IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

VIFOR FRESENIUS MEDICAL CARE RENAL PHARMA LTD. and VIFOR FRESENIUS MEDICAL CARE RENAL PHARMA FRANCE S.A.S.,	)	
Plaintiffs	)	
v.	)	C.A. No. 18-390 (MN)
TEVA PHARMACEUTICALS USA, INC.,	)	
Defendant.	)	

MEMORANDUM OPINION

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August 18, 2022
Wilmington, Delaware

NOREIKA, U.S. DISTRICT JUDGE:

Plaintiffs Vifor Fresenius Medical Care Renal Pharma Ltd ("Vifor Switzerland") and Vifor Fresenius Medical Care Renal Pharma France S.A.S. ("Vifor France") (collectively "Plaintiffs" or "Vifor") brought this Hatch-Waxman action against Defendant Teva Pharmaceuticals USA, Inc. ("Defendant" or "Teva"). Teva has filed an Abbreviated New Drug Application ("ANDA") with the U.S. Food and Drug Administration ("FDA") seeking approval to market a generic version ("ANDA product") of Vifor's Velphoro® product before expiration of United States Patent No. 9,561,251 (JTX-1 ("the '251 patent")). Plaintiffs allege that Teva's ANDA product will infringe claims 29, 30, 33, and 56 of the '251 patent. Teva denies infringement of claims 29 and 30 and asserts that all four of the asserted claims are invalid.

The Court construed the disputed claim terms on September 5, 2019. (D.I. 114).[1] In January 2021, the Court conducted a four-day bench trial. (*See* D.I. 302-305 ("Tr.")). The parties completed post-trial briefing on April 7, 2021. (D.I. 297, 299, 307, 309, 312, 313). With their briefing, the parties submitted proposed findings of fact. (D.I. 298, 300, 306, 308).

Pursuant to Rule 52(a) of the Federal Rules of Civil Procedure, and after having considered the entire record and the applicable law, the Court concludes that: (1) Teva's ANDA product infringes claims 33 and 56 of the '251 patent;[2] (2) Vifor has proved that Teva's ANDA product infringes claims 29 and 30 of the '251 patent; (3) Teva has failed to prove that claims 29, 30, 33, and 56 of the '251 patent are invalid for obviousness; and (4) Teva has failed to prove that claims

[1] This case was originally assigned to the Honorable Leonard P. Stark and reassigned to the undersigned judge on December 12, 2019. Judge Stark construed the disputed claim terms.

[2] Defendant stipulated to infringement of claims 33 and 56 if those claims are valid.

29 and 30 are invalid for lack of enablement. This opinion constitutes the Court's findings of fact and conclusions of law.

I. FINDINGS OF FACT ("FF")

A. Introduction

1. Plaintiff Vifor Switzerland is a corporation organized and existing under the laws of Switzerland and has its principal place of business at Rechenstraße 37, St. Gallen, 9011, Switzerland. (D.I. 277, Ex. 1 ¶ 2).

2. Plaintiff Vifor France is a simplified joint stock company (*société par actions simplifiée*) organized and existing under the laws of France and has its principal place of business at 100-101 Terrasse Boieldieu Tour Franklin La Défense 8 F-92042 Paris La Défense Cedex, France. Vifor France is a wholly-owned subsidiary of Vifor Switzerland. (*Id.* at Ex. 1 ¶ 3).

3. Defendant Teva is a corporation organized and existing under the laws of the State of Delaware and has its principal place of business at 1090 Horsham Road, North Wales, Pennsylvania 19454. (*Id.* at Ex. 1 ¶ 5).

4. This case concerns the '251 patent, which is listed in the FDA publication, "Approved Drug Products with Therapeutic Equivalence Evaluations" ("the Orange Book"), as having at least one claim that covers Velphoro. (D.I. 277, Ex. 1 ¶ 11).

5. Teva submitted ANDA No. 211411 ("Teva's ANDA") to the FDA on November 27, 2017 seeking approval to engage in the commercial manufacture, use, offer for sale and/or sale of its ANDA product, *i.e.*, sucroferric oxyhydroxide chewable tablets, 500 mg. (D.I. 277, Ex. 1 ¶ 14). Teva's ANDA contains a certification under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) that states that the '251 patent is "invalid, unenforceable, and/or will not

be infringed by the commercial manufacture, use or sale" of the ANDA product. (D.I. 277, Ex. 1 ¶ 15).

B. Witnesses

1. Fact Witnesses

6. Hemant Mamania testified by deposition. Dr. Mamania is a senior director and site head for the Ambernath solid oral site of Watson Pharma.[3] (Tr. at 59:2-7).

7. Parven Luthra testified by deposition. Dr. Luthra is senior director, R&D in India for Teva. (Tr. at 70:17-22).

8. Erik Philipp testified by deposition. Dr. Philip is the head of chemical and analytical development for Vifor (Tr. at 228:25-229:9) and a named inventor on the '251 patent (JTX-1).

9. Laurent Chofflon testified by deposition. Mr. Chofflon works in external development for chemistry, manufacturing, and control for Vifor. (Tr. at 268:3-15).

2. Plaintiffs' Expert Witnesses

10. Anjay Rastogi testified live at trial.[4] Dr. Rastogi is Chief of Nephrology at UCLA Health in the Department of Medicine, Division of Nephrology. (Tr. at 77:11-20). He has a medical degree and a Ph.D. in pharmacology. (PTX-555). Dr. Rastogi was the principal investigator at UCLA, one of the major sites for the Velphoro Phase III clinical studies. (Tr. at 86:17-87:16). He was also a member of the Velphoro Steering Committee. (*Id.*). The Court recognized Dr. Rastogi as an expert in pharmacology, nephrology, and the treatment of hyperphosphatemia. (Tr. at 88:10-22).

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[3] Watson Pharma is "a part of the Teva company." (Tr. at 58:22-59:1).

[4] The Court found Dr. Rastogi to be a particularly credible witness.

11. Adam Myers testified live at trial. Dr. Myers is a senior project manager at Evonik Corporation and president of Coldbrook Consulting. (Tr. at 142:11-14). Dr. Meyers has a Ph.D. in organic chemistry. (PTX-603). He has expertise in evaluation of drug performance, including various types of testing. (PTX-603; Tr. at 143:3-10). The Court recognized Dr. Myers as an expert in testing and analysis of pharmaceutical products, including dissolution testing and analysis. (Tr. at 144:5-12).

12. Carla Mulhern testified live at trial. Ms. Mulhern received a bachelor's degree in mathematics from Bucknell University and a master's degree in economics from the London School of Economics. (Tr. at 562:14-18; DTX-313A). She is a managing principal at Analysis Group, an economic and financial consulting firm. (Tr. at 561:22-562:13). Ms. Mulhern has opined on commercial success in patent infringement cases on behalf of both patent holders and alleged infringers across a variety of products and industries, including pharmaceuticals, medical devices, semiconductors, and consumer electronics equipment. (Tr. at 563:13-564:5). The Court recognized Ms. Mulhern as an expert in economics. (Tr. at 564:6-11).

13. Robert O. Williams III testified live at trial. Dr. Williams is a professor of pharmacy at the University of Texas Austin College of Pharmacy. (Tr. at 644:4-19; DTX-280). He received bachelor's degrees in biology and pharmacy from Texas A&M and the University of Texas at Austin, respectively. (*Id.*). He also received a Ph.D. in Pharmaceutics from the University of Texas at Austin. (*Id.*). Prior to entering academia, Dr. Williams worked for about ten years developing dry products, including solid oral dosage forms such as suspensions. (Tr. at 644:20-45:6). The Court recognized Dr. Williams as an expert in the design and development of pharmaceutical formulations. (Tr. at 645:15-22).

3. Defendant's Expert Witnesses

14. Stephen Z. Fadem testified live at trial. Dr. Fadem has a medical degree from the University of Oklahoma College of Medicine. (Tr. at 208:2-9). He is a practicing physician and a clinical professor at Baylor College of Medicine. (Tr. at 207:9-16). He also teaches at the DeBakey Veterans Administration Hospital in Houston, Texas. (Tr. at 207:17-19). He has been practicing nephrology and treating patients with chronic kidney disease for more than forty years. (Tr. at 207:20-208:1). The Court recognized Dr. Fadem as an expert in the diagnosis and treatment of patients that have chronic kidney disease, including patients who are on dialysis. (Tr. at 210:21-211:3).

15. Walter G. Chambliss testified live at trial. Dr. Chambliss is a professor emeritus of pharmaceutics and drug delivery and a research professor emeritus in the Research Institute of Pharmaceutical Sciences at the University of Mississippi. (Tr. at 278:2-24; DTX-1060). Dr. Chambliss received a bachelor's degree in Pharmacy, as well as a master's degree and Ph.D. (both in Pharmaceutics) from the University of Mississippi. (Tr. at 279:21-280:2). He has more than forty years of experience in research for pharmaceutical formulations, including phosphate binders, as well as experience in pharmaceutical development. (Tr. at 278:2-285:2; DTX-1060). The Court recognized Dr. Chambliss as an expert in pharmaceutical science and formulation. (Tr. at 285:10-16).

16. Robert DeForest McDuff testified live at trial. Dr. McDuff is an economics consultant at Insight Economics, a consulting firm that he co-founded in 2017. (Tr. at 742:16-43:4; DTX-148A). He received a bachelor's degree in economics and mathematics from the University of Maryland and a master's degree and a Ph.D. in economics from Princeton University. (*Id.*). He has worked on more than fifty cases evaluating pharmaceuticals and the issue of

commercial success and has published several articles on the topic of commercial success. (*Id.*). The Court recognized Dr. McDuff as an expert in economics and commercial success. (Tr. at 743:5-10).

C. The '251 Patent

17. The '251 patent, entitled Pharmaceutical Compositions, issued on February 7, 2017. (JTX-1). The '251 patent claims priority to PCT/EP2008/065444 filed on November 13, 2008, which in turn claims priority to EP 07120837 filed on November 16, 2007. (D.I. 277, Ex. 1 ¶ 8). The § 371 date is May 14, 2010. (JTX-1).

18. The inventors of the '251 patent are Ludwig Daniel Weibel and Erik Philipp. (D.I. 277, Ex. 1 ¶ 7).

19. The '251 patent is directed to pharmaceutical compositions with a high load of iron oxy-hydroxide – at least 500 mg iron oxy-hydroxide per dosage form – in a form suitable for oral administration. (*E.g.*, JTX-1 at 1:5-11, 15:23-31).

20. Vifor Switzerland is the current owner of the '251 patent. (D.I. 284).

21. Vifor asserts claims 29, 30, 33, and 56 against Teva. Claims 29, 30, and 33 are dependent on Claim 1, which claims:

> A pharmaceutical composition comprising an effective phosphate-adsorbing amount of iron oxy-hydroxide in high loading of 10 to 80% (w/w) expressed in relation to the total weight of the pharmaceutical composition, and carbohydrates, said carbohydrates compromising saccharose and starch, in a form suitable for oral administration, wherein the amount of iron oxy-hydroxide per dosage form is at least 500 mg.

22. Claim 29 adds:

> The composition according to claim 1, wherein the iron oxy-hydroxide is essentially non-bioabsorbable.

23. Claim 30 adds to claim 1:

> The composition according to claim 1, having an iron release rate of below 2.5% w/w.

24. Dependent claim 33 claims:

> The composition according to claim 32, wherein dosage form is selected from chewable tablets.

25. Claim 32, in turn, claims:

> The composition according to claim 1, which is a dosage form capable of disintegration in the oral cavity.

26. Dependent claim 56 depends from dependent claim 55, which depends from independent claim 27. Claim 27 claims:

> A method for treating hyperphosphatemia, comprising the steps of
>
> orally administering a pharmaceutical composition comprising an effective phosphate-adsorbing amount of iron oxy-hydroxide in high loading of 10 to 80% (w/w) expressed in relation to the total weight of the pharmaceutical composition, and carbohydrates, said carbohydrates comprising saccharose and starch, in a form suitable for oral administration, wherein the amount of iron oxy-hydroxide per dosage form is at least 500 mg to a patient in need thereof.

27. Claim 55 claims:

> The method according to claim 27, comprising 700 to 1700 mg iron oxy-hydroxide per dosage form.

28. Claim 56 claims:

> The method according to claim 55, comprising about 800 mg iron oxy-hydroxide per dosage form.

D. <u>Velphoro</u>

29. Vifor France holds an approved New Drug Application ("NDA") under Section 505(a) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 355(a), for sucroferric

oxyhydroxide chewable tablets, 500 mg (NDA No. 205109), sold under the trade name Velphoro. Vifor France received FDA approval for Velphoro in November 2013. (D.I. 277, Ex. 1 ¶ 10).

30. Velphoro is "a phosphate binder indicated for the control of serum phosphorus levels in patients with chronic kidney disease on dialysis." (DTX-264 at 2).

31. Patients with chronic kidney disease may suffer from hyperphosphatemia, which means their serum phosphorus levels are above the normal acceptable range for the general population. (Tr. at 84:10-14). Hyperphosphatemia can cause calcification in the blood vessels and some other tissues resulting in decreased elasticity. (Tr. at 84:15-85:2).

32. Velphoro contains iron oxy-hydroxide, sucrose (saccharose), and starch. (DTX-264 at 6). Each 2577.5 mg chewable Velphoro tablet[5] contains 2500 mg of sucroferric oxyhydroxide, which corresponds to 500 mg of iron, which in turn corresponds to 800 mg of iron oxy-hydroxide. (PTX-322 at 10; Tr. at 698:19-699:2). Thus, iron oxy-hydroxide equals 31.0 percent by weight of the Velphoro tablet. (Tr. at 699:6-11).

33. The active moiety of Velphoro, polynuclear iron(III)-oxyhydroxide (pn-FeOOH), is practically insoluble and therefore not absorbed and not metabolized. (DTX-264 at 6).

34. Velphoro satisfies all of the limitations of the four asserted claims and is an embodiment of those claims. (Tr. at 698:16-700:12; PTX-322 at 57; DTX-264 at 6).[6]

E. Person of Skill in the Art

35. Plaintiffs' expert opined that a "person of ordinary skill in the art ["POSA"] would have at least the equivalent of a master's degree in chemistry, chemical engineering, pharmacy,

[5] A chewable tablet is a dosage form capable of disintegration in the oral cavity. (JTX-1, col. 3, l. 52-67).

[6] Teva does not dispute that Velphoro practices all of the limitations of the four asserted claims.

pharmacology or pharmaceutics or a comparable field, and four years of academic research or industry experience related to pharmaceutical formulation development. Alternatively, the POSA can have a higher level of formal education such as a Ph.D. and with subsequent fewer years of relevant experience. The POSA would also have access to individuals with knowledge and experience in fields such as iron chemistry, iron biochemistry, nephrology and treatment of patients with chronic kidney disease." (Tr. at 646:3-16).

36. According to Defendant, a POSA at the relevant time would have possessed at least a bachelor's degree, and more likely a master's or Doctoral degree, in the field of pharmaceutical sciences or a related discipline, and several years of experience formulating dosage forms containing pharmaceutically active compounds. A POSA could have a lower level of formal education if such person had a higher degree of experience. Furthermore, because drug discovery and development is a multidisciplinary effort, a POSA might interface or consult with individuals having specialized expertise such as, for example, a physician with experience in the administration, dosing, and efficacy of drugs for treating hyperphosphatemia. (D.I. 300 ¶ 22).

37. There is no meaningful difference between the parties' proposed definitions. Each of the experts who opined on the definition of a person of skill in the art agreed that his opinions would not change regardless of what definition of a POSA were used. (Tr. at 216:20-22 (Fadem); Tr. at 287:7-14 (Chambliss); 645:24-647:1 (Williams)).

38. Dr. Rastogi (PTX-555), Dr. Myers (Tr. at 142:24-144:4),[7] Dr. Fadem (Tr. at 216:2-19), Dr. Chambliss (Tr. at 287:15-17), and Dr. Williams (Tr. at 644:4-19, 645:24-646:18) meet the definitions of a POSA offered by both sides.

[7] Teva asserts that Plaintiffs made no "showing or attempt to qualify Dr. Myers" as a POSA at trial. (D.I. 309 at 8, n.8). The evidence shows that Dr. Myers has a Ph.D. in organic chemistry and more than ten years of experience in analyzing pharmaceutical formulations.

F. Facts Relevant to Infringement

1. Teva's ANDA Product[8]

39. Teva's sucroferric oxyhydroxide ANDA product is a phosphate binder indicated for the control of serum phosphorus levels in patients with chronic kidney disease on dialysis. (DTX-152 at 2). The package insert instructs healthcare professionals to administer Teva's ANDA product as a phosphate binder to control serum phosphorus levels in patients with chronic kidney disease on dialysis (*i.e.*, hyperphosphatemia). (DTX-152 at 2).

40. Teva's ANDA product is a chewable tablet, which is a dosage form capable of disintegration in the oral cavity in the form of a chewable tablet. (D.I. 277, Ex. 1 ¶¶ 20-21; DTX-152 at 1, 5).

41. Teva represented to the FDA that its ANDA product "is deemed therapeutically equivalent to Velphoro®." (DTX-171 at 28; Tr. at 99:4-17).[9] It represented that its ANDA product contains "the same active ingredients . . . as well as the same route of administration, dosage and strength" and "was demonstrated to be comparable to Velphoro®." (DTX-171 at 28; *see also* PTX-7; Tr. at 97:12-23).

(PTX-603). This is consistent with Dr. Myers' testimony that he is a person of ordinary skill in the art. (*See* Tr. 186:15-16).

[8] Teva's ANDA product will be manufactured at Watson Pharma Private Ltd., which is a part of Teva. (DTX-171 at 66; PTX-7 at 1).

[9] The FDA defines "bioequivalence" as "the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study." 21 C.F.R. § 314.3(b).

42. Teva submitted an *in-vitro* bioequivalence equilibrium binding and *in-vitro* bioequivalence kinetic binding study in its ANDA for the purpose of showing that its ANDA product is bioequivalent to Velphoro in phosphate binding capacity. (D.I. 277, Ex. 1 ¶ 17).

43. Based on its showing of bioequivalence to Velphoro, Teva was able to rely upon the clinical studies conducted on Velphoro in its submissions to the FDA. (Tr. at 96:17-97:8).

44. As of the date of this opinion, Teva has not received approval (tentative or final) for its product. (D.I. 321).

2. Claims 1, 33, and 56

45. Teva does not contest that its ANDA product includes each limitation of unasserted claim 1 of the '251 patent (from which asserted claims 29, 30, 33, and 56 depend). (D.I. 277, Ex. 1 ¶ 23).

46. Teva does not contest that its ANDA product includes the additional limitation of claim 33 and Teva agrees that Plaintiffs have satisfied their burden of proof with respect to infringement of claim 33. (D.I. 277, Ex. 1 ¶ 24).[10]

47. Teva does not contest that its ANDA product includes all of the limitations of claim 56 of the '251 patent and/or indirectly infringes claim 56 of the '251 patent. Teva agrees that Plaintiffs have satisfied their burden of proof with respect to infringement of claim 56. (D.I. 277, Ex. 1 ¶ 25).

3. Claim 29

48. The only dispute about infringement of claim 29, which depends on claim 1, is whether Teva's ANDA product meets the "essentially non-bioabsorbable" limitation.

[10] In the Pretrial Order (D.I. 277, Ex. 1 ¶¶ 24-25), Teva noted that its agreement was "subject to its non-infringement defense under the reverse doctrine of equivalents." Teva, however, later dropped its reverse doctrine of equivalents defense.

49. The Court construed "essentially non-bioabsorbable" to mean "upon oral administration, the iron oxyhydroxide is not absorbed by the human body in a clinically significant amount." (D.I. 114 at 5).

50. Iron is potentially toxic when in the body in high amounts. (Tr. at 104:3-20). There are two types of iron toxicity. One is potentially fatal acute iron poisoning, which can cause vomiting, diarrhea, and bleeding. The second is iron overload (hemochromatosis), which can lead to organ damage, especially the liver. (*Id.*).

51. Iron absorption into the body also can also affect phosphate binding capacity and lower the efficacy of a phosphate binder. (Tr. at 112:1-113:20).

52. The proposed label for Teva's ANDA product states: "[s]ince the absorption of iron from sucroferric oxyhydroxide is low . . . the risk of systemic iron toxicity is low." (D.I. 277, Ex. 1 ¶ 22).

53. Teva's package insert states that the "active moiety of sucroferric oxyhydroxide, polynuclear iron (III)-oxyhydroxide (pn-FeOOH), is practically insoluble and therefore not absorbed and not metabolized" and "[t]he active moiety, polynuclear iron (III)-oxyhydroxide, is practically insoluble and cannot be absorbed." (DTX-152 at 5-6).

54. Teva's package insert includes a description of an iron uptake study using radiolabeled sucroferric oxyhydroxide drug substance in 16 chronic kidney disease patients and 8 healthy volunteers. The only source of radiolabeled iron in the study was sucroferric oxyhydroxide. (DTX-152 at 6). The study reported that, in chronic kidney disease patients, the median iron uptake was 0.04% on Day 21, which is considered "quite low and insignificant." (Tr. at 103:17-104:2 (discussing DTX-152 at 6)).

55. Physicians rely on a drug's package insert, which contains vital information such as dosing, drug interactions, and warnings, to determine whether to use a drug to treat patients, and how to use that drug treat patients. (Tr. at 99:24-100:17, 104:21-105:3). When prescribing generic drugs, physicians expect that a generic drug behaves in the same manner as the branded drug. (Tr. at 104:21-105:19).

56. Although the clinical study of iron uptake referenced in Teva's package insert was conducted by Vifor using Velphoro, not the Teva ANDA product (Tr. at 103:6-8), if the data and statements made regarding the "low and insignificant" iron uptake were untrue as to Teva's ANDA product, that would put patient safety in jeopardy (Tr. at 101:13-19).

57. Teva has not informed the FDA that any statements in the package insert for its ANDA product may be incorrect or doubtful. Nor has Teva informed the FDA that it does not know the level of absorption of iron oxy-hydroxide from Teva's ANDA product or that it requires additional clinical testing to make that determination.

58. Additional Teva documents also indicate that the iron oxy-hydroxide in Teva's ANDA product is not absorbed in clinically significant amounts. Teva's pharmaceutical development report, submitted as part of its ANDA submission to the FDA, states:

- the iron oxy-hydroxide in its ANDA product "is not intended to be absorbed *in vivo*." (DTX-172 at 3);
- a "special" feature of the product is "the fact that [i]ron from the product is not available in soluble form to be absorbed in the [gastrointestinal tract]." (DTX-172 at 7);
- "sucroferric oxyhydroxide tablets are not expected to release free iron over the GI physiology and their by [sic] avoid possibility of any adverse effects associated with high intake of iron." (DTX-172 at 14);
- that dissolution tests comparing Teva's ANDA product to Velphoro showed that "[b]oth test and reference did not show release [of iron]

> in most relevant fed state pH of GI tract" and that the results were consistent with other literature that "indicate negligible release of iron in the [gastrointestinal tract] for absorption." (DTX-172 at 22).

59. Another Teva product development document describes the "poor solubility and nonabsorbed nature" of Teva's ANDA product. (DTX-177 at 4). It also states that "[i]ron from the product is not available in soluble form to be absorbed in the [gastrointestinal tract]." (DTX-177 at 10). That exhibit describes dissolution tests that were conducted comparing Teva's ANDA product to Velphoro, which showed that "[b]oth test and reference did not show release in most relevant fed state pH of GI tract" and that the results were consistent with other literature that "indicate negligible release of iron in the [gastrointestinal tract] for absorption." (DTX-177 at 36).

60. Teva's corporate representative, Hemant Mamania, confirmed the accuracy of the statements in the documents. For example, Dr. Mamania confirmed that Teva did not doubt that the API used in Teva's ANDA product would not be absorbed from the gastrointestinal tract into systemic circulation (Tr. at 61:20-25) and that Teva relied upon the knowledge that the API used in Teva's ANDA product would not be absorbed from the gastrointestinal tract into systemic circulation in developing its formulation (Tr. at 62:1-14). Dr. Mamania also testified that he was aware that free iron absorption can lead to toxicity, and a point of developing Teva's ANDA product was to avoid having free iron that can be absorbed. (Tr. at 74:24-75:11).

61. Teva's expert, Dr. Fadem, did not address or offer opinions on the statements in Teva's pharmaceutical development documents. (Tr. at 222:2-13).

62. The iron oxy-hydroxide in Teva's proposed ANDA product is "essentially nonbioabsorbable" as that term has been construed by the Court. As that is the only disputed element, Teva's proposed ANDA product meets each and every element of claim 29.

4. Claim 30

63. As noted above, claim 30 depends on claim 1. The only disputed element regarding infringement of claim 30 is whether Teva's ANDA product meets the additional limitation of claim 30, *i.e.*, "having an iron release rate of below 2.5% w/w."

64. During claim construction, the Court construed "iron release rate below 2.5% w/w" to mean "the iron release measured in water at a pH of 3 according to European Pharmacopeia ("EP") chapter 2.9.3[11] using standard dissolution equipment and parameters as described in the monograph, where iron content is analyzed by titration after 2 hours, wherein the quantity of iron dissolved after 2 hours is less than 2.5% w/w."[12] (D.I. 114 at 7).

65. At trial, the parties disputed whether the Court's construction requires a pH of 3 (as stated) or a pH of 3.0.

66. Plaintiffs' expert, Dr. Myers, was the only witness to testify about infringement of claim 30. Teva did not offer any expert or fact testimony to rebut Dr. Myers' testing, methodology or results or his understanding and application of the Court's claim construction in his infringement analysis.

67. The '251 patent refers to pH in two places: first, referring to polymer coating, noting that "[s]uitable polymers . . . are soluble at pH of from about 1.2 to about 5" (JTX-1 at 9:10-

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11 EP 2.9.3 provides guidance for instrumentation and test parameters for performing dissolution testing on a variety of dosage forms. (PTX-246; Tr. at 146:3-9).

12 The '251 patent describes results for "[iron] release at pH 3," which was measured "according to European Pharmacopeia chapter 2.9.3 using standard dissolution equipment and parameters as described in the monograph. The test medium is water, pH 3 was adjusted using hydrochloric acid. Samples were analyzed after 2 [hours] and iron content analyzed by titration." (JTX-1 at 14:43-53).

11) and second, discussing iron release testing in Example 8 and Table 9b and referring repeatedly to pH of 3 (JTX-1 at 14:40-15:20 (including Table 9(b))).

68. The patentees understood how to specify pH to a decimal place (*e.g.*, 1.2) when they intended to do so. The patentees did not do so with respect to the pH of 3, instead expressing it as a whole number.

69. A POSA would understand that pH 3, expressed as a whole number in the patent, would mathematically encompass a range of 2.5-3.4 and would understand that, if the patent required a pH to be more specific than that range, the pH would be identified with additional decimal places. (Tr. at 162:7-15, 181:23-182:6).

70. A POSA would further understand that measurement of the iron release at a pH of 3 is intended to simulate the fed state of the stomach, which would exist in a pH range that encompasses 2.5-3.4, though almost never at a pH of exactly 3.0. (Tr. at 150:6-12, 162:7-15, 164:22-165:2).

71. Dr. Myers is the only expert who performed iron release testing consistent with the Court's construction and the process detailed in the '251 patent, which requires measurement in water at a pH of 3 according to EP 2.9.3 using standard dissolution equipment and parameters as described in the monograph.

72. Initial testing showed that the disintegration of Teva's ANDA product tablets (which occurred before dissolution)[13] caused the pH of the medium to increase from 3 to about 6 before dissolution testing began. (Tr. at 152:10-153:20, 154:2-5, 196:12-16). The disintegration

[13] Dissolution is the absorption or release of a particular analyte into the medium, which is quantitated. (Tr. 153:11-20).

caused the pH to change "pretty much instantaneous[ly]" and remained stable once dissolution began. (Tr. at 153:25-154:5).

73. Dr. Myers used hydrochloric acid to adjust the pH before addition of the tablet to account for the effect on pH during tablet disintegration. (Tr. at 154:15-25; PTX-245 at 11-12). After disintegration of Teva's ANDA Product took place, the pH of the test media stabilized to 3. (Tr. at 166:24-167:8, 184:2-7).

74. The pH of the test media was 3 when dissolution testing per EP 2.9.3 began and that pH was maintained for the duration of the dissolution testing. (Tr. at 166:24-167:8, 184:2-7; 196:17-21).

75. The Court's claim construction of the phrase "iron release rate below 2.5% w/w" does not impose a pH requirement prior to the start of dissolution testing per EP 2.9.3. (D.I. 114 at 7-9).

76. Dr. Myers conducted iron release testing on Teva's ANDA product using an Agilent '08DS dissolution instrument with a paddle configuration, which complies with the requirement of an Apparatus 2 in EP 2.9.3. (Tr. at 146:19-147:14; PTX-246 at 5-6; PTX-249 at 2).

77. Dr. Myers conducted iron release testing on Teva's ANDA product by conforming to the standard test parameters as set forth in EP 2.9.3. (Tr. at 148:13-149:15; PTX-246 at 5-6; PTX-249 at 2).

78. Dr. Myers measured the iron content using titration after 2 hours in media at a pH of 3. (Tr. at 149:16-150:14). The pH of the test media was 3 when dissolution testing per EP 3.9.2 began and that pH was maintained for the duration of the dissolution testing. (Tr. at 166:16-167:16, 184:2-7, 195:24-196:5, 196:17-21).

79. Dr. Myers measured iron release at a pH that ranged from 3.22 to 3.28 across 6 tablets of Teva's ANDA product, with an average pH of 3.25. (PTX-245 at 13-17; Tr. at 160:5-20). The 6 tested tablets of Teva's ANDA product had an average iron release rate of 1.94% w/w, ranging from 1.51 to 2.35% w/w. (*Id.*). Each of the 6 tested tablets of Teva's ANDA product had an iron release rate below 2.5% w/w. (Tr. at 167:9-16; PTX-245 at 13-17).

80. Teva relies on two documents Plaintiffs submitted to the FDA as part of the New Drug Application for Velphoro to critique Dr. Myer's testing: PTX-323 ("Section 2.3 Quality Overall Summary 2.3.S Drug Substance PA 21 Chewable Tablet" (dated November 27, 2017)) and DTX-69 ("3.2.P.5.3 Validation of the Determination of Iron Release in PA21 Chewable Tablets (PA21, Chewable Tablets)" (dated November 21, 2012)).

81. Neither DTX-69 nor PTX-323 informs a POSA how to perform the iron release test detailed in the '251 patent, which must be measured in water at a pH of 3 according to European Pharmacopeia chapter 2.9.3.

82. Both PTX-323 and DTX-69 specify the pH to two significant digits along with a permitted range: "pH 3.0 ± 0.1." (PTX-323 at 79; DTX-69 at 15). The '251 patent, in contrast, states only that the pH is "3" after 2 hours upon iron release measurement. (JTX-0001 at 14:40-15:20).

83. A POSA reading PTX-323 and DTX-69 would understand that the test methods described in those exhibits require a pH range of "3.0 +/- 0.1," which is different from a pH range of 2.5-3.4, the range encompassed by "pH 3." (Tr. at 194:4-195:15).

84. Additionally, EP 2.9.3 states that "[a] stirring speed of between 50 r/min and 100 r/min is normally chosen; it must not exceed 150 r/min." (PTX-246 at 12). DTX-69, on the

other hand, requires "[s]uspend[ing] the tablets (agitating speed 250 rpm for PA21 FP . . .)." (DTX-69 at 15).

85. Similarly, EP 2.9.3 restricts the dosage number to a single dosage unit in each vessel, instructing to "[p]lace 1 dosage unit in the apparatus." (PTX-246 at 7). In contrast, DTX-69 describes the use of multiple dosage units in a vessel. (DTX-69 at 2 ("analysing 6 samples (each consisting of 2 tablets)"); DTX-69 at 10 ("Preparations" include "2x4 tablets")).

86. A POSA reviewing PTX-323 and DTX-69 would conclude that "it's not the same test method" as that described in the '251 patent. (Tr. at 195:9-15).

87. Teva's ANDA product has an iron release rate of below 2.5% w/w as that term has been construed by the Court and satisfies each and every element of claim 30 of the '251 patent.

G. Facts Relevant to Invalidity

1. The Prior Art

a. U.S. Patent No. 6,174,442 (JTX-3)

88. U.S. Patent No. 6,174,442 ("the '442 patent") is titled "Adsorbent for Phosphate from an Aqueous Medium, Production and Use of Said Adsorbent" and issued on January 16, 2001.

89. The '442 patent "is a compound patent that describes phosphate adsorbent containing beta iron hydroxide stabilized by carbohydrate and/or humic acid." (Tr. at 654:20-24).

90. The European equivalent to the '442 patent, EP 0868125, is referenced in the Background section of the '251 patent. (Tr. at 655:19-56:1; JTX-1 at 1:27-37). The disclosure of EP 0868125 is equivalent to the disclosure of the '442 patent. (Tr. at 655:19-56:1). The '251 patent states that EP0868125 describes "new and effective phosphate adsorbers" with "superior

phosphate adsorption capacity" that "have been shown to be efficient oral phosphate binders in the treatment of hyperphosphataemia." (JTX-1 at 1:27-37)

91. As the inventors of the '251 patent explained after describing EP0868125, however, "phosphate adsorbers with high iron loadings are still not available. Factors, such as ease of administration in general, unacceptable taste, as well as storage and stability problems, limit the applicability of currently available phosphate binders." (JTX-1 at 1:38-44; Tr. at 656:10-18, 647:25-649:8).

92. The '442 patent does not describe any finished dosage forms. (Tr. at 654:25-655:1).

93. The '442 patent discloses a genus of novel phosphate adsorbents containing stabilized iron oxy-hydroxide. Specifically, the '442 patent discloses that "[t]he object of the present invention is therefore to provide adsorbents for phosphate from aqueous medium. . . . It has been shown that this object can be achieved by the adsorbents for phosphate from aqueous medium, to which the present invention firstly relates, which contain poly-nuclear beta-iron hydroxide stabilised by carbohydrates and/or by humic acid." (JTX-3 at 1:40-52).

94. The '442 patent identifies at least twelve different potential stabilizing agents, including humic acid, amylopectin, "agarose, dextran, dextrin, dextran derivatives, cellulose and cellulose derivatives, saccharose, maltose, lactose or mannitol." (JTX-3 at 2:54-57). "Saccharose" and "sucrose" are synonymous and refer to the same compound. (*See, e.g.*, Tr. at 390:4-10, 400:5-7).

95. The examples of the '442 patent disclose embodiments of six phosphate adsorbents. (JTX-3 at 3:30-6:45; 9:29-53).

96. Example 1 of the '442 patent describes the bulk synthesis of 208.3 g of an iron oxy-hydroxide suspension, to which 15 g of saccharose and 15 g of starch were added, yielding 47.2 g of powder. (JTX-3 at 3:30-51).

97. Example 1 is not a finished dosage form. (Tr. at 677:21-25). The material of Example 1 is made by rotary evaporation. (JTX-3 at 3:45-50). As Dr. Williams explained, the '442 patent Example 1 material "was concentrated at 50 degrees C in a rotary evaporator and dried at 40 degrees C under high vacuum" based on his experience when material is "dried from that rotary evaporator, you have to literally scrape it off the sides of the inside of the vessel of the rotary evaporator" and thus would not represent a finished dosage form. (Tr. at 677:21-678:18). The material of Example 1 would require additional processing before it would be suitable for formulating as a finished dosage form. (Tr. at 678:19-679:7).

98. Example 2 of the '442 patent measures the phosphate binding capacity of the material prepared in Example 1 containing iron oxy-hydroxide, starch, and sucrose for inorganic phosphate. (JTX-3 at 3:53-4:13, as recorded in Table 1).

99. Example 6 of the '442 patent describes the bulk synthesis of a powder consisting of 30.0 g saccharose added to the suspension of Example 1 consisting of 208.3 g iron oxy-hydroxide. (JTX-3 at 5:24-30). Phosphate binding data for the Example 6 formulation is provided in Table 5. (JTX-3 at 5:33-44). The Example 6 material had the best phosphate binding capacity of any of the stabilized iron oxy-hydroxides disclosed in the '442 patent. (Tr. at 663:1-5; JTX-3 at 5:33-44).

100. Example 7 of the '442 patent describes the bulk synthesis of a powder consisting of 30.0 g amylopectin added to the suspension of Example 1 consisting of 208.3 g iron oxy-hydroxide. (JTX-3 at 5:44-50). Phosphate binding data for Example 7 is provided in Table 6.

101. Example 8 of the '442 patent describes the bulk synthesis of a powder consisting of only iron oxy-hydroxide and white dextrin. (JTX-3 at 5:64-6:5). Phosphate binding data for the Example 8 formulation is provided in Table 7. (JTX-3 at 6:6-17). Example 8 had the second best phosphate adsorption data in the '442 patent. (Tr. at 663:6-15; JTX-3 at 6:6-17).

102. A POSA would understand from this data that Examples 6 (sucrose) and 8 (dextrin) have the best phosphate binding capacity. (Tr. at 399:11-20, 663:1-15).

103. The only stabilizers claimed in the '442 patent are dextrin and sucrose. Specifically, claim 7 is directed to "[a] process according to claim 2, wherein the carbohydrate comprises saccharose or dextrin or a mixture thereof." (JTX-3 at 12:1-2). The inventors of the '442 patent did not specifically claim the combination of starch and sucrose as used in Example 1. (JTX-3 at 10:36-12:24).

104. A POSA reading the '442 patent in its entirety would understand that the '442 inventors considered the disclosed phosphate binders stabilized with sucrose (Example 6) and dextrin (Example 8) to be the most promising active ingredients for development into a complete formulation. (Tr. at 663:1-664:16, *see also* Tr. at 411:2-12, 399:11-20; 391:20-392:9).

105. The '442 patent contains a generic teaching applicable to all of the stabilized iron oxy-hydroxides described that the novel stabilized iron oxy-hydroxides described can be "formulated for oral application . . . They can be formulated as such or together with customary drug additives, such as customary carriers or auxiliary materials." (JTX-3 at 3:9-13). Also, "[e]ncapsulation may be effected" or "the adsorbents" may be provided "together with auxiliary materials and additives, as granules, tablets, dragees or contained in sachets." (*Id.*). Because the '442 patent refers generally to "[t]he adsorbents according to the invention" in that statement, a

POSA would understand that this disclosure refers to all of the stabilized iron oxy-hydroxides disclosed in the '442 patent, not just Example 1. (Tr. at 392:23-393:8).

b. Hergesell (JTX-7)

106. In 1999, Hergesell and Rich published an article titled "Stabilized polynuclear iron hydroxide is an efficient oral phosphate binder in uraemic patients" in Nephrology Dialysis Transplantation ("Hergesell"). (JTX-7).

107. The '251 patent discusses Hergesell. (JTX-1 at 1:31-37; Tr. at 656:2-9). In the paragraph immediately following that discussion, the '251 patent states that "phosphate adsorbers with high iron loadings are still not available. Factors, such as ease of administration in general, unacceptable taste, as well as storage and stability problems, limit the applicability of currently available phosphate binders." (JTX-1 at 1:38-44; Tr. at 656:10-18).

108. Hergesell describes an open uncontrolled study of the efficacy and tolerability of "stabilized polynuclear iron hydroxide." (JTX-7). Hergesell discloses that a "stabilized polynuclear iron hydroxide" of the chemical formula "$[FeO_{2/3}(OH)_{5/3}H_2O\ l/m(C_6H_{10}O_5)_m]_n$" "appears to be a promising, new compound which has remarkable in vitro binding capacity for phosphate compared to the cross-linked iron Dextran." (JTX-7 at 1; Tr. at 402:4-16). Aside from this chemical formula, Hergesell does not provide any other details about the "stabilized polynuclear iron hydroxide" used in the clinical study. (JTX-7).

109. The POSA "having looked at the '442 Patent, and Hergesell sees that Hergesell discloses that there are promising compounds that have remarkable in vitro binding capacity" and "they would also see that they were given a formula with respect to the promising new compound." (Tr. at 402:12-19).

110. The chemical formula in Hergesell ("$[FeO_{2/3}(OH)_{5/3}H_2O$ l/m$(C_6H_{10}O_5)_m]_n$") contains "two different chemical compounds," one on the left and one on the right, and the chemical compound on the right is "$(C_6H_{10}O_5)_m$." (JTX-7 at 1; Tr. at 403:8-404:11).

111. $C_6H_{10}O_5$ is consistent with starch, amylopectin and dextrin. (Tr. at 404:12-405:6, 406:25-407:2). Amylopectin and dextrin are the stabilizers used in Examples 7 and 8 of the '442 patent. (JTX-3 at 5:44-50, 5:64-6:5; Tr. at 405:15-17, 407:3-10).

112. In describing "stabilized polynuclear iron hydroxide," Hergesell cites DE 195 47 356 A1 (designated as footnote 13). (JTX-7 at 1, 4).

113. DE 195 47 356 A1 is the German patent application to which the '442 patent claims priority. (Tr. at 307:1-6).

114. The chemical formula $C_6H_{10}O_5$ is not consistent with sucrose or saccharose. (Tr. at 668:2-5). The chemical formula for saccharose is $C_{12}H_{22}O_{11}$. (Tr. at 409:12-15).

115. Hergesell does not disclose the chemical formula $C_{12}H_{22}O_{11}$ (saccharose). (Tr. at 409:16-18). There is no disclosure of saccharose in Hergesell. (Tr. at 409:19-21).

116. The components of the "stabilized polynuclear iron hydroxide" in the chemical formula in Hergesell are consistent with Examples 7 and 8 of the '442 patent but not consistent with the components for sucroferric oxy-hydroxide (described in Example 1 of the '442 patent). (*See* 404:12-25, 405:15-23, 407:3-10, 668:2-5, 672:22-673:9).

117. Hergesell discloses that "powder in pre-weighed sachets were provided to patients" (Tr. at 685:21-668:1) and that patients were "given a constant dose of 3 x 2.5 g stabilized polynuclear iron hydroxide" (JTX-7 at 2). From this disclosure, however, "it's just not clear" how "much of the stabilized polynuclear iron oxyhydroxide is contained in each preweighed sachet." (Tr. at 686:2-15; JTX-7 at 2).

c. U.S. Patent No. 4,970,079 ("the '079 patent") (JTX-5)

118. The '079 patent is titled "Method and composition of oxy-iron compounds for treatment of hyperphosphatemia" and issued on November 13, 1990. (JTX-5 at 1).

119. The '079 patent discloses "three types of oxy-iron compounds . . . iron oxides, iron hydroxide and iron oxyhydroxides." (Tr. at 686:19-23; JTX-5 at 3:12-14). The '079 patent discloses "500 mg or more" of such compounds. (JTX-5 at 3:52-55; Tr. at 686:24-687:10).

120. The foreign equivalent to the '079 patent is referenced in the Background section of the '251 patent. (Tr. at 657:13-19; JTX-1 at 2:4-18). There, the '251 patent states that "[n]o specific oral formulations are disclosed" in the '079 patent, that "no specific iron loading is mentioned" and that, although there is a disclosure that "each oral dose may contain 50 mg to about 500 mg or more of oxy-iron compound," "[a]ccording to the state of the art tablets containing 500 mg oxyiron compounds . . . would be of such an enormous size that they could not be swallowed by the patient." (JTX-1 at 2:4-18; Tr. at 657:20-658:6).

121. "The '079 patent relates to unstabilized oxy-iron compounds. In the '079 patent, there is no disclosure of stabilized iron oxyhydroxide and there is no specific disclosure of how to formulate and make finished dosage forms." (Tr. at 656:19-657:2).

122. The '079 patent also teaches that "each oral dose of the therapeutic oxy-iron containing composition in accordance with this invention can contain from about 50 milligrams to about 500 milligrams or more of oxy-iron compound" and that the "amount of oxy-iron compound to be administered will depend on the severity of the patient's condition, the nature of the patient's diet, and the surface area and phosphate binding capacity of the specific oxy-iron compound used in the formulation." (Tr. at 686:24-687:10).

123. The '079 patent also discloses that "a 174-milligram dose of ferrihydrite can absorb the same amount of phosphate of ten mil as . . . Amphogel which is a commercially available aluminum hydroxide product. And it mentions a tablet or capsule containing 174 milligrams of synthetic ferrihydrite." (Tr. at 687:11-688:2). However, "the '079 [patent] does not give any details how to formulate a composition that contains 174 milligrams of ferrihydite [sic: ferrihydrite] or a method of how to make a composition." (Tr. at 688:3-8).

124. The only disclosure in the '079 patent regarding how to formulate tablets or capsules containing the oxy-iron compounds is a single passage that states "methods and excipients for preparation of both gel and solid dosage forms are well-known in the art." (Tr. at 688:19-689:2). "[T]hat's [] a really general statement" that "doesn't really tell a POSA how specifically to formulate or make dosage forms of the oxy-iron compounds of this invention." (Tr. at 689:2-5).

125. The '079 patent does not give any specific details about how to formulate a composition that contains 174 milligrams of ferrihydrite or a method of how to make a composition. (Tr. at 688:3-8).

126. The '079 patent claims "[a] therapeutic composition in oral dosage form for controlling serum phosphate in patients having need for reduced absorption of dietary phosphate, said composition comprising on a per dose basis from about 50 mg to about 500 mg of an oxyiron compound selected from the group consisting of iron oxides, iron oxyhydroxides, and iron hydroxides, and a pharmaceutically acceptable excipient for said oral dosage form." (JTX-5 at 7:18-8:2).

2. Obviousness of the Asserted Claims Based on the '442 Patent Alone

127. Independent claims 1 and 27 of the '251 patent both require "wherein the amount of iron oxy-hydroxide per dosage form is at least 500 mg." Each asserted claim is dependent on either claim 1 or 27 and, thus, incorporate by reference the "wherein the amount of iron oxy-hydroxide per dosage form is at least 500 mg" limitation. (FF ¶¶ 21-28). Claims 29, 30, and 33 of the '251 patent require a "pharmaceutical composition" with "at least 500 mg" of iron oxy-hydroxide "per dosage form" while claim 56 – which is dependent on claim 27 – further requires a higher amount of "about 800 mg iron oxy-hydroxide per dosage form." (*Id.*). Thus, all asserted claims require a "pharmaceutical composition" with "at least 500 mg" of iron oxy-hydroxide "per dosage form." (*Id.*).

128. A POSA would not have been motivated to make a single dosage form with at least 500 mg or about 800 mg of iron oxy-hydroxide based on the disclosure of the '442 patent. (Tr. at 697:4-12).

129. The '442 patent does not disclose any complete pharmaceutical compositions, let alone any high loaded compositions. (*See* Tr. at 654:25-655:1).

130. Example 1 describes the bulk synthesis of 47.2 g of SFO. (JTX-3 at 3:45-50). Thus, a POSA attempting to formulate Example 1 would need to select the amount of iron oxyhydroxide to include per dosage form. (*See* Tr. at 679:17-22).

131. "There is no discussion in Example 1 about how much iron oxyhydroxide from the powder that's been produced should be loaded in a final dosage form." (Tr. at 679:20-22).

132. The '442 patent generically discloses that "[t]he daily dose of the adsorbents according to the invention is, for example, 1 to 3 g, preferably about 1.5 g of iron." (JTX-3 at 3:19-21). A POSA would understand that this disclosure is directed to the entire class of disclosed

stabilized iron oxy-hydroxide compounds. (*See* Tr. at 392:23-393:8). 500 mg of iron corresponds to 800 mg of iron oxyhydroxide. (*See* FF ¶ 32).

133. Applying the generic disclosure of a preferred "daily dose" of "1.5 g of iron" (JTX-3 at 3:19-21) to all of the Examples would result in significantly different phosphate binding capacities at that single preferred daily dose. The Examples have different phosphate binding capacities – ranging from 100% to 69% at pH 3 and 100% to 65% at pH 5.5. (JTX-3 at 4:1-13, 5:33-44, 5:52-63, 6:6-17, 6:32-44, 9:40-52; Tr. at 662:19-663:21). This means that a 1.5 g daily dose of Example 8 would have about 30% more phosphate binding capacity than a 1.5 g daily dose of Example 7.

134. As Dr. Williams explained, the determination of the correct dose is determined during pre-formulation testing and is based on a number of factors, which would likely require testing and input from a physician. (Tr. at 659:11-660:3, 685:3-15; DTX-1006 at 4, 12). The '442 patent does not provide this information. (Tr. at 685:16-20).

135. Dr. Rastogi, a physician, explained that administering high doses of iron is particularly challenging because it can cause gastrointestinal irritation. (Tr. at 512:24-513:3; *see also* JTX-1 at 2:49-53).

136. For example, iron compositions "more often than not cause[] gastrointestinal problems," and 500 mg per dose is significantly higher than the "normal requirement [of] one milligram per day absorption of iron." (Tr. at 513:1-6).

137. The '442 patent provides no teaching about the number of administrations per day for the preferred daily dose. (Tr. at 680:9-680:16, 684:6-20). Rather, a POSA would understand this "to refer to the total daily dose" and would understand that it "doesn't provide guidance to a

POSA on . . . how to subdivide it into dosage forms. It just doesn't give that information." (Tr. at 680:12-16).

138. The '442 patent teaches generally in claim 12 that the claimed phosphate binders should be taken "simultaneously with intake of food." (JTX-3 at 12:13-17). That does not inform a POSA of the number of administrations per day. (*See* Tr. at 684:9-20).

139. As Dr. Williams explained, a POSA would understand this teaching to mean exactly what it is says – *i.e.*, "take the stabilized polynuclear beta iron oxyhydroxide when they eat food." (Tr. at 684:12-14).

140. There is nothing in the '442 patent disclosure that equates ingesting food at regular meals, let alone three meals per day. Dr. Fadem acknowledged that patients take phosphate binders not just with meals but with some snacks as well. (Tr. at 733:3-734:4).

141. The labels for other phosphate binders do not establish "general knowledge" among POSAs that phosphate binders are administered three times a day. First, a POSA would not look to the dosing regimens of non-iron based phosphate binders when seeking to formulate the stabilized iron oxy-hydroxide binders described in the '442 patent. (Tr. at 696:1-20). Second, three of the four labels on which Teva relies are not prior art. These three labels have revision dates of 2011 – years after the 2007 filing of the priority application to the '251 patent. (PTX-217 at 1, PTX-544 at 1, PTX-211 at 1). Two of the four labels upon which Teva relies state that the dosage and administration information was changed in 2009 and 2011, respectively. (PTX-217 at 1; PTX-544 at 1).

142. Third, even if a POSA did rely on those labels, they show that phosphate binders frequently have multiple doses that depend on a number of patient-specific factors. (PTX-217 at 1-3; PTX-544 at 1-2; PTX 211 at 1-2; PTX-214 at 1-3; DTX-120 at 1-3; Tr. at 722:15-723:9). For

example, Renagel® was administered as up to five tablets per administration. (PTX-214 at 1-3). Similarly, even sachets and oral suspensions required multiple dosage forms – the 1.6 g starting dose for Renvela® was administered as two 0.8 g sachets. (Tr. at 722:15-723:9; DTX-120 at 1; PTX-217 at 1). Additionally, Phoslyra™ was administered as two 5 ml oral suspensions. (PTX-211 at 1).

143. As Dr. Williams explained, once the appropriate dose is set, a POSA still needs to determine whether it can be delivered in a single dosage form, and the '442 patent provides no information about these formulation considerations. (Tr. at 685:3-20). For example, once a POSA determines the correct dose administration, the POSA would then consider a number of formulation factors to determine if that dose can be formulated in a single dosage unit or whether the dose needs to be divided among multiple dosage units. (*Id*). The '442 patent "doesn't give [] information" about whether "it's possible to load any given amount of iron oxyhydroxide [into] a given dosage form." (*Id.*).

144. A POSA would not have had a reasonable expectation of success in formulating a high loaded composition with "at least 500 mg" or "about 800 mg" of iron oxy-hydroxide per dosage form. (Tr. at 697:13-18).

145. Thus, a POSA would not have had reason to believe that a single dose containing 500 or 800 mg iron oxy-hydroxide would be successful as a pharmaceutical formulation. (*See* Tr. at 512:13-513:19 (noting that compressing 500 milligrams of iron in a small tablet is "remarkable," particularly given the "very minimal" gastrointestinal adverse events); 697:13-18).

3. Obviousness of the Asserted Claims Based on the '442 Patent in Combination with Other Prior Art

146. Teva relies on one or more of Hergesell and the '079 patent in combination with the '442 patent to argue that a combination of prior art references render the "wherein the amount of iron oxy-hydroxide per dosage form is at least 500 mg" limitation of the asserted claims obvious.

147. The Hergesell reference and '079 patent do not teach or suggest the limitations that are not disclosed in or rendered obvious by the '442 patent.

148. None of the other cited prior art references contain any specific pre-formulation data related to sucroferric oxyhydroxide. (Tr. at 660:4-17). Moreover, none of the other cited prior art references contain any pre-formulation data related to any of the stabilized polynuclear iron oxyhydroxides described in the '442 patent generally. (Tr. at 660:18-661:2).

149. Aside from the '442 patent, Hergesell is the only prior art reference Teva relies on that discusses stabilized iron oxy-hydroxide. (Tr. at 677:8-14).

a. The Relationship Between the '442 Patent and Hergesell

150. Dr. Chambliss testified that "[a]s a formulator, you would start with the '442 Patent and then you would look to see if there is any other publications out there which use that material, and you would find Hergesell. And Hergesell then directs you back to the '442 Patent. So they're very tightly tied together." (Tr. at 306:1-5). Accordingly, a POSA reviewing the '442 patent would also review and consider the disclosure in Hergesell.

151. Hergesell explicitly references the German priority application that corresponds to the '442 patent. (JTX-7 at 1; *see also* Tr. at 307:1-6).

152. Hergesell states that a "stabilized polynuclear iron hydroxide" having the chemical formula "$[FeO_{2/3}(OH)_{5/3}H_2O\ l/m(C_6H_{10}O_5)_m]_n$" "appears to be a promising, new compound which

has remarkable in vitro binding capacity for phosphate compared to the crosslinked iron dextran." (JTX-7 at 1; Tr. at 402:4-16).

153. The POSA "having looked at the '442 Patent, and Hergesell sees that Hergesell discloses that there are promising compounds that have remarkable *in vitro* binding capacity" and "they would also see that they were given a formula with respect to the promising new compound." (Tr. at 402:12-19).

154. Dr. Chambliss agreed that the chemical formula on the first page of Hergesell describes two different chemical compounds – $FeO_{2/3}(OH)_{5/3}H_2O$ and $C_6H_{10}O_5$. (Tr. at 403:18-404:11).

155. Dr. Chambliss acknowledged that the formula $(C_6H_{10}O_5)_m$ is consistent with amylopectin and dextrin. (Tr. at 405:3-6; 406:25-407:2). Amyolpectin and dextrin are the stabilizers used in Examples 7 and 8 of the '442 patent. (Tr. at 405:15-17; 407:3-10).

156. Dr. Chambliss also acknowledged that the Hergesell chemical formula is not consistent with sucrose (saccharose) and that there is no disclosure of sucrose anywhere in Hergesell. (Tr. at 409:12-21; 410:19-25). Thus, the chemical formula in Hergesell is not consistent with Example 1 of the '442 patent.

157. Because the Hergesell formula does not include sucrose and is inconsistent with Example 1 of the '442 patent, it would lead a POSA away from selecting Example 1 as the active ingredient for formulation development.

158. A POSA would not discount the Hergesell formula because its description of the iron-based compound is, according to Teva, "non-standard and erroneous." Dr. Chambliss agreed that he could understand the right side of the formula and that it describes a carbohydrate. (Tr. at 403:8-405:2).

b. The '442 Patent in combination with Hergesell and the '079 Patent do not teach or suggest "wherein the amount of iron oxy-hydroxide per dosage form is at least 500 mg"

159. Teva contends that the '079 patent and Hergesell provide motivation for a POSA to make a formulation with at least 500 mg or about 800 mg of sucroferric oxyhydroxide per dosage form. Neither reference motivates a POSA to include 500 mg or 800 mg of iron oxy-hydroxide in a single dosage form.

160. The '079 patent discloses "three types of oxy-iron compounds . . . iron oxides, iron hydroxide and iron oxyhydroxides." (JTX-5 at 3:12-14; Tr. at 686:19-23). The '079 patent discloses "500 mg or more" of such compounds. (JTX-5 at 3:52-55; Tr. at 686:24-687:10). The '079 patent, however, does not disclose any finished dosage formulations, nor does it teach how to formulate the disclosed iron oxy compounds. (Tr. at 688:9-689:5).

161. The '079 patent also teaches that 174 mg of iron oxy compound is as effective in adsorbing phosphate as the commercially available aluminum hydroxide product and mentions a tablet or capsule containing 174 milligrams of iron oxy compound. (Tr. at 687:14-688:2).

162. However, "[t]he '079 [patent] does not give any details about specifically how to formulate a composition that contains 174 milligrams of ferrihyd[rite] or a method of how to make a composition." (Tr. at 688:3-8).

163. Hergesell discloses that "powder in pre-weighed sachets were provided to patients" (Tr. at 685:21-686:1) and that patients were "given a constant dose of 3 x 2.5 g stabilized polynuclear iron hydroxide" (JTX-7 at 2). From this disclosure, it is not clear how much powder is contained in each sachet. (Tr. at 686:2-7). It is also not clear "how much of the stabilized polynuclear iron oxyhydroxide is contained in each pre-weighed sachet." (Tr. at 686:8-15).

4. Objective Indicia of Nonobviousness

a. Long Felt But Unmet Need

164. The search for safe and effective phosphate binders began in the 1970s. (Tr. at 507:8-18).

165. Aluminum-based binders were the first binders that were widely used for treating hyperphosphatemia. (Tr. at 493:21-25). Aluminum-based binders were effective but could be toxic because the aluminum is absorbed into the body. (Tr. at 494:15-17). This risk of aluminum toxicity led to discontinuation of widespread use of aluminum-based binders. (DTX-1019 at 3-4).

166. In the 1990s, calcium-based binders began to be used as a replacement for aluminum-based binders. (Tr. at 497:21-498:18; DTX-1019 at 5). Calcium-based binders, however, are also associated with adverse events including hypercalcemia, vascular calcification, and bone disease resulting from the systemic absorption of calcium. (Tr. at 498:24-499:2-16; DTX-1019 at 5). As of at least 2014, the medical field was warned that calcium-based binders should be avoided altogether. (Tr. at 499:17-24; DTX-1019 at 5; PTX-446 at 31).

167. Sevelamer-based binders are nonmetal binders in the class of polymers. (Tr. at 502:3-13). These binders are safe but not very effective so they must be administered in very large pills. (Tr. at 502:24-504:5). The large pills can result in poor patient compliance and poor therapeutic outcomes. (*Id.*).

168. Lanthanum-based binders are metal-based. (Tr. at 504:7-505:3). Lanthanum-based binders are more effective than calcium and sevelamer but, as warned on package inserts, lanthanum is difficult to chew and can result in broken teeth, which actually led to noncompliance and discontinuation. (*Id.*; PTX-544 at 1-3).

169. Aluminum-based, calcium-based, sevelamer-based, and lanthanum-based binders each failed to satisfy the need for a safe, effective, and tolerable binder. (Tr. at 506:16-507:1).

170. Velphoro satisfied the long-felt need for a safe, effective, and tolerable binder. (Tr. at 507:2-4).

171. Velphoro was able to get patients to their goal serum phosphate levels through administration of a reasonably sized, easy-to-chew tablet with a low pill burden, all of which are important for long-term compliance and efficacy. (Tr. at 508:20-509:21, 511:6-23; DTX-1020 at 2).

172. Despite being a metal-based binder, Velphoro was safe due to little to no systemic bioabsorption and thus, no iron toxicity. (Tr. at 508:14-18).

b. Commercial Success

173. Velphoro has substantial revenues from its sales in the United States since launch to September 2019, achieving net sales of approximately $481 million. (Tr. at 566:10-20).

174. Velphoro's sales have grown rapidly from about $15 million in the partial year 2014, the year of launch, to $135 million in annual sales through September 2019. That growth reflects a compound annual growth rate of about 35%. (*Id.*; DTX-313-F at 1; DTX-697).

175. These sales provide evidence of marketplace success. (Tr. at 567:2-4).

176. Velphoro competes more closely with calcium-free binders when compared to calcium-based binders. (Tr. at 569:2-12, 616:8-617:2; DTX-493, DTX-879, DTX-836).

177. Velphoro's share of the calcium-free segment rose from just under 2% in the year of launch to 11.8% in September 2019. (Tr. at 569:22-570:19, 575:25-576:10). Velphoro's shares of prescriptions in the calcium-based binder market shows a similar growth pattern and similar trajectory, rising to 8% in September 2019. (Tr. at 575:25-576:10; DTX-697; DTX-313-M at 1).

178. Velphoro's market is characterized by competition among branded and generic pharmaceutical products. (Tr. at 571:7-23). Generic products have substantially lower prices. (*Id.*).

179. Velphoro was a late entrant to a relatively crowded field of phosphate binders, including both generic and branded competitors. (Tr. at 573:3-13). Being a late entrant results in more limited market uptake than one would expect if one was an early entrant. (Tr. at 574:9-18).

180. The marketplace success of Velphoro based on its ability to penetrate the market despite being a late entrant and in the face of significant generic competition provides further confirmation of its success in the marketplace. (Tr. at 575:3-11).

c. Blocking Patent

181. Teva asserts that the '442 patent is a "blocking patent, which disincentivized others from developing the alleged invention" and "further limits" the asserted objective indicia. (D.I. 299 at 27-28).

182. The claims of the '442 patent are limited to the beta form of sucroferric oxyhydroxide, and thus the '442 patent would block entry in the marketplace with respect to only the beta form. (Tr. at 749:23-750:2, 634:11-14; JTX-3 at claim 1).

183. In contrast, the '251 patent includes other forms of the active ingredient, including alpha and gamma. (Tr. at 634:15-21; JTX-1 at claim 1 *et al*).

184. Teva offered no evidence that those in the industry were prevented from practicing the '251 patent due to the '442 patent.

5. Enablement of Claims 29 and 30

185. Claim 29 requires the "composition according to claim 1, wherein the iron oxyhydroxide is essentially non-bioabsorbable." (JTX-1 at 17:18-19).

186. The Court construed "essentially non-bioabsorbable" to mean "[u]pon oral administration, the iron oxyhydroxide is not absorbed by the human body in a clinically significant amount." (D.I. 114 at 5).

187. A clinician would understand that "clinically significant" means that "there is an effect of the drug . . . that changes the practice. And if there is iron absorption that it would change the way this drug is used and that's why the prescribing information is very important." (Tr. at 107:21-108:11).

188. Dr. Rastogi gave an example of an iron uptake amount that was "quite low and insignificant" – 0.04%. (Tr. at 103:17-104:2). He also gave an example of a drug with clinically significant iron release – "[i]f you're given a drug like Auryxia, you would expect the iron to be absorbed, not the iron levels to go down." (Tr. at 135:10-12).

189. A POSA would understand that clinical significance is determined by looking at the averages across the patient population, not any outcome for an individual patient. (Tr. at 134:1-136:3).

190. A POSA, following the disclosure in the '251 patent, could generate the claimed compositions that are essentially non-bioabsorbable without undue experimentation. The '251 patent provides numerous working examples of complete formulations, including chewable tablets with iron release rate as low as 0.2% (product 8g). (JTX-1 at 14:1-15:20). Dr. Chambliss explained that iron release rate and bioabsorbability go "hand in hand" such that if iron release is higher, the absorption is higher. (Tr. at 300:20-24). Thus, a POSA would understand that the tablets taught in the working examples of the '251 patent would be expected to be non-bioabsorbable. In addition, Example 2b is very similar to the formulation of Velphoro, a

formulation that has been shown to be essentially non-bioabsorbable. (JTX-1 at 12:39-60; PTX-322 at 10).

191. The '251 patent also provides guidance about manufacturing techniques that should be avoided in order to prevent the release of iron. (JTX-1 at 8:30-33, 10:5-9).

192. Claim 30 requires the "composition according to claim 1, having an iron release rate of below 2.5% w/w." (JTX-1 at 17:20-21).

193. The Court construed "iron release rate below 2.5%" to mean "[t]he iron release measured in water at a pH of 3 according w/w to European Pharmacopeia chapter 2.9.3 using standard dissolution equipment and parameters as described in the monograph, where iron content is analyzed by titration after 2 hours, wherein the quantity of iron dissolved after 2 hours is less than 2.5% w/w." (D.I. 114 at 7).

194. The '251 patent teaches that "[t]he inventive compositions have a low iron release rate of below 2.5% w/w, which is essential for phosphate adsorbers. In contrast thereto, compositions used for treating iron deficiency have a high iron release rate and thus are completely different form the inventive compositions." (JTX-1 at 3:6-11).

195. The patent also describes an example in which "Fe release was measured according to European Pharmacopeia chapter 2.9.3 using standard dissolution equipment and parameters as described in the monograph." (JTX-1 at 14:48-50). Six out of seven tablets tested had a release rate of less than 2.5%. (JTX-1 at 15:10-20).

196. The '251 patent contains explicit guidance about how to make the claimed pharmaceutical compositions, including information about the type and brand of starch that can be used to make chewable tablets that achieve the claimed iron release rate. (JTX-1 at 14:1-15:20). Specifically, Table 7 of the '251 patent identifies Lycatab® pregelatinized starch as being used in

chewable tablets with iron release rates below 2.5%. (JTX-1 at 14:10-23; *see also* Tr. at 381:11-16).

197. Accordingly, a POSA following the disclosure of the '251 patent would be able to readily produce compositions that satisfy claim 30.

II. LEGAL STANDARDS

A. Infringement

A patent is infringed when a person "without authority makes, uses, offers to sell, or sells any patented invention, within the United States . . . during the term of the patent." 35 U.S.C. § 271(a). Courts employ a two-step analysis in making an infringement determination. *See Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 976 (Fed. Cir. 1995). First, a court must construe the asserted claims. *See id.* Next, the trier of fact must compare the properly-construed claims to the accused infringing product. *See id.* Literal infringement occurs where "every limitation in a patent claim is found in an accused product, exactly." *Southwall Techs., Inc. v. Cardinal IG Co.*, 54 F.3d 1570, 1575 (Fed. Cir. 1995).

B. Validity

An issued patent is presumed to be valid. *See* 35 U.S.C. § 282. Therefore, to invalidate a patent, a party must carry its burden of proof by "clear and convincing evidence." *See Procter & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 993-94 (Fed. Cir. 2009). Clear and convincing evidence is evidence that "proves in the mind of the trier of fact an abiding conviction that the truth of [the] factual contentions [is] highly probable." *Intel Corp. v. ITC*, 946 F.2d 821, 830 (Fed. Cir. 1991) (internal quotation marks omitted; first modification in original). A defendant's burden to prove invalidity is "especially difficult when the prior art [on which it relies]

was before the PTO examiner during prosecution of the application." *Hewlett-Packard Co. v. Bausch & Lomb Inc.*, 909 F.2d 1464, 1467 (Fed. Cir. 1990).

1. Obviousness

A patent may not issue "if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains." 35 U.S.C. § 103(a). Obviousness is a question of law based on underlying factual findings concerning: (1) the scope and content of the prior art; (2) the differences between the claims and the prior art; (3) the level of ordinary skill in the art; and (4) objective considerations of nonobviousness. *See Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966). To prove that a patent is obvious, a party must demonstrate "that a skilled artisan would have had reason to combine the teaching of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success from doing so." *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1069 (Fed. Cir. 2012); *see also Amgen, Inc. v. F. Hoffman-La Roche Ltd.*, 580 F.3d 1340, 1362 (Fed. Cir. 2009) ("An obviousness determination requires that a skilled artisan would have perceived a reasonable expectation of success in making the invention in light of the prior art."). Although an analysis of any teaching, suggestion, or motivation to combine known elements is useful to an obviousness analysis, the overall obviousness inquiry must be expansive and flexible. *See KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 415, 419 (2007). The use of hindsight is not permitted when determining whether a claim would have been obvious to one having ordinary skill in the art. *See id.* at 421 (cautioning against "the distortion caused by hindsight bias" and obviousness "arguments reliant upon *ex post* reasoning"). To protect against the improper use of hindsight

when assessing obviousness, the Court is required to consider objective indicia of non-obviousness, such as commercial success, failure of others, unexpected results, and long-felt but unmet need. *See, e.g.*, *Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1358 (Fed. Cir. 2013).

2. Enablement

"The enablement requirement asks whether the specification teaches those in the art to make and use the invention without undue experimentation." *Enzo Life Scis., Inc. v. Roche Molecular Sys., Inc.*, 928 F.3d 1340, 1345 (Fed. Cir. 2019) (internal quotations omitted). "To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation." *MagSil Corp. v. Hitachi Glob. Storage Techs., Inc.*, 687 F.3d 1377, 1380 (Fed. Cir. 2012) (internal quotation marks omitted).

"Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). These factors may include: "(1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims." *Id.* Although "a specification need not disclose what is well known in the art," "[t]ossing out the mere germ of an idea does not constitute enabling disclosure." *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1366 (Fed. Cir. 1997). A patent "cannot simply rely on the knowledge of a person of ordinary skill to serve as a substitute for the missing information in the specification." *ALZA Corp. v. Andrx Pharm., LLC*, 603 F.3d 935, 941 (Fed. Cir. 2010).

III. DISCUSSION

A. Infringement

Vifor asserts that Teva's ANDA product infringes claims 29, 30, 33, and 56 of the '251 patent. As previously noted, the parties have stipulated to infringement of claims 33 and 56. (D.I. 277, Ex. 1 ¶¶ 23, 24, 25). Thus, the Court addresses only claims 29 and 30.

1. Claim 29

The only dispute about infringement of claim 29 is whether Teva's proposed ANDA product satisfies the limitation requiring "wherein the iron oxy-hydroxide is essentially non-bioabsorbable." (FF ¶ 48). The Court construed "essentially non-bioabsorbable" to mean "upon oral administration, the iron oxyhydroxide is not absorbed by the human body in a clinically significant amount." (FF ¶ 49).

Teva asserts that claim 29 requires *in vivo* testing to determine whether its product meets the disputed "essentially non-bioabsorbable" limitation and argues that bioequivalence alone is not sufficient. (*E.g.*, D.I. 309 at 1, 3-5). It is not, however, bioequivalence alone that is at issue. Teva has represented to the FDA that, upon oral administration, the iron oxyhydroxide formulated in its ANDA product is not absorbed in clinically significant amounts. For instance, the proposed label states that sucroferric oxyhydroxide in Teva's proposed ANDA product "is practically insoluble and therefore not absorbed and not metabolized." (FF ¶ 52). The proposed label also includes data from a clinical trial showing that iron uptake was "quite low and insignificant" when measured using radiolabeled sucroferric oxyhydroxide (the only iron source in the tested product). (FF ¶¶ 53-54).

Teva argues that these statements in the proposed label are not relevant because they were copied from the Velphoro package insert.[14] These arguments, however, ignore that Teva seeks approval to sell a product having these attributes, which is the relevant inquiry for infringement under 35 U.S.C. § 271(e). *See Sunovion Pharm., Inc. v. Teva Pharm. USA, Inc.,* 731 F.3d 1271, 1278 (Fed. Cir. 2013). Moreover, as Dr. Rastogi opined, the expectation that a generic drug behaves in the same manner as the branded drug is something that physicians rely upon when prescribing generic drugs. (FF ¶ 55). That is particularly apparent here, where if that expectation is not correct (*i.e.* if the ANDA product does ***not*** have same toxicity profile as Velphoro), patient safety may be jeopardized. (FF ¶ 56). Thus, it strains credulity for Teva to argue that it has sought FDA approval without knowing whether its proposed package insert accurately describes its ANDA product (and without knowing whether its ANDA product could prove toxic to patients).[15]

Moreover, Teva's proposed package insert is just one of the statements that Teva made to the FDA relating to the non-bioabsorbability of the iron oxyhydroxide as formulated in its ANDA product. Teva's pharmaceutical and product development reports state that the iron is "not available in soluble form to be absorbed in the [gastrointestinal tract]." (FF ¶¶ 58, 59). The same reports then describe dissolution tests comparing Teva's ANDA product to Velphoro. These tests showed that "[b]oth test and reference did not show release in most relevant fed state pH of GI tract" and that the results were consistent with other literature that "indicate negligible release of

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[14] Teva's expert, Dr. Fadem, would not confirm that the statements in Teva's package insert accurately describe Teva's ANDA product. (Tr. at 226:14-20).

[15] Teva's criticisms that Dr. Rastogi did not do *in vivo* testing are not well taken. It is wholly unclear that conducting human testing for purposes of patent infringement could pass ethical muster. (*See* Tr. at 114:4-20). Moreover, the Court agrees that it was fair for Dr. Rastogi to trust the integrity of Teva's submissions to the FDA – as Teva presumably expects the FDA and clinicians to do. (*Id.*).

iron in the [gastrointestinal tract] for absorption." (FF ¶ 58). These statements and the comparative study were not copied from Velphoro but appear to be Teva's own work. Indeed, Teva's corporate representatives confirmed the accuracy of these conclusions, and Dr. Fadem had no explanation for these representations Teva made to the FDA in any of these reports. (FF ¶¶ 60-61).

Although Teva attempts to shrug off the statements in its proposed package insert (and other development documents), the Federal Circuit has held that "[t]here is no basis to disregard the information contained on the package inserts, which are representations made to the FDA to establish that the proposed generics possess the same characteristics . . . present in [the] approved product[]." *Endo Pharm. Inc. v. Teva Pharm. USA, Inc.*, 731 Fed. App'x. 962, 974 (Fed. Cir. 2018). The fact that the relevant portions of Teva's package were copied from Velphoro does not change this analysis. In *Allergan, Inc. v. Watson Labs., Inc. – Florida*, 869 F. Supp. 2d 456, 513-14 (D. Del. 2012), the Court rejected an argument nearly identical to the one Teva presents. As here, the *Allergan* ANDA filers copied pharmacokinetic data from the reference listed drug's package insert. The *Allergan* ANDA filers argued that the Court should discount their package inserts and instead rely on a study performed by one of their experts. *Id.* at 512-13. The Court rejected this argument and found infringement based on the data from the reference listed drug that the generics copied in their package inserts. Similarly, here, holding Teva to the representations made in its package insert and pharmaceutical development documents is appropriate.

The evidence establishes that the iron oxyhydroxide as formulated in Teva's ANDA product is not absorbed in clinically significant amounts and thus Teva's ANDA product infringes claim 29.

2. Claim 30

The only dispute about infringement of claim 30 is whether Teva's proposed ANDA product satisfies "having an iron release rate of below 2.5% w/w." (FF ¶ 63). The Court construed this limitation to mean "the iron release measured in water at a pH of 3 according to European Pharmacopeia chapter 2.9.3 using standard dissolution equipment and parameters as described in the monograph, where iron content is analyzed by titration after 2 hours, wherein the quantity of iron dissolved after 2 hours is less than 2.5%." (FF ¶ 64).

At trial, one witness testified regarding infringement of claim 30 – Plaintiffs' expert, Dr. Myers, who tested six tablets in accordance with EP 2.9.3 using standard parameters and dissolution equipment (Apparatus II). (FF ¶ 66). When he measured the iron content at a pH of 3 after 2 hours by titration, the iron release rate was measured at a pH that ranged from 3.22 to 3.28 across the six tablets of Teva's ANDA product, with an average pH of 3.25. (FF ¶ 79). Dr. Myers's tests showed that the six tablets of Teva's ANDA product had an average iron release rate of 1.94% w/w, and ranged from 1.51 to 2.35% w/w. (*Id.*). Based on these test results, Dr. Myers concluded that Teva's ANDA product has "an iron release rate of below 2.5% w/w." (FF ¶¶ 79).

Teva contests Dr. Myers's results on two grounds: (1) that the final pH values that Dr. Myers observed after two hours, 3.22 to 3.29 with an average of 3.25, are not "pH 3" as required by the Court's construction and (2) that Dr. Myers never tested Teva's product at a starting pH of 3 because he adjusted the pH to 2.31 prior to adding the ANDA product tablets to the test medium. The Court addresses the arguments in turn.

a. Final pH values

Dr. Myers's tests of the ANDA product showed an average pH at the two hour time point of 3.25. (FF ¶ 79). Teva argues that this does not meet the "pH of 3" required by the Court's

construction because the Court's construction requires a pH of 3.0.[16] Federal Circuit case law, however, warns against interpreting "endpoints of the claimed range with greater precision than the claim language warrants." *U.S. Philips Corp. v. Iwasaki Elec. Co. Ltd*, 505 F.3d 1371, 1377 (Fed. Cir. 2007). In *U.S. Philips*, the Federal Circuit affirmed the district court's determination that the claim term "between 10^{-6} and 10^{-4} μmol/mm^3" means "between 1 x 10^{-6} and 1 x 10^{-4} μmol/mm^3" and rejected the accused infringer's construction of the term to mean "between 1.0 x 10^{-6} and 1.0 x 10^{-4} μmol/mm^3," noting that the specification did not intend for the quantities to be more precise. *U.S. Philips*, 505 F.3d at 1378.

That is the case here. Dr. Myers explained that a POSA reading the Court's construction and the '251 patent specification would understand that the target pH is specified to the whole number – "at a pH of 3" – not a number with additional significant figures such as "3.0." (FF ¶¶ 69, 70).[17] He explained that there is a scientific reason to specify a pH of "3" rather than 3.0, and that is because pH 3 simulates the fed state of the stomach,[18] which a POSA would know is almost never at a pH of exactly 3.0. (FF ¶ 70).

Moreover, Dr. Myers testified that, based on the level of precision specified in the Court's construction and the '251 patent specification, "at a pH of 3" comprises a pH range of between 2.5 to 3.4 using basic rounding. (FF ¶ 69). He noted that if greater precision were required, a POSA

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16 As Vifor points out, "attorney argument is not evidence and cannot rebut other admitted evidence." (D.I. 297 at 9 (citing *Elbit Sys. of Am., LLC v. Thales Visionix, Inc.*, 881 F.3d 1354, 1359 (Fed. Cir. 2018) and *Wasica Fin. GmbH v. Cont'l Auto. Sys., Inc.*, 853 F.3d 1272, 1284 (Fed. Cir. 2017))).

17 As noted above (n.7), Dr. Myers is a POSA and thus the Court recognizes his testimony as to his interpretation as relevant to a POSA.

18 The Court notes that this testimony is consistent with Teva documents, which refer to the fed state pH as the "most relevant" in connection with its testing of iron release. (*E.g.* DTX-172 at 22).

would expect to see additional significant figures explicitly stated – *i.e.*, "3.0," not "3." (FF ¶ 69). Dr. Myers's analysis regarding rounding is also consistent with Federal Circuit case law. In *San Huan New Materials High Tech, Inc. v. Int'l Trade Comm'n*, 161 F.3d 1347, 1361 (Fed. Cir. 1998), the asserted claim recited a range of 30% to 36% of chemical compound, TRE, and the accused product had up to 36.45% TRE. The Federal Circuit affirmed a finding of infringement, concluding that the number "36" was interpreted to encompass up the nearest whole number, *i.e.*, up to 36.5 rather than 36.0. *Id.* The Federal Circuit concluded that "[i]t was not shown to be error, legal or scientific, for the Commission to recognize these limits of accuracy, and to round the measured weight percentages to the nearest integer." *Id*.

Therefore, Dr. Myers's opinion that his observed pH range of 3.22 to 3.28 was "at a pH of 3" to the whole number is consistent with the Court's claim construction based on mathematical rounding principles, and it is supported by his unrebutted testimony regarding the purpose of the iron release test within the framework of the relevant art. Both the specification and the Court's construction are at the same level of precision and the Court has been given no reason to read a greater level of precision into either Judge Stark's construction or the description of the iron release testing in the specification. Had the patentee or the Court wanted to specify a pH of 3.0, it could have done so. It did not.

Teva's arguments citing two of Plaintiffs' confidential FDA submissions, PTX-323 and DTX-69, do not undermine Dr. Myers's opinions. These documents describe a particular iron release test protocol and require that the pH at two hours be "pH 3.0 ± 0.1," a more precise range than required by the '251 patent and the Court's construction. (FF ¶¶ 82-83). Moreover, the iron release test described in those documents is "not the same test method" as that described in the '251 patent. (FF ¶¶ 80-86). Because the iron release tests in the FDA submissions are not the

same as the iron release test described in the patent, neither of these documents informs a POSA how to perform the iron release test detailed in the '251 patent.

b. Initial pH Adjustment

Teva criticizes Dr. Myers for adjusting the pH of the media to 2.31 prior to adding the tablet samples. Dr. Myers explained, however, that EP 2.9.3 is a dissolution test but, before dissolution began, disintegration of the tablets occurred and that affected the pH of the media. (FF ¶ 72). To account for this, Dr. Myers adjusted the pH prior to the addition of tablets so that the pH with tablets would be 3 during dissolution and when iron release was measured as required. (FF ¶¶ 73-74). Neither the specification nor the Court's construction requires the pH of the media to be any specific value prior to tablets being placed in the media and iron release measurement. (FF ¶ 75). Thus, Dr. Myers's adjustment of the pH of the media prior to tablet disintegration complied with the Court's claim construction and, in fact, ensured that the dissolution test would be conducted "at a pH of 3."

Dr. Myers's testing established that Teva's ANDA Product has an iron release rate below 2.5%, which is in accordance with the Court's claim construction order and the '251 patent specification. Therefore, Teva's ANDA Product infringes claim 30.

B. Validity

1. Obviousness

a. The '442 Patent Does Not Render The Asserted Claims Obvious

Each of the asserted claims requires a "pharmaceutical composition" with "at least 500 mg" of iron oxy-hydroxide "per dosage form." (FF ¶ 127). Defendant failed to prove by clear and convincing evidence that the claimed "dosage form" of "at least 500 mg" would have been obvious to a POSA at the time of the invention in view of the '442 patent.

The '442 patent generally teaches that a "daily dose of the absorbents according to the invention is, for example, 1 to 3 g, preferably about 1.5 g of iron." (JTX-3 at 3:19-21; FF ¶¶ 132-133). The '442 patent does not teach how the daily dose would be administered (*i.e.*, as a single dosage form or across multiple dosage forms) or whether the daily dose would be different for the phosphate binders provided in the examples of the '442 patent. (FF ¶¶ 93-105, 137-140). Even so, Defendant argues that a POSA would have understood that the 1.5 g daily dose of iron would be administered as three individual doses comprising 500 mg of iron because this is "clearly established" by the teachings of the '442 patent and the POSA's "general knowledge" regarding the administration of phosphate binders. (D.I. 299 at 3-4, 4 (citing product labels of different phosphate binders that are administered three times per day)). The Court disagrees. A POSA would not have understood that the '442 patent's teachings of a "daily dose of . . . 1.5 g of iron" would be split into three 500 mg doses because the '442 patent provides no teaching about the number of administrations per day for the daily dose. (FF ¶¶ 129-140). Further, Defendant's evidence of a POSA's "general knowledge" regarding the administration of phosphate binders is neither clear nor convincing and is outweighed by Plaintiff's competing evidence that not all phosphate binders are administered three times per day. (FF ¶¶ 141-142); *see also Arendi S.A.R.L. v. Apple Inc.*, 832 F.3d 1355, 1362 (Fed. Cir. 2016) ("[O]ur cases repeatedly warn that references to 'common sense' – whether to supply a motivation to combine or a missing limitation – cannot be used as a wholesale substitute for reasoned analysis and evidentiary support, especially when dealing with a limitation missing from the prior art references specified.").

Even if the Court were convinced that a POSA would have understood that the '442 patent's "daily dose of . . . 1.5 g of iron" would be administered as three 500 mg doses, Defendant still must show by clear and convincing evidence that each 500 mg dose would be

packaged in a single "dosage form." Defendant argues that packaging each 500 mg dose in a single dosage form would have been obvious to a POSA based on the '442 patent's general teaching that dosages "can" be formulated for oral application as "tablets . . . or contained in sachets, for example" and the POSA's motivation, consistent with their "general knowledge," to "reduce patients' pill burden[.]" (D.I. 299 at 4-5). The Court is not persuaded. Contrary to Defendant's assertion, a POSA would not have understood the '442 patent to teach that 500 mg of iron would be packaged in a single dosage form. (FF ¶¶ 137, 143). Instead, the '442 patent provides no information regarding how much iron can be loaded in each dosage form. (*Id.*). And Defendant's reliance on a POSA's "general knowledge" to "reduce pill burden" is unconvincing and undermined by Plaintiff's evidence that other phosphate binders were administered across multiple dosage forms. (FF ¶ 142; *see also* FF ¶¶ 145-147); *see also Cardiac Pacemakers, Inc. v. St. Jude. Med., Inc.*, 381 F.3d 1371, 1377 (Fed. Cir. 2004) ("Recognition of a need does not render obvious the achievement that meets that need.").

As is often the case, this obviousness issue comes down to weighing competing facts – particularly competing expert testimony – regarding what a POSA would have found obvious at the time of the invention. Here, in considering and weighing the evidence presented at trial, the Court generally found Plaintiff's experts to be more credible. Moreover, Defendant's obviousness arguments rely on taking broad teachings from the '442 patent, then extrapolating onto them additional limitations based on what a POSA allegedly would have known or done. As such, Defendant's arguments suffer from significant and improper hindsight bias. *See Ortho-McNeil Pharm., Inc. v. Mylan Lab'y, Inc.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008) ("Mylan's expert, . . . simply retraced the path of the inventor with hindsight, discounted the number and complexity of the alternatives, and concluded that the invention of topiramate was obvious. Of course, this

reasoning is always inappropriate for an obviousness test based on the language of Title 35 that requires the analysis to examine 'the subject matter as a whole' to ascertain if it '***would have been obvious at the time the invention was made.***'" (emphasis in original) (citation omitted)). Thus, the Court finds that Defendant has not shown by clear and convincing evidence that the claimed compositions "wherein the amount of iron oxy-hydroxide per dosage form is at least 500 mg" were obvious based on the '442 patent alone. (FF ¶¶ 144-145). Because the "wherein the amount of iron oxy-hydroxide per dosage form is at least 500 mg" limitation is present in each of the asserted claims, the Court need not consider Defendant's other arguments regarding the obviousness of the asserted claims in view of the '442 patent alone.

b. The Asserted Claims are Not Obvious in View of the '442 Patent in Combination with Hergesell and the Other Prior Art Asserted.

Defendant also argues that the '442 patent in combination with Hergesell and other prior art render the asserted claims obvious. (D.I. 299 at 12-19).

First, in addition to referring to the teachings of the '442 patent discussed above, Defendant argues that Hergesell "confirmed the general practice of administering phosphate binder 3 times per day 'with meals[.]'" (D.I. 299 at 13; JTX-7 at 2 ("[P]atients were subsequently given a constant dose of 3 x 2.5 g stabilized polynuclear iron hydroxide . . . provided as a powder in preweighed sachets. The material was suspended in water and ingested together with meals.")). The Court is not convinced by Defendant's argument. Foremost, Hergesell does not refer to iron oxy-hydroxide formulations comprising saccharose. (FF ¶¶ 108-116, 154-156). This is important because iron oxy-hydroxide formulations comprising saccharose are required by the asserted claims and are what is taught by the '442 patent in Example 1, which Defendant relies on. (FF ¶¶ 150-157). Thus, because Hergesell's formulations are different than the formulation described in Example 1 of the

'442 patent, a POSA would not look to the teachings of Hergesell regarding dosages in their obviousness analysis of Example 1 of the '442 patent. (FF ¶¶ 150-158).

Even if the Court were convinced that, based on the teachings of the '442 patent and Hergesell, a POSA would have understood that the '442 patent's "daily dose of . . . 1.5 g of iron" should be split into three 500 mg doses, Defendant still must prove that each 500 mg dose would be packaged as a single "dosage form." In this regard, Defendant argues, in addition to the teachings of the '442 patent alone discussed above, that the '442 patent in combination with teachings of the '079 patent or Hergesell teach a single 500 mg dosage form. (D.I. 299 at 12-13).

Regarding the '079 patent, Defendant argues that the "[t]he backdrop of those teachings of the '442 Patent was the earlier [U.S. Patent No. 4,970,079 patent ("the '079 Patent")], which [a POSA would have understood to have] already disclosed and suggested a 'unitary solid dosage form such as a compressed tablet' containing '500 mg or more' of iron oxy-hydroxide in 'each oral dose.'" (D.I. 299 at 12-13 (citing '079 Patent at 3:36-55 ("[T]he oxy-iron compound can be formulated as a liquid or gel suspension, or in a unitary solid dosage form such as a compressed tablet or capsule. . . . Thus, each oral dose of the therapeutic oxy-iron containing composition in accordance with this invention can contain from about 50 mg to about 500 mg or more of oxy-iron compound.")). Again, however, the Court is not convinced in this regard. The '079 patent broadly describes "oxy-iron compounds," including at least iron oxides, iron hydroxide and iron oxyhydroxides. (FF ¶¶ 119-126; 160; '079 Patent at 3:12-63). The '079 patent then teaches a dosage of an oxy-iron "composition in accordance with this invention can contain from about 50 mg to about 500 mg or more of oxy-iron compound," where this teaching is not specific to which of the species of oxy-iron compounds may fall into different portions of that range. ('079 Patent at 3:52-55). Additionally, when considering the '079 patent's teachings, a POSA would

recognize that the '079 Patent does not describe any finished dosage formulations or how to formulate the disclosed oxy iron compounds. (FF ¶ 171). Moreover, the '079 patent teaches that a relatively smaller 174 mg dosage of one iron oxide compounds (ferrihydrite) was effective. (FF ¶¶ 123-125, 161-162). Thus, the Court finds that Defendant has not shown by clear and convincing evidence that a POSA would combine the teachings of the '442 patent and '079 patent to formulate a 500 mg, single dosage form. Indeed, the '079 patent's broad teaching directed to the genus of oxy-iron compounds cannot be assumed to apply to all species for this obviousness analysis. *See In re Baird*, 16 F.3d 380, 382 (Fed. Cir. 1994) ("The fact that a claimed compound may be encompassed by a disclosed generic formula does not by itself render that compound obvious."); *In re Jones*, 958 F.2d 347 (Fed. Cir. 1992) ("declin[ing] to extract from [the case law] the rule that . . . regardless of how broad, a disclosure of a chemical genus renders obvious any species that happens to fall within it.").

Regarding Hergesell, Defendant argues that "Hergesell confirmed [providing the phosphate binder] with a high load of iron oxy-hydroxide in a ***single*** dosage form (i.e., a sachet powder packet) containing approximately 800 mg of iron oxy-hydroxide." (D.I. 299 at 13). The Court disagrees. First, as explained above, Hergesell's teachings regarding the dosages are not applicable to Example 1 of the '442 patent. (*See* FF ¶¶ 108-116, 150-158). Even so, Hergesell only teaches "a constant dose of 3 x 2.5 g stabilized polynuclear iron hydroxide . . . provided as a powder in preweighed sachets." (Hergesell at 2; FF ¶ 163). From this, a POSA would not understand how much powder is contained in each sachet (*i.e.*, 10 sachets including 250 mg with each 2.5 g dose, or one sachet containing 2.5 g) or how much iron oxyhydroxide would be included per 2.5 g. (FF ¶ 163). Because of this, the Court finds that Defendant has not shown by clear and

convincing evidence that a POSA would combine the teachings of the '442 patent and Hergesell to formulate a 500 mg, single dosage form.

Thus, having considered and rejected each of Defendant's arguments that the "dosage form" of "at least 500 mg" limitation is obvious (the '442 patent alone and the '442 patent in addition to other prior art), the Court finds that the Defendant has not shown by clear and convincing evidence that the claimed compositions "wherein the amount of iron oxy-hydroxide per dosage form is at least 500 mg" were obvious. Because the "wherein the amount of iron oxy-hydroxide per dosage form is at least 500 mg" limitation is present in each of the asserted claims, the Court need not consider the Defendant's other arguments regarding the obviousness of the asserted claims.

c. Objective Indicia

Plaintiff has asserted that several objective indicia of non-obviousness, long-felt but unmet need, unexpected results, and commercial success further support that the asserted claims are not obvious. As discussed above (FF ¶¶ 164-184), the Court has found that Velphoro satisfied a long-felt but unmet need and has enjoyed some measure of commercial success, both of which provide further support the finding of non-obviousness. Having found that Defendant failed to establish a *prima facie* case of obviousness for the asserted claims, however, the Court, does not address that evidence again in detail here.

2. Enablement

As a preliminary matter, Defendant argues that claims 29 and 30 "broadly claim functional properties without any formulation-limiting details" and, according to the Federal Circuit's ruling in *Amgen*, this "weighs heavily against enablement." (D.I. 299 at 28-29 (*citing Amgen Inc. v. Sanofi*, 987 F.3d 1080 (Fed. Cir. 2021))). The Court, however, disagrees that claims 29 and 30

lack "any formulation-limiting details." Instead, claims 29 and 30, which depend on claim 1, set forth a specific "pharmaceutical composition comprising . . . iron oxy-hydroxide in high loading . . . and . . . carbohydrates comprising saccharose and starch . . . wherein the amount of iron oxy-hydroxide per dosage form is at least 500 mg." (JTX-1 at 15:23-31). These formulation-limiting details must be considered in an enablement analysis.

a. Claim 29

Regarding claim 29, Defendant argues that a POSA would not be able to determine what level of iron absorption is "clinically significant." (D.I. 299 at 29-30). In construing the claims, however, Judge Stark concluded that "[b]ased on the description in the specification, a POSA would know the bounds of the claim term with reasonable certainty" because even though "the claim does not set forth a specific amount of iron oxy-hydroxide that may be absorbed, a POSA would know that any absorption would be minimal and unintentional compared to the absorption of iron deficiency treatments." (D.I. 114 at 6). Consistent with this, Dr. Rastogi explained that clinical significance would be readily understood by a healthcare provider, and he gave several examples of drugs that both do and do not release clinically significant amounts of iron. (FF ¶¶ 186-187). Here, to make and use the claimed invention, a POSA could follow the working examples, which the '251 patent states are "essentially non-bioabsorbable." (FF ¶¶ 190-191).

Teva also argues that claim 29 requires undue experimentation because a POSA would have to test "each and every individual patient" to "determine whether a particular product, when administered to a particular patient, would satisfy the claimed function." (D.I. 299 at 29-30). The Court, however, credits Dr. Rastogi's testimony that this is not how a POSA would understand "clinical significance," which is determined by looking at patient population averages, not any individual outcomes. (FF ¶ 189).

For these reasons, the Court finds that Defendant failed to prove by clear and convincing evidence that claim 29 is invalid for lack of enablement.

b. Claim 30

With respect to claim 30, Defendant argues that undue experimentation is required to achieve the claimed release rate based on "Plaintiffs' argument that the brand of starch may impact the release rate." (D.I. 299 at 30). In making this argument, however, Defendant ignores that the '251 patent identifies a specific brand of starch that can be used to make formulations with an iron release rate below 2.5%. (FF ¶ 196). Moreover, Teva misconstrues the law of enablement. Under Teva's logic, Plaintiffs need to enable every potential combination and brand of starch. But enablement requires only a sufficient disclosure that would allow a POSA to practice the claim invention. *See Invitrogen Corp. v. Clontech Labs., Inc.*, 429 F.3d 1052, 1071 (Fed. Cir. 2005) ("The enablement requirement is met if the description enables any mode of making and using the invention." (citation omitted)). Here, the '251 patent gives explicit guidance how to make the claimed pharmaceutical composition, including information about the type and brand of starch that can be used to achieve the claimed iron release rate. (FF ¶¶ 194-196). Nothing more is necessary.

For these reasons, the Court finds that Defendant failed to prove by clear and convincing evidence that Claim 30 is invalid for lack of enablement.

IV. CONCLUSION

As discussed herein, after considering the entire record and the applicable law, the Court concludes that (1) Teva's ANDA product infringes claims 33 and 56 of the '251 patent; (2) Vifor has proved that Teva's ANDA product infringes claims 29 and 30 of the '251 patent; (3) Teva has failed to prove that any of claims 29, 30, 33, and 56 of the '251 patent are invalid for obviousness

and; (4) Teva has failed to prove that either of claims 29 and 30 is invalid for lack of enablement.

An appropriate order will be entered.