediate dose.

125. Referring to Figure 6 below, the Exhibit 2037 provides an example of how a controlled release formulation of a drug that undergoes saturable first-pass metabolism can significantly reduce bioavailability relative to the immediate formulation:

> At low oral doses, propranolol AUCs are equivalent (7) irrespective of whether the drug is given as an immediate or controlled release formulation (Figure 6). As the dose of drug

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increases, the ratio of the dose adjusted AUC of the controlled release formulation relative to AUC of the immediate release formulation falls significantly. This decline occurs because relatively more drug escapes hepatic biotransformation at the higher rates of drug input associated with the immediate release formulation. At the highest doses, propranolol AUC ratios for the immediate release and controlled release formulation again approach unity as comparable amounts of drug escape hepatic biotransformation irrespective of the rate of administration. Data such as that presented in Figure 6 suggest that the pharmacologic response to propranolol may vary widely between immediate and controlled release formulations even when they are given at comparable doses.

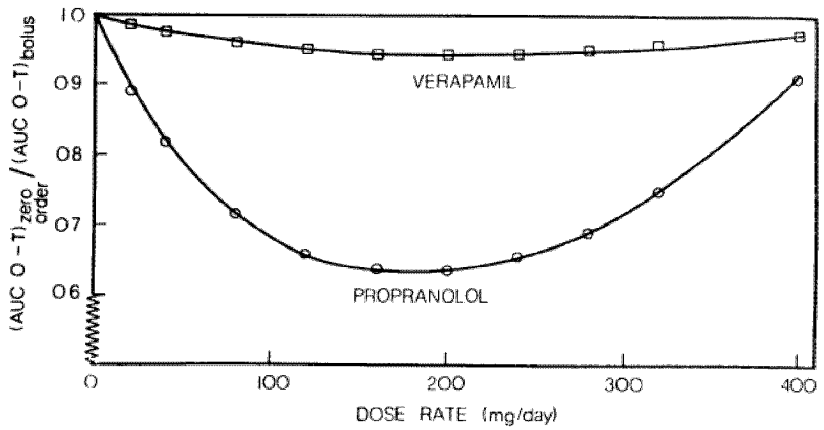

FIGURE 6: THE RATIO AUC $_{0-T}$ FOR A CONTROLLED RELEASE PRODUCT TO AUC $_{0-T}$ FOR AN IMMEDIATE RELEASE PRODUCT VERSUS THE INFUSION RATE OF VERAPAMIL AND PROPRANOLOL (7).

(Ex. 2037 at 209-10, Figure 6).

126. Because first-pass effects are often exacerbated by controlled release formulations, these formulations slowly deliver smaller amounts of drug, thereby

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keeping drug concentrations in the liver steady but low enough for the enzymes to metabolize, are better suited to drugs that experience insubstantial first-pass metabolism. In contrast, for drugs that are subject to substantial liver metabolism, an immediate release dosage form is best since it provides a quick bolus of drug that can overwhelm the liver enzymes.

127. Indeed, the prior art taught away from trying to design ER formulations of drugs that undergo extensive first-pass metabolism. Exhibit 2040 is a chapter authored by Yihong Qiu & Guohua Zhang entitled Research & Development Aspects of Oral Controlled-Release Dosage Forms, in Handbook of Pharmaceutical Controlled Release Technology ("Qiu Chapter"). This book was published in 2000 and was therefore available to a person of ordinary skill in the art at the time of the invention. According to the Qiu Chapter, first-pass metabolism is a factor affecting the feasibility in developing oral controlled release formulations:

> For drugs with saturable first-pass metabolism (hepatic or gut), bioavailability will be decreased due to slow systemic input from the controlled release systems, ***thus limiting the chance of success of a controlled release system***.

(Ex. 2040 at 465, Table 2 (emphasis added)).

128. Exhibit 2041 is an excerpt of a book entitled, *Extended-Release Dosage Forms* 103 (1987) by Leszek Krowczynski ("Krowczynski"). This book

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was published in 1987 and was therefore available to a person of ordinary skill in the art at the time of the invention. According to Krowczynski:

> The design of an extended-release dosage form should also account for the possibility of an 'absorption window' for a given drug. This means whether or not it is absorbed exclusively within a short part of the GI tract, or if there is a first-pass effect (the loss of drug as it passes through the gastrointestinal membranes and the liver for the first time during the absorption process). ***Such a situation makes the formulation of the oral extended-release dosage form impossible in most cases***.")

(Ex. 2041 at 103 (emphasis added)).

129. A primary reason why a drug that undergoes extensive first-pass metabolism is generally incompatible with an controlled release dosage form is because disproportionately greater quantities of drug need to be delivered over time in order to overcome the resulting low bioavailability, which in turn can raise safety and other concerns. In the context of an immediate release formulation of a drug that undergoes extensive first-pass metabolism and therefore has a considerably low bioavailability, a higher dosage strength may be necessary in order to maintain optimal blood levels of the drug in a patient. This elevated dose will be magnified in a controlled release formulation, which inherently contains a greater drug quantity (e.g., two-fold to three-fold) than the immediate release

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formulation. Moreover, the demand for more drug is further compounded by the lower bioavailability that results from the extended release formulation due to the exacerbated first-pass effects.

130. Exhibit 2042 is an article authored by N. W. Read & Keith Sugden entitled Gastrointestinal Dynamics and Pharmacology for the Optimum Design of Controlled-Release Oral Dosage Forms ("Read Article"). The Read Article was published in the book CRC Critical Reviews in Therapeutic Drug Carrier Systems in 1987. Accordingly, the Read Article was available to a person of ordinary skill in the art at the time of the invention. The Read Article explains why controlled release formulations are generally unsuited for drugs that undergo extensive first-pass metabolism:

> Hepatic or gut wall enzymes have a limited capacity. Thus, bioavailability of a drug which has a large first-pass metabolism, such as propanalol, may increase with dose because a greater proportion of the drug will avoid degradation and enter the systemic circulation. If, however, the drug is released slowly from the dosage form, concentrations in the intestinal mucosa or the liver may be insufficient to saturate the enzymes and this may result in a drastically reduced bioavailability. Satisfactory blood levels can then only be achieved if large doses are used, risking toxicity if the sustained-release preparation were to be disrupted early or if the effects of the metabolizing enzymes were reduced by disease or

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drugs. ***Thus, drugs that undergo extensive first-pass metabolism are not generally suitable for administration from a controlled-release device***.

(Ex. 2042 at 240 (emphasis added) (citations omitted)).

131. The Read Article's statement about being "disrupted early" is in reference to "dose-dumping," in which an unintentional and unexpected failure of the delivery system causes large amounts of drug to be dumped out of the dosage form and into the patient's bloodstream. The risk of dose-dumping is particularly concerning for controlled release formulations of potentially dangerous narcotic drugs such as oxymorphone. Moreover, dose-dumping is unpredictable because it may be caused by faulty manufacture of the formulation or by reaction with certain gastrointestinal contents such as food. (See Ex. 2040 at 481 (Dose-dumping "may be caused by a product's faulty manufacture or by its susceptibility to the influence of food or other variables in the GI tract.")).

132. These prior art teachings are consistent with the information provided in the Fiske Declaration (Exhibit 2043) submitted during the prosecution of the '216 patent. I have read the Fiske Declaration and agree with its contents.

133. Accordingly, one skilled in the art would have been taught away from attempting to achieve an extended release formulation of a drug with low bioavailability due to extensive first-pass metabolism, like oxymorphone, and

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would not have reasonably expected such a formulation to successfully achieve pain relief over at least a 12 hour period.

B. Dr. Palmieri's Testimony Regarding the Relevance of First-Pass Metabolism Associated With Oxymorphone Is Wrong

134. During his deposition, Dr. Palmieri provided testimony that is wrong. I understand that Dr. Palmieri testified as follows:

> Q. Do you know if oxymorphone is subject to first pass effect?
>
> A. I don't recall. However, since first pass effect usually occurs with nonoral drugs, specifically rectal administration, as it pertains to this matter at hand, it's not material.
>
> Q. So you didn't consider a first pass effect to be a consideration in forming your opinions in your declaration; is that right?
>
> A. Not that I recall.

(Palmieri Tr., Ex. 2012 at 125:10-19). This testimony contradicts common knowledge in the pharmaceutical arts. Indeed, it is well-established that suppositories are often formulated because administration of a drug via the rectum forgoes first-pass metabolism in the liver—exactly the opposite of what Dr. Palmieri's testimony. Similarly, drugs administered intravenously do not undergo first-pass metabolism. Given its significant first-pass metabolism, it is not surprising that at the time of the invention oxymorphone in an oral dosage form

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had been pulled from the market and was available only in injection and suppository forms. (*See* Ex. 2063 at 44).

135. Accordingly, Dr. Palmieri's testimony that the extent of first-pass metabolism of an oral oxymorphone composition is "not material" is incorrect. Based on oxymorphone's substantial first-pass metabolism, the prior art as a whole would have taught away from oral extended release oxymorphone formulations.

C. The Prior Art Taught Away From Using Oxymorphone in Controlled Release Formulations

136. Were a person of ordinary skill motivated to attempt to make a controlled release formulation of oxymorphone, the skilled artisan would first consider its pharmacokinetic properties, among other things:

> Before a drug is incorporated into the controlled delivery matrix it is important to have a sound knowledge of the pharmacokinetic profile of the drug, the efficacy of absorption from different regions of the tract, the therapeutic window, and the susceptibility to degradation by pH, by gastrointestinal enzymes, and by bacteria.").

(Ex. 2042 at 253). This is particularly true in view of the fact that oxymorphone was known to undergo extensive first-pass metabolism. (*See* Ex. 2039 at 1036 ("Oxymorphone undergoes extensive hepatic metabolism in humans.")). An ordinarily skilled artisan investigating the pharmacokinetic properties of

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oxymorphone would have appreciated that the oral bioavailability of immediate release oxymorphone is only about 10%. (Ex. 1001 at 2:15-16).

137. The artisan would have recognized that this value is exceptionally low relative to other opioids that had previously been incorporated into controlled release formulations. For example, oxycodone, which is the only opioid tested in Maloney, has an oral bioavailability of 60-87%. (*See* Ex. 2044 at 2537). In view of oxymorphone's discouraging bioavailability and the well-documented principle that a drug that experienced extensive first-pass metabolism was incompatible with controlled release formulations, a person of ordinary skill in the art would have been discouraged from pursuing a controlled release oxymorphone formulation and would have concluded that there was not a reasonable expectation of success for developing the claimed therapeutically effective controlled release formulation of oxymorphone.

138. It would have been expected that a disproportionately higher dose would be required in a controlled release formulation of oxymorphone because the more gradual introduction of the drug into the liver allowed additional drug metabolism and therefore resulted in lower bioavailability. However, increased doses of narcotics, like oxymorphone, raise safety and toxicity concerns, particularly given abuse potential. Contrary to this conventional wisdom in the art, the inventors unexpectedly discovered that oxymorphone could be made into a

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controlled release formulation with at least 12 hours of analgesic effectiveness, despite its low bioavailability.

D. Nothing in Maloney Overcomes This Teaching Away

139. A person of ordinary skill in the art would not have reasonably expected to successfully achieve an analgesically effective controlled release oxymorphone tablet based on the teachings of Maloney. First, Maloney does not show that any of its controlled release formulations, which are limited to oxycodone only, are analgesically effective. Without any *in vivo* pharmacokinetic data disclosed in Maloney, a person of ordinary skill in the art would not have known whether the Maloney formulations worked:

> In the absence of *in vivo* data, it is generally ***impossible*** to make valid conclusions about bioavailability from the dissolution data alone.

(Ex. 2020 at 145 (emphasis added)). This is especially true given that the claims are directed to controlled release oxymorphone compositions whereas Maloney discloses an *in vitro* dissolution profile for oxycodone only. Thus, a person of ordinary skill in the art would not have reasonably expected the Maloney formulations to provide analgesia for at least 12 hours.

140. Second, in view of oxymorphone's known extensive first-pass hepatic metabolism, a person of ordinary skill in the art would not have believed that, even if effective for oxycodone (a compound having a significantly higher oral

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bioavailability than oxymorphone), the formulation teachings of Maloney would lead to an analgesically effective controlled release formulation of oxymorphone—let alone one that provided 12 hours of analgesic effect as required by claim 1 of the '216 patent. In fact, a person of ordinary skill in the art would have been led away from developing a controlled release oxymorphone composition due to its extensive first-pass metabolism—or at least would not have reasonably expected that such a composition would successfully yield effective pain therapy over a 12 hour period.

E. Oshlack Actually Teaches That Bioavailability Is a Critical Consideration in Pharmaceutical Development and Therefore Discourages the Skilled Artisan From Attempting the Claimed Invention

141. In my opinion, the express disclosure of Oshlack reinforces that a person of ordinary skill in the art would not have been motivated by the teachings of Oshlack to develop a controlled release oxymorphone formulation. Although oxymorphone is expressly disclosed and claimed in Oshlack, there is no data in Oshlack suggesting that its alleged oxymorphone compositions are therapeutically effective over a 12 hour period, or any amount of time for that matter. Instead, oxymorphone—along with more than 100 other drugs—is merely listed as a prophetic example, apparently because it is in the opioid class of drugs.

142. Oshlack, however, repeatedly emphasizes the importance of bioavailability when designing sustained release dosage forms:

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> "[I]n order for a dosage form to be effective for its intended purpose, the dosage form must be bioavailable."

(Ex. 1007 at 5:10-12).

> "The dissolution time and the ***bioavailability*** determined for a composition are two of the ***most significant fundamental characteristics for consideration*** when evaluating sustained-release compositions."

(*Id.* at 2:47-50 (emphasis added)). Oshlack therefore would have directed one of ordinary skill in the art away from developing controlled release oxymorphone due to the drug's exceptionally low bioavailability.

143. Despite the fact that Oshlack repeatedly emphasizes the importance of a drug's bioavailability in successfully developing a controlled release product, Dr. Palmieri admitted he did not even consider the bioavailability of oxymorphone or how its oral bioavailability compares to the only opioids tested in Oshlack (notably, none of the experimental examples in Oshlack involve oxymorphone). (Palmieri Tr., Ex. 2012 at 62:2-6, 74:14-75:2).[3] Had he done so, Dr. Palmieri would have seen substantial differences:

[3] I note that Dr. Palmieri, when questioned by Amneal's counsel, later testified that he did consider bioavailability and referred to the equianalgesic table in the Gordon reference (Ex. 1011) to support that testimony. (Palmieri Tr., Ex. 2012 at 207:9-209:13). However, Gordon itself—a reference written by and intended for nurses—acknowledges that the validity of such equianalgesic tables are questionable. (Ex. 1011 at 215).

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Opioid	Oral Bioavailability	Source
Oxymorphone HCl	10%	(Ex. 1001 at 2: 15-16).
Morphine Sulfate	40%	Physicians' Desk Reference[4] 2524 (54th ed. 2000) (entry for MS CONTIN (controlled release morphine sulfate) notes: "[b]ecause of pre-systemic elimination (i.e., metabolism in the gut wall and liver) only about 40% of the administered dose reaches the central compartment") (Ex. 2044 at 2524).
Oxycodone HCl	60-87%	2000 PDR at 2537 (entry for OxyContin (controlled release oxycodone hydrochloride) notes: "[o]xycodone is well absorbed from OXYCONTIN tablets with an oral

[4] The 2000 PDR provides drug label information. This information is the result of extensive clinical trials and must be approved by the FDA. It is therefore one of the more reliable sources for identifying a drug's bioavailability. Although the scientific literature occasionally refer to morphine as having extensive first-pass metabolism, its oral bioavailability is about four times greater than oxymorphone. Accordingly, a person of ordinary skill in the art would not have taken the successful incorporation of morphine sulfate into a controlled release formulation as a predictor of success for oxymorphone.

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Opioid	Oral Bioavailability	Source
		bioavailability of from 60% to 87%. The relative oral bioavailability of OXYCONTIN to immediate-release oral dosage forms is 100%.") (Ex. 2038 at 2537).
Hydromorphone HCl	60%	Wolfgang A. Ritschel, Handbook of Basic Pharmacokinetics …including Clinical Applications 491 (5th ed. 1999) ("Ritschel Handbook")[5] (noting oral bioavailability (f) of hydromorphone to be 60%) (Ex. 2045 at 491).
Tramadol HCl	75%	2000 PDR Supplement A at A248 (entry for ULTRAM (immediate release tramadol hydrochloride) notes: "[t]ramadol is well absorbed orally with an absolute

[5] The entry for DILAUDID (immediate release hydromorphone hydrochloride) in the 2000 PDR does not identify hydromorphone's bioavailability. Therefore, the Appendix of the Ritschel Handbook is cited for this information. The Appendix lists "*mean* data" for "Pharmacokinetic Parameters of Important Drugs," which was compiled from "more than a thousand publications." (Ex. 2045 at 479 (emphasis in original)). The use of mean data derived from a number of sources alleviates any reliability concerns.

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Opioid	Oral Bioavailability	Source
		bioavailability of 75%") (Ex. 2046 at A248).

144. In view of the drastically lower bioavailability of oxymorphone compared to these other opioids, one of ordinary skill in the art would not have reasonably expected the successful design of an effective oxymorphone controlled release formulation based on the existence of an effective controlled release formulation of any of these other opioids.

145. The '216 Patent teaches that in order to provide an analgesically effective controlled formulation of oxymorphone, "it is important in the present invention that appropriate blood plasma levels of oxymorphone and 6-hydroxyoxymorphone be achieved and maintained for sufficient time to provide pain relief to a patient for a period of 12 to 24 hours." (Ex. 1001 at 6:43-46). Thus, to the patient, it is the level of oxymorphone and 6-hydroxyoxymorphone in the blood plasma that is most important. Further, it is these levels that dictate the efficacy of the dosage form. This is self-evident: a patient needs the drug in his/her bloodstream for efficacy. And, in the special case of oxymorphone, that means overcoming the substantial first-pass effects.

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146. At the time of the invention, however, it was unknown what dissolution rate would be needed to do so. As the '216 patent expressly teaches, the release rate "is a critical variable in attempting to control the blood plasma levels of oxymorphone and 6-hydroxyoxymorphone in a patient." (Ex. 1001 at 10:44-46). Indeed, prior to the work of the inventors, no one knew of any release rate for an oxymorphone ER formulation that would provide adequate blood plasma levels over a 12-hour period. A person of ordinary skill in the art could not have taken a dissolution profile for one opioid controlled release formulation, substituted in oxymorphone, tweaked the formulation to obtain the same dissolution profile, and reasonably expected that the resulting formulation would be therapeutically effective. This is because *in vitro* dissolution rates are meaningless for predicting therapeutic effectiveness of a drug without an appropriate connection to *in vivo* blood levels. (*See* Ex. 2040 at 476 ("Unless it can be demonstrated that the in vitro release behavior reflects the in vivo performance in humans, the data can be of no relevant value in predicting or judging the clinical effectiveness of a drug product.")).

147. Accordingly, without the benefit of hindsight or the inventive effort and substantial experimentation completed by the inventors, a person of ordinary skill in the art would not have known the appropriate dissolution profile for

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controlled release oxymorphone to achieve therapeutically effective blood levels of oxymorphone and/or 6-hydroxyoxymorphone for at least 12 hours.

F. Dr. Palmieri's Opinions Are Undermined by His Deposition Testimony

148. In reviewing Dr. Palmieri's deposition transcript, I believe his opinions are undercut by the fact that he admittedly did not consider critical aspects of the issues at hand such as: (1) the differences in bioavailability among opioids; (2) the characteristics of oxymorphone including how it is distributed, its metabolism and whether it is subject to the first-pass effect; or (3) secondary indicia of non-obviousness including commercial success of the '216 patent's commercial product. In fact, Dr. Palmieri admitted that he did no independent research whatsoever on oxymorphone or any of the above issues. (Palmieri Tr., Ex. 2012 at 120:1-9). In my opinion, however, a person of ordinary skill in the art at the time of invention would have understood the aforementioned aspects to be essential to any comparison of the teachings of the prior art and the invention claimed in the '216 patent. Consequently, Dr. Palmieri's opinions should be entitled to little or no weight.

149. Dr. Palmieri asserts that the working examples in Oshlack render the claimed invention obvious, even where none of the working examples describe or test oxymorphone. Yet, Dr. Palmieri did not consider bioavailability differences between oxymorphone and other opioids when writing his declaration. (*Id.* at

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62:5; 74:19). He did not even know the bioavailability of oxymorphone, oxycodone, morphine, tramadol or hydromorphone. (*Id.* at 57:14; 69:19-20; 70: 2-7). Also, according to Dr. Palmieri, there is no equation to determine the bioavailability of oxymorphone from other opioids. (*Id.* at 76:19-21). But, as I discuss above, bioavailability is a critical aspect of a drug. In this case, one skilled in the art would have been taught away from attempting to achieve a controlled release formulation of a drug with low bioavailability due to extensive first-pass metabolism, like oxymorphone, and would not have expected such a formulation to successfully achieve pain relief over at least a 12 hour period.

150. Dr. Palmieri further asserts that the equianalgesic table in Exhibit 1011, which is an article entitled *Opioid Equianalgesic Calculations* by Gordon ("Gordon"), would allow a person skilled in the art to switch between oxymorphone and other opioids. (Palmieri Tr., Ex. 2012 at 100:11-17). After reviewing Gordon, however, he realized that Gordon does not provide data for controlled release opioids. (*Id.* at 110:7-113:16). He then stated that if the data was not known that he could design a clinical study to determine an equianalgesic dose. (*Id.*). According to Dr. Palmieri, other than a clinical study, there is no other way to determine an equianalgesic dose between a controlled release oxymorphone formulation and another formulation. (*Id.* at 113:12-16). He admitted that a person skilled in the art could not switch from one drug to another without *in vivo*

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data. (*Id.* at 68:9-69:6). But Dr. Palmieri refused to answer when asked if he agreed with the JOURNAL OF PALLATIVE MEDICINE that switching from one opioid is complicated and involves more than a simple conversion table, and that exact conversion factors and procedures are still unknown. (*Id.* at 115:20-116:3).

151. In my opinion, Gordon does not teach a person skilled in the art how to switch between oxymorphone and other opioids in formulations. In fact, Gordon illustrates the unpredictability of dosing. To be sure, Dr. Palmieri admits that Gordon says equianalgesic conversion tables are fraught with errors and uncertainties. (*Id.* at 102-116). Gordon also does not teach bioavailability, controlled release formulations or 12-hour dosing.

152. In addition, for controlled release formulations, Dr. Palmieri admitted that although one of skill in the art may vary the excipients to release a drug slower, clinical trials are required to confirm that the minimal therapeutic concentration is obtained. (*Id.* at 87:15-88:10). Further, he acknowledged that dissolution data for one drug will not predict the bioavailability of another drug. (*Id.* at 89:16-91:7). In particular, the bioavailability of each drug will depend on the differences in the drugs. (*Id.*). Thus, to compare the bioavailability of a new drug with an old drug, the new drug would require a clinical dose finding study. (*Id.* at 69:10-15). In my opinion, a clinical study is not routine. Knowing whether

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controlled release oxymorphone would work was the result of the inventors' inventive work.

153. Accordingly, Dr. Palmieri's reliance on Gordon is wrong and his failure to consider bioavailability differences between oxymorphone and other opioids completely undermines his opinions.

154. Moreover, Dr. Palmieri was completely unaware of other oxymorphone characteristics that I believe one of skill in the art would have considered in rendering an analysis of the comparison of the prior art and the '216 patent invention. For example, he did not know how oxymorphone is distributed (Palmieri Tr. at 57:20), how oxymorphone is excreted (*id.* at 58:6), nor did he consider the differences in how oxymorphone is metabolized compared to other opioids (*id.* at 79:8). In addition, Dr. Palmieri did not know if oxymorphone experiences a first pass effect. (*Id.* at 125:9). In fact, according to Dr. Palmieri, the first pass effect is immaterial because it usually occurs in non-oral drugs. (*Id.* at 125:10-19). He thought it only applied to rectally-administered drugs. (*Id.* at 125:10-19). As discussed above, however, that belief is flatly wrong.

155. Further, Dr. Palmieri relies on the teachings in Exhibit 1012, an article entitled Relative Bioavailability of Controlled Release Morphine Tablets (MST Continus) in Cancer Patients ("Poulain"), to argue that multiple peaks in plasma concentration are inherent to oxymorphone compositions. (*Id.* at 141:18-142:16).

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But, as Dr. Palmieri admits, Poulain only discusses the use of morphine. (*Id.*). Dr. Palmieri also failed to consider whether other opioids have multiple peaks. (*Id.* at 148:21 to 149:16). In my opinion, his use of Poulain's morphine as a proxy for oxymorphone is not supportable.

156. Finally, contrary to what one of skill in the art would consider, Dr. Palmieri did not analyze secondary considerations of non-obviousness such as commercial success of the product covered by the '216 patent. According to Dr. Palmieri, his "task was to look at the claims, certain specific claims of the '216 patent, not to look at post marketing studies of the commercially available product." (*Id.* at 157: 15-19).

157. In light of the above, in my opinion, the assertions, statements, and opinions provided in Dr. Palmieri's Declaration are not credible and should be entitled to little or no weight.

IX. THERE IS NO EVIDENCE SHOWING THAT THE CLAIMED FOOD EFFECTS ARE INHERENT IN THE FORMULATIONS DISCLOSED IN OSHLACK

158. I have been asked to provide my opinion on whether Amneal's Petition sufficiently demonstrates by a preponderance of the evidence (*i.e.*, more likely than not) that the claimed food effects in claims 31, 32, 35, 36, 38-41, 49-51, and 56 are inherent properties of any oxymorphone composition, regardless of formulation. In my opinion, Amneal's Petition does not.

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159. Although I am not a lawyer, I considered the following statements regarding the legal standard for proving that a claimed feature is an inherent property of a prior art composition in forming my opinions:

- Inherency requires that the feature be "necessarily present" in the prior art reference.
- Inherency may not be established by probabilities or possibilities.
- A claimed feature is inherent in a prior art reference if it is the natural result flowing from the explicit disclosure of the reference.

160. Amneal has provided no evidence whatsoever demonstrating that the claimed effects on the pharmacokinetic parameters of C_{max} and $AUC_{(0-inf)}$ under fed versus fasted conditions are "necessarily present" or the "natural result flowing from the explicit disclosure" of Oshlack. Amneal's Petition relies solely on the opinions of Dr. Palmieri. But Dr. Palmieri's opinions regarding the alleged inherency of the claimed food effects are contradicted by the clinical studies described in the '216 patent and are not based on sufficient scientific data.

A. The Claimed Food Effects Should Be Determined Using a Ratio of Least-Squares Means of Natural Log-Transformed Data

161. As summarized in the chart below, several of the challenged claims of the '216 patent recite specific effects on C_{max} and $AUC_{(0-inf)}$ exhibited by subjects when administered the claimed oxymorphone compositions with food versus

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without food. In some claims, administration of the claimed oxymorphone composition with food increases the oxymorphone C_{max} by "at least 50%" and, in other claims, by "about 58%." In some claims, administration of the claimed oxymorphone composition with food increases the oxymorphone $AUC_{(0\text{-}inf)}$ by "less than 20%" and, in other claims, by "about 18%."

Claims	Limitation
31, 35, 36, 38, 40, 41, 49, 50, 56	"the oxymorphone C_{max} is at least 50% higher when the dosage form is administered to the subject under fed as compared to fasted conditions"
32, 39, 51	"the oxymorphone C_{max} is about 58% higher when the dosage form is administered to the subject under fed as compared to fasted conditions"
35, 40	"the difference in the oxymorphone area under the curve ($AUC_{(0\text{-}inf)}$) between fed and fasted conditions is less than 20%"
50	"the oxymorphone $AUC_{(0\text{-}inf)}$ is no more than 20% higher when the dosage form is administered to the subject under fed as compared to fasted conditions"

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Claims	Limitation
36, 41	"the difference in the oxymorphone area under the curve ($AUC_{(0-inf)}$) between fed and fasted conditions is about 18%"

162. In determining whether the formulations disclosed in Oshlack inherently meet any of these limitations, it is important to understand how a person of ordinary skill in the art would calculate the percentage increase using the data obtained from a clinical study. The '216 patent states that the mean values "are arrived at using standard statistical methods as would be employed by one skilled in the art of pharmaceutical formulation and testing for regulatory approval." (Ex. 1001 at 4:1-4). "Study 3" in the specification of the '216 patent describes the claimed food effects for 20 mg oxymorphone controlled-release tablets as follows:

> The presence of a high fat meal had a substantial effect on the oxymorphone C_{max}, but less of an effect on oxymorphone AUC from oxymorphone controlled release tablets. ***Least Squares (LS) mean C_{max}*** was 58% higher and ***LS mean $AUC_{(0-t)}$ and $AUC_{(0-inf)}$*** were 18% higher for the fed condition (Treatment B) compared to the fasted condition (Treatment A) ***based on LN-transformed data***.

('216 Patent, Ex. 1001 at 17:44-50 (emphasis added)).

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> The effect of food on oxymorphone bioavailability from the oral solution was more pronounced, particularly in terms of AUC. ***LS mean C_{max}*** was 50% higher and ***LS mean $AUC_{(0-t)}$ and $AUC_{(0-inf)}$*** were 32-34% higher for the fed condition (Treatment D) compared to the fasted condition (Treatment C) ***based on LN-transformed data***.

('216 Patent, Ex. 1001 at 17:59-65 (emphasis added)). Based on this disclosure, a person of ordinary skill in the art would understand that the claimed food effects are determined using a ratio of least-squares means of C_{max} and $AUC_{(0-inf)}$ under fed and fasted conditions derived from natural log-transformed data. This is consistent with regulatory recommendations and the scientific literature at the time of the invention.

163. Exhibit 2047 is a true and correct copy of a guidance statement from the Division of Bioequivalence of the Office of Generic Drugs of the United States Food and Drug Administration ("FDA"). (*Id.*). This guidance was published in July 1992 and is entitled *Statistical Procedures for Bioequivalence Studies Using a Standard Two-Treatment Crossover Design*. (*Id.*) According to this guidance, the FDA adopted a testing procedure termed the "two one-sided tests procedure" to determine whether "average values for pharmacokinetic parameters measured after administration of a test product and reference product are comparable" (*i.e.*, bioequivalent). (*Id.* at 1). In performing this comparison of pharmacokinetic data

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of the reference drug and proposed generic formulation, the FDA recommended using log-transformed data to compare pharmacokinetic parameters obtained from different treatments. (*Id.* at 7).

164. The FDA based its recommendation on three rationales. (*Id.* at 5-7). From a clinical standpoint, it concluded that the primary comparison in a bioequivalence study is the ***ratio of the pharmacokinetic parameters of the test and reference products***. (*Id.* at 5). Log transformation of the data is the statistically appropriate technique to evaluate such ratio. (*Id.*). From a pharmacokinetic standpoint, log transformation of the data permits the clearance of the drug, which is a function of the specific subject, to be treated properly in the analysis. (*Id.* at 5-6). And from a statistical standpoint, C_{max} and AUC tend to be skewed, and their variances tend to increase as the means increase. (*Id.* at 6-7). Log transformation remedies this situation and makes the variances independent of the mean. (*Id.*). Accordingly, the FDA's recommendation to use ratios of means based on log-transformed data for pharmacokinetic studies involving different treatments was the standard at the time of the invention. This is confirmed by the scientific literature at the time.

165. Exhibit 2048 is a true and correct copy of an article entitled *Logarithmic Transformation in Bioequivalence: Application With Two*

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Formulations of Perphenazine. This article was published in the JOURNAL OF PHARMACEUTICAL SCIENCES in 1993. As this article notes:

> It is commonly believed that the distribution of many biological parameters have much longer right tails than would be expected had the parameters come from a normal distribution. Keeny and Keeping state that if an outcome random variable is affected by many random causes, each of which produces a small proportional effect, the resulting distribution can be represented by the log normal distribution. ***Applying this random process to pharmacokinetics, one can expect that a concentration measured at any time is a function of many random processes (absorption, metabolism, elimination) that act proportionally to the amount of drug present. Therefore, it can be envisaged that AUC or Cmax may take on a log normal distribution*** due to environmental and genetic influences on the many random processes from which the parameters arise.

(Ex. 2048 at 138 (emphasis added) (citations omitted)). This article concludes that logarithmic transformation of pharmacokinetic data is appropriate because "sample sizes are too small in bioequivalence studies and too susceptible to extreme values to state with any certainty the actual distribution of pharmacokinetic parameters or their differences within a subject." (*Id.* at Abstract).

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166. Exhibit 2049 is a true and correct copy of an article entitled *The Log Transform Is Special* authored by Oliver N. Keene. This article was published in the journal STATISTICS IN MEDICINE in 1995. According to this article:

> ***When the magnitude of an effect is commonly perceived in terms of a percentage change between treatments, this is usually a good indication that the clinical importance relates to a ratio scale. It seems perverse to base the statistical analysis on absolute values when changes to small responses are more clinically important than changes to large responses.*** Where baseline information is available, a common approach is to analyze the percentage change of a variable from baseline. Patients with small baseline values can have greatly inflated influence on the analysis of percentage change and this is generally a poor way of incorporating baseline information. ***A log transformation weights observations automatically according to a ratio scale and reduces problems associated with percentage changes from baseline.***

(Ex. 2049 at 812-13 (emphasis added)). This article also notes that "[r]ecent consensus statements and regulatory guidelines have ***unequivocally favored*** the prior use of log transformation" "for ratios [of pharmacokinetic parameters] between treatments." (Ex. 2049 at 813 (emphasis added)).

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167. In January 2001, the FDA reiterated its recommendation on using log-transformed pharmacokinetic data for analyzing bioequivalence studies in its Guidance for Industry entitled *Statistical Approaches to Establishing Bioequivalence*. Exhibit 2050 is a true and correct copy of this guidance. (Ex. 2050). The FDA states:

> ***This guidance recommends that [bioequivalence] measures (e.g., AUC and Cmax) be log-transformed using either common logarithms to the base 10 or natural logarithms (see Appendix D).*** The choice of common or natural logs should be consistent and should be stated in the study report. ***The limited sample size in a typical [bioequivalence] study precludes a reliable determination of the distribution of the data set.*** Sponsors and/or applicants are not encouraged to test for normality of error distribution after log-transformation, nor should they use normality of error distribution as a reason for carrying out the statistical analysis on the original scale. Justification should be provided if sponsors or applicants believe that their [bioequivalence] study data should be statistically analyzed on the original rather than on the log scale.

(Ex. 2050 at 9 (emphasis)).

168. In December 2002, the FDA officially expressed the same recommendation of using log-transformed pharmacokinetic data to determine the

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effect of food on the bioavailability of drugs. Exhibit 2051 is a true and correct copy of the FDA's Guidance for Industry entitled *Food-Effect Bioavailability and Fed Bioequivalence Studies*. In this publication, the FDA states the following with respect to food-effect studies:

> An equivalence approach is recommended for food-effect BA (to make a claim of no food effects) and fed BE studies, analyzing data using an average criterion. ***Log-transformation of exposure measurements (AUC and C_{max}) prior to analysis is recommended.*** The 90 percent CI for the ratio of population geometric means between test and reference products should be provided for AUC_{0-inf}, AUC_{0-t}, and Cmax (*see* guidance for industry on Statistical Approaches to Establishing Bioequivalence). For IND or NDA food-effect BA studies, the fasted treatment serves as the reference. For ANDA fed BE studies, the RLD administered under fed condition serves as the reference treatment.

(Ex. 2051 at 6-7 (emphasis added)). When conducting food-effect studies for the purpose of obtaining regulatory approval to market a drug, the FDA therefore recommends using a ratio of the means of the pharmacokinetic parameters based on natural log-transformed data.

169. Based on the specific teachings of the '216 patent as well as the general knowledge at the time of the invention, a person of ordinary skill in the art

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would understand that the claimed food effects on C_{max} and $AUC_{(0\text{-}inf)}$ are determined using a ***ratio*** of the ***least squares*** means of C_{max} and $AUC_{(0\text{-}inf)}$ based on natural log-transformed pharmacokinetic data. This distinction is important because, as discussed above, the '216 patent describes some pharmacokinetic parameters as ***arithmetic*** means. (*See*, *e.g.*, '216 patent, Ex. 1001 at Tables 14, 23). But when determining the extent of the pharmacokinetic food effects for a specific oxymorphone formulation, a person of ordinary skill in the art would ***not*** use a ratio of arithmetic means to determine the increase in C_{max} and $AUC_{(0\text{-}inf)}$ under fed and fasted conditions. A skilled artisan would use a ratio of least-squares means based on natural log-transformed data consistent with the specification of the '216 patent.

170. To calculate the ratio of C_{max} and $AUC_{(0\text{-}inf)}$ of oxymorphone under fed and fasted conditions, a person of ordinary skill in the art would have first calculated the least squares means of the C_{max} and $AUC_{(0\text{-}inf)}$ based on natural log-transformed data. Because the data is natural log-transformed, a person of ordinary skill in the art would have calculated the percentage change in C_{max} and $AUC_{(0\text{-}inf)}$ under fed versus fasted conditions by using rules associated with logarithmic functions.

171. The natural logarithm function, $\ln(x)$, is the inverse function of the exponential function, e^x. Therefore:

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$$e^{\ln(x)} = x \tag{3}$$

172. If x is the ratio of, for example, C_{max} of oxymorphone under fed versus fasted conditions, then Equation 3 becomes:

$$e^{\ln\left(\frac{Cmax\ oxy\ fed}{Cmax\ oxy\ faster}\right)} = \frac{Cmax\ oxy\ fed}{Cmax\ oxy\ fasted} \tag{4}$$

173. Under the quotient rule for logarithms:

$$e^{\ln\left(\frac{x}{y}\right)} = e^{\ln x - \ln y} \tag{5}$$

Using the quotient rule, a person of ordinary skill in the art would have calculated the ratio of least squares means of C_{max} under fed versus fasted conditions as follows:

$$e^{\ln(Cmax\ oxy\ fed) - \ln(Cmax\ oxy\ fasted)} = \frac{Cmax\ oxy\ fed}{Cmax\ oxy\ fasted} \tag{6}$$

Using the ratio obtained from Equation 6, a person of ordinary skill in the art would have calculated the percent change in C_{max} under fed versus fasted conditions according to Equation 7:

$$\%\ increase\ in\ Cmax = \left(\frac{Cmax\ oxy\ fed}{Cmax\ oxy\ fasted} - 1\right)\ x\ 100 \tag{7}$$

174. Similar calculations can be performed to calculate the percent change in $AUC_{(0\text{-}inf)}$ under fed versus fasted conditions.

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B. The Evidence Unmistakably Shows That the Claimed Food Effects Are Not Inherent Properties of Oxymorphone Itself

175. In its Petition, Amneal contends that the claimed food effects "are properties of ***any*** oxymorphone composition" and are therefore inherent in the formulations allegedly disclosed in Oshlack. (Petition at 35 (emphasis added)). Amneal's contention relies on Paragraph 118 of the Palmieri Declaration, in which Dr. Palmieri opines that the claimed food effects "are properties of ***any*** oxymorphone composition. . . ." (Palmieri Decl., Ex. 1003 (emphasis added)). I disagree because when all of the evidence is considered, it is unmistakable that these claimed properties are not necessarily present in all formulations containing oxymorphone—and therefore are not inherent to oxymorphone.

1. Increase in $AUC_{(0\text{-}inf)}$ of "about 18%" and "less than 20%"

176. As expressly disclosed in the '216 patent, subjects administered an oral solution of oxymorphone in "Study 3" exhibited an increase in the least squares mean of $AUC_{(0\text{-}t)}$ and $AUC_{(0\text{-}inf)}$ of oxymorphone of 32-34% higher under fed versus fasted conditions. ('216 Patent, Ex. 1001 at 17:59-64). Accordingly, this oral formulation of oxymorphone does not have an increase in $AUC_{(0\text{-}inf)}$ of "about 18%" or "less than 20%" and the claimed effect cannot be inherent in oxymorphone. [redacted].

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177. [redacted]

178. The magnitude of this [redacted] increase falls outside of the claimed food effects on $AUC_{(0\text{-}inf)}$, as recited in claims 35, 36, 40, 41, and 50. Accordingly, the claimed $AUC_{(0\text{-}inf)}$ effects are not inherent properties of all oxymorphone compositions.

179. In forming his opinions relating to these limitations, Dr. Palmieri testified at his deposition that he did not consider this express disclosure in the

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’216 patent. Remarkably, at his deposition, he refused to provide any opinion as to whether 32-34% was outside the scope of the claimed “less than 20%” and “about 18%” limitations. (Palmieri Tr., Ex. 2012 at 171:10-174:2, 178:21-182:9, 192:15-193:17, 202:6-15).

2. Increase in C_{max} of “at least 50%” and “about 58%”

180. The specification of the ’216 patent describes two studies in which immediate release oxymorphone formulations (both liquid solution and tablets) were studied under fed and fasted conditions. “Study 3” describes a clinical study involving an oral oxymorphone solution (*i.e.*, a liquid). (’216 patent, Ex. 1001 at 15:42-20:59). When administered under fed conditions, the C_{max} of oxymorphone in the oral solution increases 50% compared to fasted conditions. (*Id.* at 17:61-64).

[redacted] Based on this data, the percent increase in C_{max} when the oral oxymorphone solution is administered under fed conditions can be calculated using Equations 6 and 7 above:

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181. The magnitude of this increase falls outside of the claimed increase of "about 58%" as recited in claims 32, 39, and 51. Accordingly, this pharmacokinetic food effect is not an inherent property of all oxymorphone compositions, regardless of formulation.

182. Again, Dr. Palmieri failed to consider this express disclosure of the '216 patent in forming his opinions relating to the alleged inherency of the claimed "about 58%" food effect. During his deposition, Dr. Palmieri again remarkably refused to admit that 50% is not "about 58%." (Palmieri Tr., Ex. 2012 at 174:3-178:19, 182:14-192:14, 199:20-202:15).

183. "Study 5" of the '216 patent describes a similar study involving an immediate release oxymorphone tablet formulation (*i.e.*, a solid). (Ex. 1001 at 23:61-26:31). With respect to the pharmacokinetic data obtained in Study 5, the specification provides only the arithmetic means of oxymorphone, (*Id.* at 24:46-48, Table 23)—not the least squares means of the natural log-transformed data. But analysis of the underlying clinical study again shows that the immediate release formulation does not meet the limitations requiring an increase in C_{max} of "at least 50%" or "about 58%" and therefore these limitations cannot be inherent in oxymorphone itself.

184. The clinical study described in [redacted]

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[redacted] The results from this clinical study are being used because they demonstrate, contrary to Amneal's assertion, that the claimed effects of food on C_{max} are ***not*** inherent properties of all oxymorphone compositions. [redacted]

185. [redacted]

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186. This increase in C_{max} under fed conditions is less than the "at least 50%" range recited in claims 31, 35, 36, 38, 40, 41, 49, 50, and 56 and the "about 58%" range recited in claims 32, 39, and 51. Accordingly, these claimed effects on C_{max} under fed conditions are not inherent properties of any oxymorphone composition, regardless of formulation.

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[6] [redacted] This further supports my opinion above that the claimed $AUC_{(0\text{-}inf)}$ effects under fed versus fasted conditions are not inherent properties of any oxymorphone composition, regardless of formulation.

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C. There Is No Evidence Showing That All Controlled Release Oxymorphone Compositions Necessarily Exhibit the Claimed Food Effects

187. Dr. Palmieri opines that "there are no data in the '216 patent suggesting that these so-called food effect properties are unique to specific controlled release oxymorphone formulations." (Palmieri Decl., Ex. 1003 at ¶ 94). The lack of such data in the specification of the '216 patent, however, is not sufficient to show that all controlled release oxymorphone formulations would necessarily exhibit the claimed food effects.

188. Dr. Palmieri also opines that a "POSA would have understood that the food effect would be the same for controlled release oxymorphone formulations with the same release rates, as the food effect is primarily related to absorption of the drug after it is release[d]." (Palmieri Decl., Ex. 1003 at ¶ 94).[7] According to Dr. Palmieri, therefore, because the release rates of the Oshlack formulations allegedly overlap with those of the claimed formulations as measured by *in vitro* dissolution, the Oshlack formulations would necessarily exhibit the claimed food effects. (*Id.* at ¶ 117-118). However, Dr. Palmieri cites to no scientific evidence or data showing that the claimed food effects are primarily related to absorption.

[7] Dr. Palmieri provided this opinion in reference to the Maloney publication (Exhibit 1006). I understand that the Board denied review of the challenged food effect claims based on the Maloney reference. However, Dr. Palmieri relies on this rationale as a basis for his opinions with respect to Oshlack, and I therefore address it.

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189. It is my opinion that Dr. Palmieri's unsupported opinion is not sufficient to show that the claimed food effects are ***necessarily*** exhibited by the alleged Oshlack formulations.

X. SECONDARY CONSIDERATIONS OF NONOBVIOUSNESS

190. I have been asked to assess whether any secondary considerations of nonobvious support the patentability of the claims of the '216 patent. In my opinion, three secondary considerations support the patentability of the claims of the '216 patent: (i) the commercial success of Opana® ER; (ii) a long-felt but unmet need satisfied by Opana® ER; and (iii) unexpected multiple peak plasma concentrations within the dosing interval of Opana® ER.

A. The Commercial Success of Opana® ER Flows from Novel Aspects of the Claims

191. I have reviewed the Declaration of Marv Kelly (Exhibit 2053), in which he concludes that Patent Owner's Opana® ER product has been commercially successful. I agree with Mr. Kelly on this point.

1. Opana® ER Is Covered by the Claims of the '216 Patent

192. I have been asked to provide my opinion on whether Patent Owner's Opana® ER products are covered by the claims of the '216 patent. I have compared Patent Owner's Opana® ER product to claims 1, 2, 6, 12-14, 17, 21-43, 45-51, and 54-71. Based on my analysis, which is provided in Exhibits 2066 and 2067, the Opana® ER product falls within the scope of these claims.

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2. The Commercial Success Is Connected to Novel Aspects of the Claims of the '216 Patent

193. In my opinion, the commercial success of Opana® ER flows from its unique and novel dissolution profile and pharmacokinetic characteristics.

194. As I have detailed above, the claimed dissolution profile was not previously known in the prior art. For example, claim 13 recites that about 15% to about 50% by weight of the oxymorphone is released after about 1 hour in an *in vitro* dissolution test using the Paddle Method at 50 rpm. Oshlack discloses a dissolution profile in which about 1% to 42.5% by weight of the oxymorphone is released after about 1 hour using the Basket Method at 100 rpm. (Ex. 1007 at 11:64-12:8). The Oshlack dissolution profile is different from the claimed dissolution profile. Amneal concedes as much in its Petition, as it alleges that the two dissolution profiles merely overlap. (Petition at 26). The claimed dissolution rate is therefore novel, and there is no evidence sufficient to suggest what the dissolution rates in Oshlack would be using the claimed dissolution method.

195. Also as I have detailed above, the claimed multiple-peak feature of claim 1 was not previously known in the prior art for oxymorphone and is not an inherent property of any oxymorphone composition regardless of formulation. Thus, this element of the claims is novel.

196. In my opinion, these novel features—the unique dissolution profile and multiple peaks in the oxymorphone plasma concentration—are directly

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responsible for the therapeutic efficacy of Opana® ER. As I describe above, the claimed dissolution ranges are central to the invention of the '216 patent because they result in the analgesic effectiveness of the claimed controlled release oxymorphone formulations. (*See*, *e.g.*, Ex. 1001 at 3:12-17, 3:34-40, 5:31-39, 6:43-46, 10:44-46). And the multiple plasma concentration peaks contribute to that analgesia. Without this effective analgesia, Opana® ER would not be prescribed by doctors and would therefore not be commercially successful.

197. I also note that the oxymorphone formulations recited in claims 10 and 11 of Oshlack have not been shown to be therapeutically effective. Indeed, Oshlack does not contain any clinical data demonstrating that its dissolution profile results in a therapeutically effective oxymorphone composition. Moreover, a search of the FDA's *Orange Book* shows that Oshlack has only been listed to cover Palladone®, a hydromorphone composition that was actually pulled from the market due to safety concerns relating to the controlled release matrix of Oshlack. (Ex. 2054; Ex. 2055). It has never been listed to cover any oxymorphone composition. (Ex. 2054). Thus, there is no evidence that the dissolution profiles disclosed in Oshlack would result in a therapeutically effective oxymorphone composition, much less a commercially successful one. This is in stark contrast to the dissolution profile claimed in the '216 patent, which covers the commercially successful Opana® ER.

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198. It is therefore my opinion that the commercial success of Opana® ER is connected to the dissolution profile and multiple-peak feature claimed in the '216 patent, both of which directly provide a therapeutic regimen for the treatment of pain.

B. The Claimed Invention of the '216 Patent Addressed a Long-Felt But Unmet Need

199. I have analyzed whether, at the time of the invention of the '216 patent, there was a long-felt need in the field of pain management for an extended release opioid that was addressed by the '216 patent. In 2001, before the invention, there were only two oral extended release opioids available to prescribers desiring such treatment options. Those were OxyContin® (oxycodone ER) and morphine ER. Indeed, as shown in Exhibit 2056, which is the "List of Extended-Release and Long-Acting Opioid Products" available from the FDA, all of the oral extended release opioid products were approved after 2001, except for Oxycontin® and morphine ER. This was in contrast to a large number of immediate release options available (*e.g.*, oxycodone, morphine, hydrocodone, hydromorphone, codeine, meperidine, levorphanol, and pentazocine).

200. Each opioid has a different efficacy and side effect profile (e.g., euphoria, nausea, constipation, tolerance). Accordingly, different patients respond better to different opioids. Because there were only two extended release opioids available in 2001, more extended release opioids were needed to address patients

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who either did not respond or could not tolerate doses of extended release oxycodone or morphine. Patent Owner's extended release oxymorphone filled some of that need.

201. Moreover, it was well known at the time that prescribers prefer to rotate among opioids, particularly for treating chronic pain. Opioid rotation is believed to lead to better patient outcomes. And, because there were only two ER opioids available in 2001, the rotation options were quite limited. Therefore, I believe there was a long-felt need at the time for an additional treatment option.

202. Despite the need for controlled release forms of opioid pain medications, oxymorphone's properties seemingly precluded development, particularly given that the only commercially available oral oxymorphone formulation, which was an immediate release formulation, had been pulled from the market more than 20 years previously. I believe that by ignoring conventional scientific wisdom at the time, the inventor's efforts and substantial experimentation resulted in a controlled release oxymorphone product that satisfied this long-felt need.

203. Indeed, the therapeutic advantages of Opana® ER have been recognized in the scientific literature as satisfying a long-felt need. For example, Exhibit 2057 is an article entitled *Oxymorphone Extended-Release Tablets (Opana*

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ER) For the Management of Chronic Pain. In this article, a number of benefits are highlighted:

> ***Oxymorphone ER is a valuable addition to the limited selection of LA opioids available to physicians in the U.S., providing a much-needed option for patients*** requiring pain management or opioid rotation. There is strong clinical evidence supporting its use for cancer pain, chronic low back pain, and other chronic non-cancer pain. This drug is generally well tolerated in opioid-naïve and opioid-experienced patients, providing 12-hour analgesia and maintaining its effects over time."

(Ex. 2057 at 329 (emphasis added)). And in comparison to controlled release oxycodone, Opana® ER surprisingly has a lower daily average consumption over a 90-day period. (Ex. 2058; Ex. 2059).

204. Accordingly, the commercial embodiment of the '216 patent, Opana® ER, has proved to be a valuable addition to the prescribers' armamentarium to treat chronic pain. And as discussed above, it is the therapeutic efficacy derived from the novel, claimed dissolution profile and pharmacokinetic characteristics that have led doctors to prescribe Opana® ER.

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XI. PROPOSED AMENDED CLAIMS 83 AND 84 ARE PATENTABLE OVER THE PRIOR ART

205. I understand that Patent Owner has filed a contingent motion to amend. I have been asked to provide my opinion on whether proposed amended claims 83 and 84 are patentable over the prior art.

206. The proposed amended claims are as follows:

> 83. (Proposed substitute for claim 21) A pharmaceutical tablet prepared by:
>
> a. mixing oxymorphone or a pharmaceutically acceptable salt of oxymorphone and one or more controlled release excipients; and
>
> b. forming the tablet,
>
> wherein upon placement of the tablet in an in vitro dissolution test comprising USP Paddle Method at 50 rpm in 500 ml media having a pH of 1.2 to 6.8 at 37° C., about 15% to about 50%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 1 hour in the test; and wherein **the tablet is a 12-hour dosage form for the treatment of pain in a human subject**~~**upon oral administration to a human subject the tablet alleviates pain for 12 to 24 hours**~~.
>
> 84. (Proposed substitute for claim 31) A method for treating pain in a human subject in need of acute or chronic pain relief, comprising the steps of:

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(a) providing a **12-hour** solid oral dosage form of a controlled release oxymorphone formulation with a release rate profile designed to provide adequate blood plasma levels over ~~**at least**~~ 12 hours to provide sustained pain relief over this same period comprising about 5 mg to about 80 mg oxymorphone or a pharmaceutically acceptable salt thereof wherein oxymorphone is the sole active ingredient, and wherein upon placement of the composition in an in vitro dissolution test comprising USP Paddle Method at 50 rpm in 500 ml media having a pH of 1.2 to 6.8 at 37° C., about 15% to about 50%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 1 hour in the test; and

(b) administering a single dose of the dosage form to the subject, wherein the oxymorphone C_{max} is at least 50% higher when the dosage form is administered to the subject under fed as compared to fasted conditions.

A. The Proposed Amended Claims Are Narrower in Scope Than the Original Claims

207. Proposed amended claim 83 is narrower in scope than claim 21. Claim 21 recited that the pharmaceutical tablet, "upon oral administration to a human subject[,]" "the tablet alleviates pain for 12 to 24 hours." Thus, claim 21 encompasses 12-hour and 24-hour tablets for the treatment of pain in a human subject. Proposed amended claim 83 narrows the claimed subject matter to 12-

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hour tablets for the treatment of pain in a human subject and does not broaden the claim in any other way.

208. Similarly, the method of proposed amended claim 84 is limited to using a 12-hour dosage form, whereas the method of original claim 31 encompassed both 12-hour and 24-hour dosage forms under the Board's broadest reasonable interpretation.

209. It is therefore my opinion that the proposed claim amendments do not broaden the subject matter of original claims 21 and 31.

B. The Proposed Amended Claims Are Supported by the Written Description

210. I understand that for purposes of its motion to amend, Patent Owner is relying on a priority date of October 15, 2001, for the proposed amended claims 83 and 84. I understand that this priority date is derived from three United States patent applications to which the '216 patent claims priority: (i) U.S. Serial No. 11/427,438 (the "'438 application") (Ex. 2060); (ii) U.S. Serial No. 10/190,192 (the "'192 application") (Ex. 2061); and (iii) U.S. Provisional Serial No. 60/329,444 (the "'444 application") (Ex. 2062).

211. I have analyzed the specifications of these applications and conclude that they provide written description support for the subject matter of proposed amended claims 83 and 84. My analysis is summarized in the following chart:

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Proposed Claim	Limitation	Citation to Specification
83	A pharmaceutical tablet prepared by: a. mixing oxymorphone or a pharmaceutically acceptable salt of oxymorphone	¶¶ 0024, 0025, Table 2 ('438 App. Ex. 2060); ¶¶ 0024, 0025, Table 2 ('192 App. Ex. 2061); ¶¶ 0014, 0015 Table 2 ('444 App., Ex. 2062).
	and one or more controlled release excipients; and	¶¶ 0042-43, 0046, 0048, 0051, 0052, 0054, 0056 ('438 App., Ex. 2060); ¶¶ 0039-0040, 0043, 0045, 0048, 0049, 0051 ('192 App., Ex. 2061); ¶¶ 0036,0030-0031, 0034, 0036, 0039, 0040, 0042 ('444 App., Ex. 2062).
	b. forming the tablet,	¶ 0027 ('438 App., Ex. 2060); ¶ 0027 ('192App., Ex. 2061); ¶ 0017 ('444 App., Ex. 2062).

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Proposed Claim	Limitation	Citation to Specification
	wherein upon placement of the tablet in an in vitro dissolution test comprising USP Paddle Method at 50 rpm in 500 ml media having a pH of 1.2 to 6.8 at 37° C., about 15% to about 50%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 1 hour in the test;	¶ 0027 ('438 App., Ex. 2060); ¶ 0027 ('192 App., Ex. 2061); ¶ 0017 ('444 App., Ex. 2062).
	and wherein the tablet is a 12-hour dosage form.	¶¶ 0008, 0019, 0022, 0023, 0026, 0042 ('438 App., Ex. 2060); ¶¶ 0008, 0019, 0023, 0026, 0039 ('192 App., Ex. 2061); ¶¶ 0008, 0009, 0012, 0013, 0016, 0029 ('444 App., Ex. 2062).
84	A method for treating pain in a human subject in need of acute or chronic pain relief, comprising the steps of:	¶ 0026 ('438 App., Ex. 2060); ¶ 0027 ('192 App., Ex. 2061); ¶ 0013 ('444 App., Ex. 2062).

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Proposed Claim	Limitation	Citation to Specification
	(a) Providing a 12-hour solid oral dosage form of a controlled release oxymorphone formulation with a release rate profile designed to provide adequate blood plasma levels over ~~at least~~ 12 hours to provide sustained pain relief over this same period	¶¶ 0027, 0019, 0026, 0042, 0062, Table 5, Figure 5, Table 9, Fig. 6, original claim 1 ('438 App., Ex. 2060); ¶¶ 0026, 0019, 0023, 0059, Table 5, Figure 5, Table 9, Figure 6 ('192 App., Ex. 2061); ¶¶ 0009, 0013, Table 5, Figure 5, Table 9, Figure 6, 0017 ('444 App., Ex. 2062).
	comprising about 5 mg to about 80 mg oxymorphone or a pharmaceutically acceptable salt thereof wherein oxymorphone is the sole active ingredient, and	¶ 0025, Table 2 original claim 1 ('438 App., Ex. 2060); ¶ 0025, Table 2 ('192 App., Ex. 2061); ¶ 0015, Table 2 ('444 App., Ex. 2062).

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Proposed Claim	Limitation	Citation to Specification
	wherein upon placement of the composition in an in vitro dissolution test comprising USP Paddle Method at 50 rpm in 500 ml media having a pH of 1.2 to 6.8 at 37° C., about 15% to about 50%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 1 hour in the test; and	¶ 0022 ('438 App., Ex. 2060); ¶ 0022 ('192 App., Ex. 2061); ¶ 0012 ('444 App., Ex. 2062).
	(b) administering a single dose of the dosage form to the subject, wherein the oxymorphone C_{max} is at least 50% higher when the dosage form is administered to the subject under fed as compared to fasted conditions.	¶ 0097 ('438 App., Ex. 2060); ¶ 0084 ('192 App., Ex. 2061); ¶ 0074 ('444 App., Ex. 2062).

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212. Thus, a person of ordinary skill in the art at the time of the invention would have understood that the inventors were in possession of the subject matter of proposed amended claims 83 and 84.

C. The Proposed Amendments Obviate the Grounds on Which Institution Was Granted

213. I understand that the Board instituted review of claims 13, 14, 17, 21-43, 45-51, and 54-71 of the '216 patent in view of the combination of Oshlack and the Handbook of Dissolution. Even if the Board were to find that the dissolution profile disclosed in Oshlack, as measured by the Basket Method at 100 rpm, would have rendered obvious the claimed dissolution profile, as measured by the Paddle Method at 50 rpm, the proposed amendments would obviate the grounds on which institution was granted.

214. The proposed amended claims are both directed to 12-hour dosage forms having a specific dissolution profile. In contrast, Oshlack discloses a dissolution profile for a 24-hour dosage form. In the absence of *in vivo* pharmacokinetic data, the *in vitro* dissolution profile for a 24-hour dosage form would not inform a person of ordinary skill in the art how to formulate a therapeutically effective 12-hour dosage form containing the same active ingredient. This is because the duration of action is different for each dosage form, which requires a different dissolution profile for each dosage form. Even Dr. Palmieri admitted this, as he testified that a 12-hour dosage form would be

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expected to have a faster release rate than a 24-hour dosage form. (Palmieri Tr., Ex. 2012 at 80:10-22).

215. A person of ordinary skill in the art, however, could not have reasonably predicted how much faster of a release rate would be necessary to obtain a therapeutically effective 12-hour dosage form because Oshlack fails to disclose any *in vivo* pharmacokinetic data for any oxymorphone composition. Dr. Palmieri admitted this during his deposition, noting that he would need *in vivo* pharmacokinetic data from a clinical study:

> Q. What if you had a formulation – we'll call it Formulation 1. Formulation 1 has an active ingredient in it. We'll call it Active A. Okay? So you have Formulation 1 were [sic] Active Ingredient A, and you have a dissolution profile measured over 12 hours. Are you with me so far?
>
> * * *
>
> Q. And you have no in vivo data. You have no serum concentrations. All right?
>
> * * *
>
> Q. And could you predict the in vivo plasma concentrations for Formulation 1 with Active A over a 24-hour period based on the dissolution data that I've described that you have?
>
> * * *

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A. In your hypothetical question, as I understand it sitting here today, which I have not thought about in this hypothetical situation, my answer would be probably not. However, I could then obtain plasma concentrations with routine experimentations. And then, if I was so inclined, given the state of the art at the time of this invention, predict, if I have similar dissolution profiles, I would have similar plasma concentrations with different formulations but the same API.

(Palmieri Tr., Ex. 2012 at 84:11-86:9). Dr. Palmieri's testimony is consistent with *Applied Biopharmaceutics*, which notes that "[i]n the absence of *in vivo* data, it is generally impossible to make valid conclusions about bioavailability from the dissolution data alone." (Ex. 2020 at 145 (emphasis added)).

216. Because Oshlack does not provide any *in vivo* pharmacokinetic data with respect to any oxymorphone composition, a person of ordinary skill in the art would not have been motivated to use the dissolution profile disclosed in Oshlack for a 24-hour dosage form to achieve the claimed dissolution profile for a 12-hour dosage form. Nor would a person of ordinary skill in the art have reasonably expected to achieve the claimed dissolution profile for a 12-hour dosage form based on the disclosure of the dissolution profile in Oshlack for a 24-hour dosage

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form. Thus, proposed amended claims 83 and 84 would obviate the grounds of review on which review of the original claims was instituted.

D. The Proposed Amended Claims Are Patentable Over the Closest Prior Art of Which I Am Aware

217. In preparing my opinions regarding the proposed amended claims, I have considered the prosecution history of the '216 patent, the prior art Amneal cited in its Petition in this proceeding, and the prior art Amneal cited in IPR2014-01365. Other than Oshlack, discussed above, the following references are the closest known prior art to the proposed claims of which I am aware: (i) Maloney; (ii) the Penwest Pharmaceuticals Company's Form S-1 Statement (Ex. 1009); (iii) U.S. Patent No. 5,128,143 to Baichwal (Ex. 1010) ("Baichwal I"); (iv) U.S. Patent No. 5,135,757 to Baichwal (Ex. 2064) ("Baichwal II"); and (v) U.S. Patent No. 5,662,933 to Baichwal (Ex. 2065) ("Baichwal III"). However, all of these references suffer the same deficiencies as Oshlack: they do not provide (i) any dissolution profile for a 12 hour oxymorphone composition or (ii) any *in vivo* pharmacokinetic data for oxymorphone from which a 12 hour dosage form having the claimed dissolution profile could be formulated.

218. It is therefore my opinion that proposed amended claims 83 and 84 are patentable over the closest prior art of which I am aware.

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XII. CERTIFICATION OF EXHIBITS

219. I certify the authenticity of Exhibits 2013-2028, 2030-2052, 2054-2069, an 2083-2089 and that they are true and correct copies of the originals.

220. I also certify that the information and data provided in Exhibits 2013-2028, 2030-2052, 2054-2069, an 2083-2089 are the type of information and data that pharmaceutical scientists routinely use and rely on in forming opinions regarding the various aspects of drug formulation, dissolution, and pharmacokinetics discussed in this declaration.

XIII. CONCLUSIONS

221. For the reasons I have detailed above, it is my opinion that Amneal has failed to show by a preponderance of the evidence (*i.e.*, more likely than not) that any of the challenged claims are not patentable in view of (i) Maloney or (ii) the combination of Oshlack and the Handbook of Dissolution Testing.

222. To the extent the Board disagrees, it is my opinion that Patent Owner's proposed amended claims are patentable over the closest prior art of which I am aware.

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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 Untied States Code.

Dated: October 27, 2014

Diane J. Burgess