UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

HELSINN HEALTHCARE S.A.,	:	CIVIL ACTION NO. 12-2867 (MLC) (DEA)
Plaintiff,	:	
v.	:	**MEMORANDUM OPINION**
DR. REDDY'S LABORATORIES, LTD., *et al.*,	:	
Defendants.	:	

COOPER, District Judge

I. Background

This is a patent dispute between Plaintiff Helsinn Healthcare S.A. ("Helsinn") and Defendants Dr. Reddy's Laboratories, Ltd. and Dr. Reddy's Laboratories, Inc. (together, "DRL"). Helsinn holds New Drug Application ("NDA") No. 21-372 for Aloxi®, a branded drug product used to treat chemotherapy-induced nausea and vomiting whose active pharmaceutical ingredient is palonosetron. (Pretrial Order, dkt. 168 at 9.)[1] DRL submitted NDA No. 203050 to the FDA pursuant to the Hatch-Waxman Act, 21 U.S.C. § 505(b)(2), seeking approval to market its own palonosetron product (the "Accused Product").[2] (Id. at 11.) DRL's NDA included so-called "Paragraph IV" certifications that its product would not infringe Helsinn's patents and/or that those patents are invalid or unenforceable. (Id.) The patents covered by DRL's Paragraph IV certifications include U.S. Patent Nos. 7,947,724 ("the '724 patent"); 8,729,094 ("the '094 patent"); and 9,066,980 ("the '980 patent") (collectively, the "Asserted Patents").[3] In light of DRL's Paragraph IV certifications, Helsinn brought this case asserting infringement of the '724 patent. Helsinn also brought Civil Case No. 14-4274 in this court asserting infringement of the '094 and '980 patents, which the

[1] The Court will cite to documents filed on the Electronic Case Filing System ("ECF") by referring to the docket entry numbers as "dkt." Pincites reference ECF pagination. Unless otherwise noted, all ECF references refer to the docket in Case No. 12-2867.

[2] This case arises from DRL's submission of a so-called "Paper NDA" under § 505(b)(2). There is separate and ongoing litigation regarding various Abbreviated New Drug Applications filed under 21 U.S.C. § 505(j) to manufacture generic versions of Helsinn's branded palonosetron product.

[3] The '724 patent issued on May 24, 2011 from U.S. Patent Application No. 11/186,311. The '094 patent issued on May 20, 2014, from U.S. Patent Application No. 13/902,132. The '980 patent issued on June 20, 2015, from U.S. Patent Application No. 13/902,299. Each application claimed priority from U.S. Provisional Patent Application No. 60/444,351 ("the '351 application"). (Dkt. 168 at 8.) Helsinn is the assignee of each of the Asserted Patents. (Id.)

parties agreed to consolidate with this case to determine certain questions of infringement and validity. (Dkt. 108.)

Helsinn contends that DRL's Accused Product infringes thirteen claims in the Asserted Patents. (Dkt. 168 at 9.) DRL has raised the defense of non-infringement for three of those claims and argues that the other ten are invalid. DRL does not challenge the validity of the three claims for which it argues non-infringement, and has stipulated that its Accused Product would infringe the other ten claims if they are found valid and enforceable. (Dkt. 63; dkt. 116.) Accordingly, the claims and defenses in this case are as follows:

Patent	Asserted Claim	Defense Raised
'724	9	Non-Infringement
'094	22	Invalidity
'094	23	Invalidity
'094	24	Invalidity
'094	25	Invalidity
'094	27	Non-Infringement
'980	1	Invalidity
'980	2	Invalidity
'980	3	Invalidity
'980	4	Invalidity
'980	5	Invalidity
'980	6	Non-Infringement
'980	16	Invalidity

Prior to trial, we held a Markman claim construction proceeding. That proceeding resulted in our April 2015 opinion on claim construction (dkt. 92), described in more detail in Section II.B, infra. We also considered and denied a motion for partial summary judgment by Helsinn. (Dkt. 141.) We held a six-day trial from June 20–28, 2016 to determine whether the Asserted Patents would be infringed by DRL's proposed product and whether certain claims of the Asserted Patents are invalid. During the first portion of the trial, we considered DRL's

non-infringement defenses. On the question of infringement, we heard testimony from Helsinn's experts Dr. Christian Schöneich and Dr. John Gladysz, as well as DRL's experts Dr. Arthur Kibbe, Dr. Harry Brittain, and Dr. Robert Hancock. During the second portion of the trial, we considered DRL's invalidity defenses.[4] On that issue, we heard testimony from Helsinn's expert Dr. Schöneich and DRL's expert Dr. Joanne Broadhead. After the trial, the

[4] In assessing DRL's validity challenges, we have applied the definition of the Person of Ordinary Skill in the Art ("POSA") adopted during the claim construction process:

> [A POSA] . . . would have formal education or training in pharmaceutical science or a related area and experience in pharmaceutical formulation development, including experience in intravenous solution formulation development.
>
> Specifically, the POSA would have had a general understanding and knowledge of basic principles of formulation development. The POSA would have been familiar with the general strategies, procedures and tools of pharmaceutical formulation development, including preformulation studies, formulation screening and optimization, and experimental design. The POSA would have also been generally familiar with the commonly used textbooks in the field of formulation development, and would have general knowledge of the relevant references and/or printed publications in the field of pharmaceutical formulation.
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> The POSA would have also been familiar with the typical components of an intravenous solution, including the active ingredient, solvent or carrier, pH buffering agent, pH adjusting agent, tonicifying agent, stabilizing agent (e.g., "chelating agent," antioxidant, preservative), solubilizing agent and dispersing agent. Moreover, the POSA would have been familiar with the commonly used pH buffers (e.g., citrate), tonicifying agents (e.g., sodium chloride, dextrose and mannitol) and "chelating agents" (e.g., "EDTA"). The POSA would have also had a general understanding of the structure based reactivity of drug molecules and would have been familiar with the major degradation pathways for drug molecules, including oxidation and hydrolysis. The POSA would have also been aware of the typical approaches to prevent or control the common degradation pathways for drug molecules.
>
> The POSA would have also collaborated with persons from other relevant disciplines, such as medicinal chemists, pharmacologists, pharmacokineticists, clinicians and statisticians, to discuss issues regarding safety and efficacy requirements.

(Dkt. 92 at 21–23.)

parties submitted proposed findings of fact and conclusions of law (dkts. 199, 200, and 200-1) and filed responsive trial briefs (dkts. 216 and 217).

For the reasons discussed in Section II, infra, we find that the asserted claims in the '724, '094, and '980 patents are infringed. For the reasons discussed in Section III, infra, we also find that the asserted claims are not invalid for lack of written description or lack of enablement.

II. Infringement

Helsinn asserts that DRL's accused palonosetron product infringes thirteen patent claims across the '724, '094, and '980 patents. The parties have stipulated to infringement for ten of those thirteen claims.[5] DRL has raised non-infringement defenses for the other three

[5] Specifically, the parties have stipulated infringement for claims 22–25 of the '094 patent and claims 1–5 and 16 of the '980 patent. (Dkt. 63; dkt. 116.)

claims: claim 9 of the '724 patent,[6] claim 27 of the '094 patent,[7] and claim 6 of the '980 patent.[8] For each of the three claims, Helsinn and DRL have stipulated that infringement will be determined based on the "chelating agent" limitation in the claims. (Dkt. 63; dkt. 116.)

Accordingly, our infringement analysis centers on a single overarching question: whether the sodium acetate trihydrate in DRL's Accused Product is a "chelating agent." As discussed below, the meaning of the term "chelating agent" was debated extensively during the Markman claim construction process. Even after our claim construction opinion (dkt. 92), the parties continued to debate at trial what Helsinn needed to prove to meet its infringement

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[6] Claim 9 of the '724 patent depends from claim 8, which is included here for context:

> 8. A pharmaceutically stable isotonic intravenous solution for reducing emesis or reducing the likelihood of emesis comprising: (a) from 0.01 mg/ml to 5 mg/ml palonosetron or a pharmaceutically acceptable salt thereof, at a pH of from 4.0 to 6.0; and (b) an aqueous pharmaceutically acceptable carrier ***including a chelating agent***.
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> 9. The solution of claim 8 wherein the palonosetron or pharmaceutically acceptable salt thereof is in concentration of about 0.05 mg/ml.

('724 patent at col. 10, lines 14–24) (emphasis added).

[7] Claim 27 of the '094 patent depends from claim 22, which is included here for context:

> 22. A method for reducing the likelihood of cancer chemotherapy-induced nausea and vomiting, comprising intravenously administering to a human in need thereof a pharmaceutical single-use, unit-dose formulation comprising a 5 mL sterile aqueous isotonic solution buffered at a pH of about 5.0±0.5, said solution comprising: about 0.05 mg/mL palonosetron hydrochloride based on the weight of its free base; and a tonicifying effective amount of mannitol; wherein said solution optionally comprises one or a combination of a citrate buffer and a chelating agent, wherein said formulation is stable at 24 months when stored at room temperature, and wherein said intravenous administration to said human occurs before the start of the cancer chemotherapy.
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> […]
>
> 27. The method of claim 22, wherein said solution ***comprises a chelating agent***.

('094 patent at col. 11, line 18 to col. 12, line 6; id. at col. 12, lines 18–19) (emphasis added).

burden. Against the backdrop of that underlying legal dispute, and at times arguing their positions in the alternative, the parties presented voluminous evidence at trial.

We conclude that Helsinn has satisfied its evidentiary burden and find that DRL's Accused Product infringes the asserted '724, '094, and '980 patent claims. Our analysis proceeds in four parts. First, we briefly review in Section II.A the relevant legal standards for infringement. Second, we revisit in Section II.B our Markman ruling and resolve the parties' dispute over what Helsinn must prove to satisfy the "chelating agent" claim term limitation. Third, we discuss in Section II.C the array of scientific and expert evidence presented by both parties at trial. Finally, in Section II.D we provide factual findings and conclusions of law.

A. Legal Standard for Infringement

Determining whether an accused product infringes a particular patent requires a two-step analysis. First, the court must determine the scope and meaning of the patent claims, including if necessary through the claim construction process. See Int'l Rectifier Corp. v. IXYS Corp., 361 F.3d 1363, 1369 (Fed. Cir. 2004). Second, the court must determine how the properly construed claims compare to the allegedly infringing product. Id. Under the

[8] Claim 6 of the '980 patent depends from claim 1, which is included here for context:

> 1. A pharmaceutical single-use, unit-dose formulation for intravenous administration to a human to reduce the likelihood of cancer chemotherapy-induced nausea and vomiting, comprising a 5 mL sterile aqueous solution, said solution comprising: (a) palonosetron hydrochloride in an amount of 0.25 mg based on the weight of its free base, (b) optionally a chelating agent, and (c) a tonicifying agent in an amount sufficient to make said solution isotonic, wherein said formulation is stable at 24 months when stored at room temperature.
>
> […]
>
> 6. The pharmaceutical formulation of claim 1, wherein said formulation ***comprises a chelating agent***.

('980 patent at col. 9, line 47 to col. 10, line 4; col. 10, lines 14–15) (emphasis added).

second step, the comparison of the claims to the accused product requires a factual determination that every claim limitation (or its equivalent) is found in the accused product. See Warner-Jenkinson Co. v. Hilton Davis Chem. Co., 520 U.S. 17, 29 (1997). In the Hatch-Waxman context, the relevant comparison is between the asserted patent and the product that will be sold following ANDA approval. See Alcon Research Ltd. v. Barr Labs., Inc., 745 F.3d 1180, 1186 (Fed. Cir. 2014). The patent holder generally bears the burden of proving infringement by a preponderance of the evidence. See Medtronic, Inc. v. Mirowski Family Ventures, LLC, 134 S. Ct. 843, 849 (2014); Egyptian Goddess, Inc. v. Swisa, Inc., 543 F.3d 665, 679 (Fed. Cir. 2008).

B. Framework for Assessing Infringement

1. Our Claim Construction of "Chelating Agent"

We construed the term "chelating agent" following extensive briefing from the parties and an evidentiary hearing that included expert testimony. (Dkt. 92.) As discussed in Section II.B.2, infra, the parties disagree on the meaning of certain aspects of our Markman opinion and its relationship to what Helsinn needed to prove at trial. We summarize here the key points of our Markman ruling to provide context for that dispute.

For our purposes, the scientific terminology can be summarized as follows. A "multidentate ligand" is an ion or molecule that is capable of bonding with a metal ion through two or more bonding sites. (Dkt. 92 at 11.) When a multidentate ligand bonds with a metal ion, it may form a ring structure called a "chelated complex," or simply a "chelate." (Id. at 12.) The process of forming the ring structure is called "chelation." (Id.) All parties agree that certain compounds (such as ethylenediaminetetraacetic acid, or "EDTA") are

"chelating agents," at least in part because they are multidentate ligands that can form chelate ring structures after bonding with metal ions.

The claim construction process sought clarification on the meaning of the term "chelating agent" in the asserted patents, setting the stage for the question before us now: whether a particular molecule included in the Accused Product should be considered a "chelating agent."

During the claim construction process, DRL sought a narrower construction of "chelating agent," arguing that any excipient alleged to satisfy that claim term limitation needed to ***actually*** form ***stable*** chelated complexes by reacting with metals ***in an aqueous pharmaceutical solution***. (Dkt. 92 at 15.) Helsinn sought a broader construction, contending that an excipient "structurally capable" of forming chelate ring structures should be considered a chelating agent. (Id. at 15–16.)[9] Accordingly, our Markman ruling focused on three questions raised by the parties' proposed constructions: (1) Does the term "chelating agent" mean that an excipient ***actually*** forms a chelated complex? (Or, alternatively, is it merely ***capable*** of forming a chelated complex?); (2) Does the term "chelating agent" mean that the excipient actually forms (or is capable of forming) a chelated complex ***in an aqueous pharmaceutical preparation***?; and (3) Does the term "chelating agent" mean that the excipient forms a ***stable*** chelated complex? We summarize our Markman findings on each of those questions below.

[9] We approached claim construction, as we must, from the perspective of a person of ordinary skill in the art ("POSA") on January 30, 2003, the effective filing date of the relevant patent application. (Dkt. 92 at 21–23.)

(i) Scope Limitation: Actually Chelating vs. Capable of Chelating

With regard to the first question—whether a chelating agent must ***actually*** form a chelated complex—we concluded that the intrinsic and extrinsic evidence presented did not support such a limitation. Much of our analysis focused on whether the claim language, specification, and prosecution history of the '724 patent provided a basis to limit the term "chelating agent" to compounds that can be empirically proven to form chelate ring structures. (Dkt. 92 at 24–43.) We found that the intrinsic record did not support such a limitation nor did it provide any basis to confine the term "chelating agent" to commonly used chelating agents like EDTA or citric acid. (Id. at 44.)

We also extensively considered extrinsic evidence on the question. DRL's expert Dr. Kibbe argued that a pharmaceutical formulator looking for an excipient with a particular function (e.g., to act as a chelating agent) would select one that was understood to actually perform that function in the pharmaceutical context. (Id. at 56–58.) According to him, a POSA[10] would understand "chelating agent" to mean something that has been "documented as effective in chelating heavy metals in pharmaceutical systems." (Id. at 59.) Conversely, a POSA would not select a chelating agent on the "mere[] hope" that it "had the structural capability to chelate." (Id. at 58.) DRL's expert Dr. Hancock likewise focused on the idea of the molecule acting as an "agent"—that is, performing a particular function. (Id. at 74.) As he explained, a claim construction that focused on the "structural capability" to chelate would sweep in hundreds of molecules that would realistically never be used as chelating agents because the resultant bonds would be too weak to serve any useful purpose. (Id. at 74.)

[10] We adopted the POSA description of DRL's expert, Dr. Kibbe. (Dkt. 92 at 21–23; supra note 4.)

Helsinn's expert Dr. Schöneich argued against DRL's proposed construction, contending that the "ordinary meaning" of a chelating agent was simply a multidentate ligand structurally capable of being involved in chelation. (Id. at 47–48.) He pointed persuasively to scholarly evidence that a compound need not always ***actually*** chelate to be considered a chelating agent. (Id. at 49–50.) His testimony was also consistent with the '724 patent itself, which did not discuss whether any included chelating agent was actually chelating.

After reviewing the evidence and testimony, we concluded that neither the intrinsic nor extrinsic evidence supported a claim construction that made quantitative demands of the chelating agent in terms of whether and how much actual chelating it can do in the patented formulation. (Id. at 86.) In short, we did not limit the scope of "chelating agent" to molecules that can be shown to ***actually*** form chelate rings in a particular environment.

(ii) Scope Limitation: Chelating in Liquid Pharmaceutical Formulation

DRL also sought to limit the scope of chelating agents to molecules that would chelate "in an aqueous liquid pharmaceutical preparation." (Dkt. 92 at 8.)

There is no serious dispute that "chelating agents" are used in both the pharmaceutical context and in other contexts, such as in cosmetics and food. (Id. at 78–80.) DRL's experts conceded that the "functional definition" of a chelating agent was not limited to pharmaceutical preparations, and DRL offered no standard chemical texts that limited the term that way. (Id. at 78.) Instead, DRL's primary Markman argument was that the context of the '724 patent (i.e., the fact that it disclosed a pharmaceutical preparation) limited the scope of the term "chelating agent" beyond its ordinary meaning to something that could or would chelate in a pharmaceutical preparation. (Id. at 60, 71–72.)

Helsinn argued—and we ultimately agreed—that neither the intrinsic nor extrinsic evidence presented justified narrowing the ordinary meaning of "chelating agent" which can describe compounds both in and outside of the pharmaceutical context. (Id. at 52.) We also noted DRL's troubling inconsistency on the contours of this proposed limitation. The expert declarations of Dr. Hancock and Dr. Kibbe, for example, argued that a chelating agent must chelate specifically in a palonosetron formulation. (Id. at 72.) At the Markman hearing, however, Dr. Hancock admitted that the construction "doesn't require palonosetron to be read into it." (Id. at 72–73.) Similarly, DRL's proposed construction in the Joint Claim Construction Chart referenced an "aqueous liquid pharmaceutical formulation" (id. at 8), but when pressed at the Markman hearing, Dr. Hancock conceded that the patent specification was not confined to "aqueous" pharmaceutical preparations. (Id.) We also noted that Dr. Hancock in another case testified about "chelating agents" and did not limit his explanation to pharmaceutical preparations. (Id. at 75–76.)

Regardless of the precise nature of DRL's proposed limitation—e.g., whether chelation must occur in a palonosetron composition or any pharmaceutical preparation, or whether the pharmaceutical preparation must be in an aqueous solution—we rejected DRL's efforts to narrow the scope of the term "chelating agent" beyond its ordinary meaning based on the intrinsic and extrinsic evidence presented. Accordingly, we concluded that the term "chelating agent" did not require evidence of chelation specifically in the context of a pharmaceutical product.

(iii) Scope Limitation: Necessity of Stability in Chelate Complexes

We also concluded that the evidence presented did not support limiting the scope of the term "chelating agent" to multidentate ligands capable of forming ***stable*** chelated complexes. We observed that the intrinsic record is silent as to the stability of any chelated complex formed as a result of the addition of a chelating agent. (Dkt. 92 at 85.) Thus, much of the dispute focused on the parties' extrinsic evidence.

DRL's Markman experts, Dr. Kibbe and Dr. Hancock, argued that a chelating agent must form stable chelate ring structures because otherwise the chelating agent would be functionally useless. (Id. at 61, 66.) As they noted, common chelating agents like EDTA form very stable bonds. (Id. at 67–70.) We found, however, that a stability requirement would be unduly vague and ambiguous, particularly given the lack of sufficient guidance from DRL on what tests would be required to assess whether any chelate bonds were sufficiently stable. (Id. at 71, 83–85.) Accordingly, we rejected DRL's proposed limitation that a "chelating agent" must form stable chelate ring structures.

(iv) Construction of "Chelating Agent"

Having rejected DRL's proposed constructions limiting the scope of the term "chelating agent," we selected a definition consistent with its ordinary and customary meaning across scholarly references. (Id. at 87.) Because Helsinn's proposed construction of "chelating agent" was relatively circular (i.e., that it was "structurally capable of being

involved in chelation"), we construed "chelating agent" to mean "a multidentate ligand that can form a ring structure by reacting with a metal ion." (Id. at 91.)

2. DRL's "Second Step" Argument

DRL now contends that the "second step" of the infringement analysis—properly applying the construed claim to the accused product—requires Helsinn to demonstrate that DRL's Accused Product contains a chelating agent that is actually chelating, or at the very least is capable of chelating, in a liquid pharmaceutical preparation. Helsinn protests DRL's position as an improper attempt to relitigate our prior claim construction. The question necessarily impacts our infringement analysis because the bulk of Helsinn's evidence does not directly address whether the alleged chelating agent in DRL's product acts as a multidentate ligand capable of forming ring structures with metal in liquid pharmaceutical preparations, but rather whether it acts as a multidentate ligand capable of forming a ring structure with a metal ion.

DRL leans heavily on two Federal Circuit cases for the proposition that the second step of an infringement analysis can (and should here) limit the scope of a claim term construed in isolation. We turn now to those cases.

Power Mosfet Techs., L.L.C. v. Siemens AG concerned a patent in which the relevant claim required a "contact layer ***contacting*** with . . . semiconductor regions to form [an] ***interface***." 378 F.3d 1396, 1407 (Fed. Cir. 2004) (emphasis added). At the district court, a special master construed the terms "contacting" and "interface" separately, concluding that "contacting" could be satisfied by physical ***or*** electrical contact, while "interface" required a "necessarily physical" boundary. Id. at 1403–04. After adopting the special master's

constructions and holding a bench trial, the district court found that the defendants' products did not infringe the patent because, inter alia, the accused products did not have the requisite physical "interface," even though the products did satisfy the "less demanding" requirement that there be physical ***or*** electrical "contact[]." Id. Thus, construed as a whole, "the physical touching requirement of 'interface' as construed by the Special Master . . . overrode the less demanding 'physical ***or electrical***' requirement of 'contacting' imposing a requirement of physical contact when combined." Id. at 1404 (emphasis in original). The Federal Circuit upheld the district court's conclusion that a finding of infringement required the narrower claim limitation to be satisfied. Id. at 1408–09.

Pozen, Inc. v. Par Pharm., Inc. concerned two patents in which the relevant claims covered "unit doses" (or "unit dosages") of two separate drugs for "concomitant administration." 696 F.3d 1151, 1157–58 (Fed. Cir. 2012). The district court construed the term "concomitantly administering" to cover both simultaneous administration and close-in-time sequential administration. Id. at 1160. The parties had previously agreed that the term "unit dose" referred to "single drug administration entities." Id. At trial, the issue before the court was whether the patents were invalid as obvious based on prior art. Id. Despite its earlier, broader construction of "concomitant administration," the district court at trial focused only on whether the prior art disclosed "simultaneous administration" of the two drugs. Id. The Federal Circuit upheld the district court's approach, explaining that: "[w]hen considering the claim language as a whole the term 'unit dose' ***necessarily limits*** concomitant administration to mean simultaneous administration because a single drug administration entity cannot be administered in any other fashion." Id. (emphasis added).

DRL argues that Power Mosfet and Pozen stand for the proposition that while a claim term may be construed a particular way when considered in isolation during claim construction, the application of a claim ***as a whole*** to a particular product may necessarily narrow the scope of the construed claim term. In that vein, DRL argues that while we rejected various scope limitations to "chelating agent" in our Markman ruling, the "second step" of our infringement analysis must address whether the acetate in DRL's Accused Product is capable of (or is actually) forming chelate rings with metal ions in the context of the accused liquid pharmaceutical preparation. Helsinn casts DRL's "second step" argument as a backdoor effort to revisit issues that we resolved in our Markman ruling. (Dkt. 216 at 19–20.) In Helsinn's view, DRL's proposed framework for analysis would functionally narrow the scope of the term "chelating agent" in essentially the same way that DRL sought to narrow the term at claim construction.[11]

After carefully considering the parties' arguments, we conclude that our infringement analysis does not require us to limit the scope of what constitutes a "chelating agent" beyond how we construed that term during the claim construction process.

DRL contends that two cases—Power Mosfet and Pozen—support the proposition that a court's infringement analysis may require reconciling separate claim limitations that may be in tension with one another. For example, in Power Mosfet, one claim term ("contacting")

[11] As Helsinn notes, DRL declined to move for reconsideration of our Markman ruling. Although we take at face value that DRL is not simply seeking an end-run around our Markman ruling, we do note that a motion for reconsideration would have been a proper way to challenge that ruling. See, e.g., Church & Dwight Co. v. Abbott Labs., No. 05-2142, 2008 WL 2566193, at *2 (D.N.J. June 24, 2008) (denying motion for a new trial because defendant's "arguments [we]re repetitious of the arguments it made prior to this Court's claim construction ruling" and it "filed no motion for reconsideration").

was construed to require either physical or electric contact, while a separately construed claim term ("interface") in the same claim was construed to require physical contact. 378 F.3d at 1403–04. For its infringement analysis, the court required the satisfaction of the narrower, "physical only" interface claim limitation. Id. at 1408–09. In Pozen, one claim term ("concomitant administration") was construed to cover both simultaneous and sequential administration of a drug, while a separate claim term ("unit dose") was by the parties' agreement understood to cover single drug administration entities. 696 F.3d at 1160. Recognizing that single drug dosages would necessarily require simultaneous administration, the district court reconciled the two claim terms by limiting its focus to "simultaneous" administration—an approach upheld by the Federal Circuit. Id.

In DRL's view, we must similarly reconcile the term "chelating agent" and other claim terms relating to pharmaceutical preparations. For example, claim 8 of the '724 patent covers:

> ***A pharmaceutically stable isotonic intravenous solution*** for reducing emesis or reducing the likelihood of emesis comprising: a) from 0.01 mg/ml to 5 mg/ml palonosetron or a pharmaceutically acceptable salt thereof, at a pH of from 4.0 to 6.0; and b) ***an aqueous pharmaceutically acceptable carrier including a chelating agent***.

('724 patent at col. 10, lines 14–21) (emphasis added). Claim 27 of the '094 patent and claim 6 of the '980 patent refer to "pharmaceutical single-use, unit-dose formulation[s]" and also contain other claim terms. Reconciling the term "chelating agent" with other claim terms, DRL argues, necessarily requires Helsinn to produce evidence that the accused chelating

agent is, or can, form the requisite chelate rings in a pharmaceutical preparation.[12] (Dkt. 217 at 7–8.)

We disagree with DRL that the term "chelating agent" must be so limited and that Pozen and Power Mosfet should control our analysis here. First, it bears repeating that we did not construe the term "chelating agent" in a vacuum. We explicitly analyzed in our Markman ruling whether the claim as a whole (including the other claim terms DRL now cites) limited the scope of the term "chelating agent."[13] Unlike in Power Mosfet—where two separate claim terms were construed in isolation from one another—we construed a single claim term with reference to the full array of intrinsic evidence including the words in the claims as a whole. Second, we see no irreconcilable tension between the "chelating agent" limitation in the asserted claims and other claim limitations. As we explained in our Markman ruling, the fact that the asserted claims pertain to pharmaceutical preparations does not mean that the term "chelating agent" must be divorced from its ordinary and plain meaning, which we concluded is not limited to pharmaceutical preparations. (Dkt. 92 at 78–80.) Accordingly, we face a different situation than the court in Pozen, where one possible construction of "concomitant administration" (i.e., "sequential" administration) simply did not make sense when the claim covered single drug administration entities. Here, our construction of the term "chelating agent," which does not require the accused agent to form chelate ring structures specifically in pharmaceutical preparations, can be applied sensibly to the Accused Product.

[12] As discussed in Section II.B.1, supra, DRL has alternately framed the inquiry as whether chelate rings are formed in palonosetron specifically, aqueous pharmaceutical solutions, or pharmaceutical preparations more generally.

[13] See Dkt. 92 at 25 (explaining that the term "chelating agent" "is used in claim 8 ***without any additional words to define or limit it in the claim language itself***") (emphasis added).

We note further that DRL's proposed "second step" analysis would essentially unravel our careful construction of the term "chelating agent." Helsinn, of course, presented its case at trial in light of our explicit holding that the term did not require a showing that the accused chelating agent actually form ring structures in a pharmaceutical preparation. And to the extent DRL now contends that Helsinn must demonstrate that the accused chelating agent be "structurally capable" of chelating ***in a pharmaceutical preparation***, we note that such an approach might practically eviscerate our claim construction. After all, requiring Helsinn to put on evidence that the accused chelating agent is "capable" of forming chelate rings in a pharmaceutical formulation might require evidence of "actual" chelation in that context—a claim term scope limitation that we explicitly considered and rejected.

Our Markman ruling provided guidance to the parties on the meaning of the term "chelating agent." Although we acknowledge that the "second step" of the infringement analysis may sometimes entail reconciling claim terms that may conflict with one another, we find no conflict here that warrants narrowing the scope of the term "chelating agent" as we construed it. Accordingly, we find that Helsinn had the burden of proof at trial to demonstrate for infringement purposes that the Accused Product contains a "multidentate ligand that can form a ring structure by reacting with a metal ion."

C. Summary of Evidence

We turn now to the question of whether Helsinn carried its burden to establish by a preponderance of the evidence that DRL's Accused Product satisfied the "chelating agent" claim term limitation by containing a "multidentate ligand that can form a ring structure by reacting with a metal ion." The specific dispute at hand is whether the acetate present in the

Accused Product satisfies that claim limitation. We summarize in this section the parties' arguments and the evidence presented at trial.

1. Helsinn's Evidence

DRL's product contains sodium acetate trihydrate, which the parties agree dissociates into acetate in solution (as in the Accused Product). (Dkt. 175 at 51; dkt. 176 at 52.) Helsinn contends that acetate is a chelating agent under the Court's Markman ruling because it is a multidentate ligand that can bind with a metal ion to form a four-membered chelate ring. To support that contention, Helsinn called Dr. Christian Schöneich during its case-in-chief and Dr. John Gladysz as a rebuttal expert. We accepted Dr. Schöneich as an expert in the field of pharmaceutical chemistry and stability. (Dkt. 175 at 49.) We accepted Dr. Gladysz as an expert in the fields of organic, inorganic, and organometallic chemistry, including how chelating agents bond with metal ions and methods of detecting chelate bonds in solids and solutions. (Dkt. 182 at 14–15.)

As part of their expert testimony at trial, Helsinn's expert witnesses pointed to textbooks and scholarly references that they claim support a finding that acetate is a multidentate ligand capable of forming a chelate ring structure with a metal ion. Specifically, Helsinn highlighted three textbooks: (1) Cotton Basic (PTX-229); (2) Cotton Advanced (PTX-270); and (3) Crabtree (PTX-234).[14] Dr. Schöneich emphasized the credentials of these

[14] Helsinn submits that another textbook, Food Chemistry (PTX-648), expressly includes acetate on a list of chelating agents. Food Chemistry was not offered as substantive evidence at trial and was not listed in the pretrial order. Accordingly, DRL argues that it may not be used as evidence for Helsinn's case-in-chief. (Dkt. 204 at 2–6.) Because it was not listed on the pretrial order or produced in discovery, we now decline to admit Food Chemistry as evidence for Helsinn's case-in-chief. However, as we stated on the record at trial in response to DRL's objection, we considered the

textbook authors. (Dkt. 175 at 65–72.) Cotton Basic (PTX-229) refers to carboxylates like acetate as bidentate ligands, which are one type of multidentate ligand. (Dkt. 175 at 66–68.)[15] Cotton Advanced (PTX-270) and Crabtree (PTX-234) describe acetate as a bidentate ligand that can form a four-membered chelate ring. (Dkt. 175 at 71–74.)

In addition to textbook references, Helsinn submitted 15 peer-reviewed scholarly articles that it claims show that acetate can form chelate rings with various metal ions. (Dkt. 175 at 77.) Briefly, the references are as follows:

(1) Ishioka (PTX-260) shows acetate forming a chelating bidentate structure with zinc through x-ray crystallography.[16] (Dkt. 175 at 79–83.)

(2) Sakohara (PTX-273) shows acetate forming a bidentate (chelate) bond with zinc through infrared ("IR") spectroscopy.[17] (Dkt. 175 at 86–88.)

(3) Bryant (PTX-274) shows acetate forming chelate rings with lead through x-ray crystallography. (Dkt. 175 at 89–90.)

(4) Schürmann (PTX-231) shows acetate forming chelate rings with lead through x-ray crystallography. (Dkt. 175 at 92–95.)

(5) Weber (PTX-216) shows acetate forming a chelate ring with iron through x-ray crystallography. (Dkt. 175 at 96–100.)

(6) Favas (PTX-221) shows acetate forming chelate rings with gadolinium through x-ray crystallography. (Dkt. 175 at 100–02.)

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evidence as it was used for impeachment purposes. (Dkt. 176 at 132–33.) We note also that DRL addressed Food Chemistry in its redirect examination of its expert, Dr. Kibbe. (Id. at 127–130.)

[15] Cotton Basic was also cited by DRL's expert Dr. Hancock in his claim construction declaration. (Dkt. 92 at 65.)

[16] X-ray crystallography is a technique that measures x-ray diffraction to assess the structure of crystals, including their position and bonding arrangement. Helsinn's experts contend that x-ray crystallography can accurately measure the structure of molecules that were formed in solution. (Dkt. 175 at 81–82; dkt. 182 at 69, 78.)

[17] IR spectroscopy uses infrared light to measure characteristics of materials and can help identify whether any bonds present are bidentate, unidentate, or bridging bonds. (Dkt. 175 at 84–85.)

(7) Martell (PTX-280) shows acetate forming a chelate ring with lanthanum through x-ray crystallography. (Dkt. 175 at 102–10.)

(8) Jia (PTX-230) shows acetate forming a chelate ring with ruthenium through x-ray crystallography and IR spectroscopy. (Dkt. 175 at 110–14.) The authors concluded the bonding was bidentate based on x-ray crystallography and IR spectroscopy comparisons to known known complexes containing bidentate ruthenium-acetate complexes. (Id. at 112-13.)

(9) Deepa (PTX-228) shows acetate forming a chelate ring with tungsten through IR spectroscopy. (Dkt. 175 at 115–17.)

(10) Warthen (PTX-226) shows acetate forming a chelate ring with copper through x-ray crystallography. (Dkt. 175 at 119–121.)

(11) Li (PTX-264) shows acetate forming a chelate ring with copper. Per Helsinn, Li also demonstrates the robustness of the acetate-copper chelate bond because it remained stable for two weeks and the acetate was not replaced by other chloride ions or water during that time. (Dkt. 175 at 122–24.)

(12) Quilès (PTX-236) shows acetate forming a chelate ring with copper in solution through Raman spectroscopy.[18] (Dkt. 175 at 125–30.)

(13) Jiang (PTX-272) shows acetate forming chelate rings with uranyl ions in solution through extended x-ray absorption fine structure spectroscopy ("EXAFS").[19] (Dkt. 175 at 132–39.)

(14) Feldman (PTX-223) shows acetate forming a chelate ring with a uranyl ion through x-ray crystallography. (Dkt. 175 at 139–42.)

(15) Kakihana (PTX-237) shows acetate forming chelate rings with uranyl ions in aqueous solution through IR spectroscopy. (Dkt. 175 at 142–44.)

Helsinn contends these scholarly references show that acetate can form chelate rings with metal ions under various experimental conditions, including in a variety of solvents and temperatures. The references also offer evidence through a variety of detection methods,

[18] Raman spectroscopy analyzes the energy of light scattered from a sample and can be used to assess the type of bonds (e.g., unidentate, bidentate, or bridging) present. (Dkt. 175 at 126–27.)

[19] EXAFS is another technique that can be used to detect the bonding arrangement of molecules in solution. (Dkt. 175 at 134–35.)

including x-ray crystallography, EXAFS, IR spectroscopy, and Raman spectroscopy. Per Helsinn, x-ray crystallography is the "gold standard" for determining bonding arrangements and can establish the presence of chelate rings in solution.[20] (Dkt. 182 at 18–19.) Further, the articles analyze acetate-metal bonding with metals used in various common applications, including insulin formulation (Ishioka, PTX-260), treatment of lead poisoning (Bryant, PTX-274), medical imaging dyes (Favas, PTX-221), preparing electrochromic film (Deepa, PTX-228), and fertilizers (Warthen, PTX-226).

DRL's overarching objection to Helsinn's evidence is that Helsinn did not provide evidence of acetate's ability to form chelate ring structures in the context of DRL's Accused Product or pharmaceutical preparations generally.[21] DRL notes that Helsinn did not submit any experimental data regarding DRL's Accused Product, an omission DRL finds particularly egregious because Helsinn's expert Dr. Schöneich acknowledged it was possible to do such testing. (Dkt. 175 at 148.) Accordingly, DRL frames Helsinn's case as based on "speculative evidence" that "simply present[s] textbooks showing hypothetical structures in a vacuum." (Dkt. 217 at 9.) Likewise, DRL argues that Helsinn's scholarly references should be discounted because they describe the behavior of acetate outside of the context of pharmaceutical preparations:

[20] DRL's expert Dr. Hancock testified that x-ray crystallography can help provide information on the types of bonds present, at least in the solid state. (Dkt. 178 at 157–60, 187.) As we recounted in our Markman ruling, DRL's expert has testified that one could "probably" determine whether a ligand formed a chelate bond with a metal ion based on a crystallized sample. (Dkt. 92 at 62.)

[21] As explained in Section II.B, supra, DRL believes this distinction is critical because it contends the relevant infringement inquiry is whether there is evidence of chelation (or at least the potential for chelation) in that environment.

- DRL contends that 11 of Helsinn's articles (Ishioka, Sakahara, Bryant, Schurrmann, Weber, Favas, Martell, Jia, Deepa, Warthen, and Li) should be discounted because they analyze materials in solid state rather than in solution. (Dkt. 217 at 10.) As DRL's expert Dr. Brittain explained, "solution phase coordination chemistry is entirely different than solid state coordination chemistry." (Dkt. 176 at 172.)
- DRL notes that three articles (Feldman, Kakihana, and Jiang) relate to acetate binding with uranyl, which Helsinn's expert Dr. Gladysz testified may not be a metal ion. (Dkt. 182 at 91–92.)[22] Dr. Brittain testified that uranyl has unique properties that make evidence of its solid-state behavior particularly irrelevant for how it would behave in solution. (Dkt. 178 at 21–22.) DRL expert Dr. Hancock also testified that he believed acetate-uranyl bonding was unidentate and that Feldman (PTX-223) improperly concluded such bonding was bidentate. (Dkt. 178 at 113–19.)
- DRL contends that nine articles (Bryant, Schurrmann, Favas, Martell, Jia, Deepa, Jiang, Feldman, and Kakihana) should be discounted because they analyze acetate bonding with toxic metals that would rarely (if ever) be used in the pharmaceutical context because of their toxicity. (Dkt. 176 at 31–32.)[23]
- DRL contends that four articles (Martell, Jia, Warthen, and Li) should be discounted because they analyzed materials where, unlike in DRL's Accused Product, co-ligands were present that could alter the way acetate bonds to metal. (Dkt. 178 at 135–36.)
- DRL contests the relevance of Quilès through testimony and experimentation from Dr. Hancock showing that acetate/copper bonding is "undoubtably [sic] unidentate." (Dkt. 178 at 113.) DRL also submits Niekerk (DTX-203) showing that acetate bonds with copper in a bridging (as opposed to chelating) fashion. (Id. at 113–14.)

Helsinn's general response to these objections was that it does not need to provide evidence that acetate is capable of forming chelate rings in DRL's palonosetron product (or in liquid pharmaceutical preparations more generally). (Dkt. 216 at 24.) As discussed in Section II.B, supra, we agree. We do note, however, that Helsinn submitted evidence in the alternative that its references ***do*** provide support for the idea that acetate is capable of forming

[22] Helsinn disputes the relevance of this distinction, and asserts that acetate was bonding with the "metal ion (i.e., uranium) contained within uranyl." (Dkt. 216 at 18–19; see also dkt. 175 at 131.)

[23] At trial, DRL's expert Dr. Kibbe conceded that many of the metals contained in Helsinn's references (i.e., copper, iron, zinc, gadolinium, lead, ruthenium, tungsten, and lanthanum) could in fact be present in a pharmaceutical preparations or packaging. (Dkt. 176 at 118–120.)

chelate rings in the context of liquid pharmaceutical solutions. For example, Helsinn defended its references analyzing ***solid-state*** materials, arguing that the presence of an acetate-metal chelate ring determined by x-ray crystallography means that the same acetate-metal bonding arrangement ***also*** existed in solution before crystallization. (See, e.g., dkt. 175 at 81–22; dkt. 182 at 32–38.)[24]

Notably, DRL's experts conceded at times that Helsinn's references show that acetate is capable of forming chelate rings under certain circumstances, even if not specifically in the context of pharmaceutical products. DRL's expert Dr. Brittain testified that, "[i]f you want to prove that acetate forms a four-membered ring in the solid state, then you look at the papers that were cited by Dr. Schöneich, and in those solid-state structures, authors have concluded that such a bonding type exists." (Dkt. 178 at 46–47; see also id. at 30.) He also testified that "in certain solid state structures acetate appeared to have a configuration that might lead one to believe that it was a bidentate ligand." (Dkt. 176 at 143.) Indeed, one of the references in Dr. Brittain's report, Downie (DTX-170), showed solid-state bidentate acetate chelation. (Dkt. 178 at 29.) Dr. Kibbe acknowledged that the authors of the scholarly articles proffered by Helsinn had concluded that acetate can form bidentate bonds with metal ions. (Dkt. 176 at 108–09.) And DRL's expert Dr. Hancock agreed that "[a]cetate is a multidentate ligand that can form a ring structure by reacting with a metal ion" under certain circumstances. (Dkt. 178

[24] Although we do not assess in this opinion whether Helsinn would have satisfied its burden of proof at trial under DRL's proposed framework (i.e., that Helsinn needed to prove that acetate was capable of forming chelate rings in the context of a liquid pharmaceutical solution), we do note that Helsinn provided colorable evidence that acetate would be capable of forming chelate rings with metal ions in that context.

at 127–37.) Indeed, he opined in his expert report that "[w]hile it is true that acetate can form bidentate structures, it is rare for acetate to do so." (Id. at 129.)

2. DRL's Evidence

DRL called three expert witnesses to testify on infringement questions: Dr. Arthur Kibbe, Dr. Harry Brittain, and Dr. Robert Hancock. We accepted Dr. Kibbe as an expert in the field of pharmaceutical formulation and development. (Dkt. 176 at 13–14.) We accepted Dr. Brittain as an expert to testify in the field of pharmaceutical formulations, including excipients and their structure and functionality. (Id. at 140.) We accepted Dr. Hancock as an expert in the field of the structure and function of metal complexes, including chelates. (Dkt. 178 at 73.)

DRL offered two broad categories of its own affirmative evidence, in addition to attacking the sufficiency of Helsinn's infringement evidence. First, DRL submitted testimony that acetate would never be selected or used as a chelating agent by pharmaceutical formulators. Second, DRL offered evidence that acetate should be considered a unidentate ligand (and consequently cannot be considered a "multidentate ligand" as required by our claim construction). DRL contends as an overarching matter that it should prevail even if the evidence is ambiguous on the latter point because Helsinn has the burden of proof. (Dkt. 217 at 11.)

Regarding whether acetate would ever be used as a chelating agent in a pharmaceutical preparation, Dr. Brittain opined that he was not aware of any pharmaceutical formulations that used acetate as a chelating agent and he contrasted acetate with other chelating agents such as malic acid and citrate. (Dkt. 176 at 141–49.) Dr. Kibbe explained how he would have chosen

a chelating agent if he were formulating a pharmaceutical product and that he would not have chosen acetate for that purpose. (Id. at 61–62.) Dr. Hancock testified that the amount of acetate needed to achieve the same complexing strength as EDTA (the chelating agent in Helsinn's palonosetron product) would be in the "thousands of tons" and could not fit in the vials in which the drug is sold. (Dkt. 178 at 121–22.) As discussed in Section II.B.2, supra, however, Helsinn was not obligated to demonstrate under our claim construction that acetate would actually chelate in a pharmaceutical formulation or that it would form particularly strong or stable bonds.

Regarding whether acetate is a unidentate or multidentate ligand, DRL offered textbook evidence, scholarly references, and expert testimony in support of its contention that acetate should be considered a unidentate ligand. We turn first to the textbook and scholarly references:

(1) Martell and Calvin (DTX-134) refers to acetate as a unidentate donor, meaning it acts as a unidentate ligand. (Dkt. 178 at 75–76.)

(2) Essington (DTX-136) refers to acetate as an example of a monodentate ligand and also refers to the "complexation of copper by acetate (monodentate)." (Dkt. 178 at 77–78.)

(3) Dickerson (DTX-139) lists acetate in a table under the heading "Common Monodentate Ligands." (Dkt. 178 at 76–77.)

(4) Prabhumirashi (DTX-140) discusses oxalate as an example of a bidentate ligand and "the stronger coordination of the oxalate ion to the copper (II) due to its chelating bidentate nature as compared to the unidentate coordination by acetate ion." (Dkt. 178 at 81–82.)

(5) Grenthe (DTX-143) contemplates investigating a monodentate carboxylate ligand and suggests acetate. Another portion of the article notes that a particular "ligand acts in much the same way as acetate, i.e., as a monodentate ligand." (Dkt. 178 at 78–79.)

(6) Kolat (DTX-144) studies rare earth ions and states: "[a] study involving monodentate ligands such as acetate may lead to a better understanding of such phenomena." (Dkt. 178 at 79–80.)

(7) Banerjea (DTX-145) lists acetate on a list of monodentate ligands. (Dkt. 178 at 79–80.)

(8) Hancock and Martell (DTX-179) describes acetate as a unidentate ligand. (Dkt. 178 at 85–86.)

(9) Caminiti (DTX-225) supports the argument that zinc acetate forms a monodentate bond in the solid state. (Dkt. 178 at 96–97.)

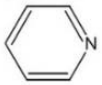
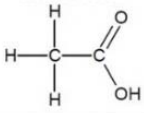
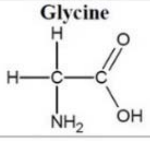
DRL submits that its textbook references should carry more weight because they are more advanced textbooks. Dr. Hancock, for example, testified that Martell and Calvin (DTX-134) is aimed at researchers, while Helsinn's Cotton (PTX-229; PTX-270) and Crabtree (PTX-234) references are aimed at students. (Dkt. 178 at 94–95.)

DRL's experts also testified that acetate should be considered a unidentate ligand. First, DRL's experts testified that acetate should be considered a unidentate ligand because it has only a single carboxylic acid functional group. (Dkt. 176 at 77, 157–58.) Dr. Kibbe opined that a multidentate ligand must have multiple functional groups; for example, the common chelating agent EDTA has six functional groups. (Id. at 77–78.) In his view, the single functional group in acetate is at odds with one definition of "chelate" that requires "a reaction of two or more groups" of a ligand with a metal ion. (Id. at 76–77, 108.) Dr. Brittain similarly noted that Dwyer (DTX-175) defines a multidentate ligand as having at least two appropriate functional groups. (Id. at 158–160.)[25]

[25] Helsinn disputes the relevance of the number of functional groups and explained that the two oxygen atoms in acetate are capable of simultaneously binding to a metal ion to form a four-membered chelate ring. (Dkt. 175 at 61–63.) Helsinn also contends, and we agree, that our

DRL's experts also offered their own experimental evidence that acetate is a unidentate ligand based on "association constant" data.[26] Dr. Brittain testified that the association constant of a compound increases significantly when a molecule forms a chelate ring structure. (Dkt. 176 at 176–77.) He explained that the association constants for acetate and various metal ions are consistent with acetate being a unidentate ligand. (Dkt. 178 at 8–9.) To help demonstrate this point, Dr. Brittain compared acetate to pyridine (a known monodentate ligand) and glycine (a known bidentate ligand). (Dkt. 176 at 180–83.) As demonstrated by DTX-417, prepared by Dr. Brittain, the comparison shows that acetate is much more similar to pyridine, which he submits supports a finding that acetate is a unidentate ligand.[27] (Id. at 183–93.)

DTX-417

	Known Monodentate Ligand		Known Bidentate Ligand
	Pyridine 	**Acetic Acid** 	**Glycine** 
Metal Ion	**Association Constant** (Exhibit H) Values reported for studies conducted at an ionic strength of 0.5	**Association Constant** (Exhibit I) Values reported for studies conducted at zero ionic strength	**Association Constant** (Exhibit G) Values reported for studies conducted at zero ionic strength
Mn(II)	1.4	25.1	1,549
Fe(II)	4.0	25.1	20,417
Co(II)	15.5	28.8	117,490
Ni(II)	74.1	26.9	1,513,561
Cu(II)	363.1	166.0	36,307,805 363,078,050
Zn(II)	9.8	37.2	239,883

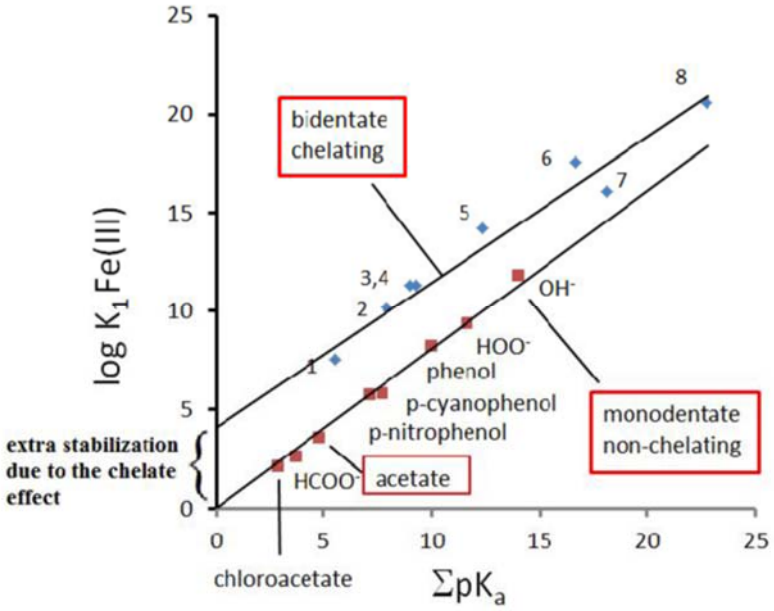
construction of "chelating agent" does not require that a ring structure be formed from a ligand that has multiple functional groups.

[26] Association constants measure the affinity of a particular anion (such as acetate) for a particular positively charged cation (such as a metal) in solution. (Dkt. 176 at 175–76.) Association constants are sometimes referred to as "formation constants" or "stability constants." (Id. at 174.)

[27] Helsinn disputes the evidentiary value of association constants, and notes that Dr. Brittain conceded that "whether a compound is a chelating agent cannot be based solely on the value of [its] formation constant." (Dkt. 178 at 51.)

Dr. Hancock also offered data (reflected in DTX-405, DTX-406, and DTX-407) in support of DRL's contention that acetate should be considered a unidentate ligand.[28]

DTX-405



The y-axis of the chart above reflects formation constants; the x-axis reflects the strength of the bonds formed between a hydrogen ion and a particular ligand. Dr. Hancock explained that higher y-axis values for materials corresponds to additional stabilization as a result of the "chelate effect" while lower y-axis values correspond to monodentate (and, by extension, non-chelating) materials because those materials lack the chelate effect. (Dkt. 178 at 101–06.) The upshot of the data is that acetate behaves more closely like other unidentate ligands, at least with certain metals.

[28] Although DTX-405 reflects bonding with iron ions, DTX-406 and DTX-407 reflect similar findings with uranyl and copper, respectively. (Dkt. 178 at 108–10.) The parties dispute whether these exhibits are admissible; Helsinn contends they should be considered merely demonstrative exhibits, while DRL claims that the charts are admissible as the content of a voluminous writing under Federal Evidence Rule 1006. (Dkt. 204 at 1–2, 5.) We agree with Helsinn that DTX-405, DTX-406, and DTX-407 are demonstrative exhibits and consider them as demonstrative aids to Dr. Hancock's expert testimony. We also will treat DTX-401 as a demonstrative aid rather than an exhibit in evidence. (Id. at 1–2.)

Helsinn's rebuttal expert Dr. Gladysz criticized the testimony offered by Dr. Hancock on several grounds. First, Dr. Gladysz noted that Dr. Hancock's findings were not peer-reviewed and should be looked upon skeptically as they contradict other scientific evidence.[29] (Dkt. 182 at 43–45.) Second, he explained that Dr. Hancock's analysis did not rely on sufficient numbers of data points to provide credible conclusions. (Id. at 47–48.) Third, the association constant data used in Dr. Hancock's experiment, adapted from work by Martell and Smith, may be unreliable because different sources may report different values for those constants. (Id. at 48–52.) Fourth, Dr. Hancock's chart included carbonate and phosphate as unidentate ligands, even though those ligands can act as chelating agents. (Id. 182 at 59–62.) Finally, Dr. Gladysz explained that even if acetate did not form a bidentate bond with the metals in a particular experiment, it might still chelate with other metals in other circumstances. (Dkt. 182 at 43.)

D. Findings of Fact and Conclusions of Law

After carefully reviewing the evidence, testimony, and briefing provided by the parties, we conclude that Helsinn has proved by a preponderance of the evidence that DRL's Accused Product infringes the asserted claims of the '724, '980, and '094 patents. This conclusion flows from our factual findings, recounted below, that sodium acetate trihydrate present in the Accused Product satisfies the "chelating agent" claim limitation as "a multidentate ligand that can form a ring structure by reacting with a metal ion." Our findings are as follows.

[29] For example, Jiang (PTX-272), which relied on EXAFS data, discloses an association constant for an acetate-uranyl complex that is similar to the value used by Dr. Hancock, but that reference concluded there was a bidentate chelate bond present. (Dkt. 182 at 53–56.)

A ligand is a molecule that can bind to a metal ion. (Dkt. 175 at 55.) Ligands can form different types of bonds with metal ions, such as unidentate, multidentate, and bridging bonds. (Id. at 52–53.) A multidentate ligand is a molecule that has at least two atoms which can simultaneously make a bond with a metal ion. (Id. at 55.) Bidentate bonds are a type of multidentate bond consisting of two bonds between a ligand and a single metal ion, forming a "chelate" ring structure. (Id. at 53.) A particular molecule may form a chelate bond in certain circumstances, but not others. (Dkt. 178 at 126.)

DRL's Accused Product contains sodium acetate trihydrate. When placed in aqueous solution, sodium acetate trihydrate dissociates into sodium, acetate, and water. (Dkt. 175 at 51.) Acetate is capable of forming a pair of simultaneous bonds with metal ions. (Id. at 61–63.) Specifically, under certain circumstances, the two oxygen atoms in acetate are capable of simultaneously binding to a metal ion to form a four-membered chelate ring. (Id.)

Numerous scholarly references from peer-reviewed journals support the conclusion that acetate can under some circumstances act as a multidentate ligand capable of forming chelate ring structures. See, e.g.: Ishioka (PTX-260); Sakohara (PTX-273); Bryant (PTX-274); Schürmann (PTX-231); Weber (PTX-216); Favas (PTX-221); Martell (PTX-280); Jia (PTX-230); Deepa (PTX-228); Warthen (PTX-226); Li (PTX-264); Quilès (PTX-236); Jiang (PTX-272); Feldman (PTX-223); and Kakihana (PTX-237). These articles demonstrate that acetate can form chelate rings with metal ions under various experimental conditions, including in a variety of solvents and temperatures. Acetate-metal chelate rings have been demonstrated through a variety of experimental detection methods, including x-ray crystallography, extended x-ray absorption fine structure spectroscopy, infrared spectroscopy,

and Raman spectroscopy. Further, these chelate rings were detected in various applications of acetate and with a variety of metal ions, including: (1) zinc chelation used in insulin formulations; (2) lead chelation used in treatment of lead poisoning; (3) iron chelation used in fertilizers); (4) gadolinium chelation used in medical imaging dyes; (5) lanthanum chelation used in medical imaging dyes; (6) ruthenium chelation used in industrial processes; (7) tungsten chelation used in preparing electrochromic films; and (8) copper chelation used in fertilizers and for contaminated pharmaceuticals. That acetate is a multidentate ligand capable of forming a ring structure with a metal ion under certain circumstances is further supported by expert testimony from both Helsinn and DRL.

DRL submitted some evidence that acetate under some circumstances forms unidentate bonds. At best, we find that this evidence supports only the conclusion that acetate forms unidentate bonds in certain circumstances while forming multidentate bonds in other circumstances.

We construed the term "chelating agent" to mean a "multidentate ligand that can form a ring structure by reacting with a metal ion." Under the second step of the infringement analysis, Helsinn needed to prove by a preponderance of the evidence that DRL's accused palonosetron product contains a chelating agent under our claim construction. Based on a review of all of the evidence presented at trial, and as reflected in the findings of fact above, we conclude that Helsinn proved by a preponderance of the evidence that the acetate present in DRL's product is a multidentate ligand that can form a ring structure by reacting with a metal ion. Accordingly, the Accused Product contains a "chelating agent," which the parties have stipulated is the determinative issue to establish infringement here. We therefore find

that DRL's Accused Product infringes claim 9 of the '724 patent, claim 27 of the '094 patent, and claim 6 of the '980 patent.

III. Invalidity

DRL challenges claims 22, 23, 24, and 25 of the '094[30] patent and claims 1, 2, 3, 4, 5, and 16 of the '980[31] patent as invalid for lack of enablement and lack of adequate written description.[32] (Dkt. 168-1 at 266.)

Although both of these invalidity challenges are founded in 35 U.S.C. § 112(a),[33] the statute "mandates satisfaction of two separate and independent requirements: an applicant must both describe the claimed invention adequately and enable its production and use." Alcon Research, 745 F.3d at 1188.

The purported invalidity of the asserted claims relates to the stability of the formulations at room temperature. Each asserted claim of the '094 patent requires a

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[30] The asserted claims 22, 23, 24, and 25 of the '094 patent are:

> 22. A method for reducing the likelihood of cancer chemotherapy-induced nausea and vomiting, comprising intravenously administering to a human in need thereof a pharmaceutical single-use, unit-dose formulation comprising a 5 mL sterile aqueous isotonic solution buffered at a pH of about 5.0.+-.0.5, said solution comprising: about 0.05 mg/mL palonosetron hydrochloride based on the weight of its free base; and a tonicifying effective amount of mannitol; wherein said solution optionally comprises one or a combination of a citrate buffer and a chelating agent, wherein said formulation is stable at 24 months when stored at room temperature, and wherein said intravenous administration to said human occurs before the start of the cancer chemotherapy.
>
> 23. The method of claim 22, wherein said intravenous administration to said human occurs over a period of time of 10 to 60 seconds.
>
> 24. The method of claim 22, wherein said intravenous administration reduces the likelihood of acute nausea and vomiting in said human.
>
> 25. The method of claim 22, wherein said intravenous reduces the likelihood of delayed nausea and vomiting in said human.

('094 patent at col. 11, line 18 to col. 12, line 15.)

formulation that is stable at 24 months. Claims 1, 2, 3, 4, and 5 of the '980 patent require a formulation that is stable at 24 months; claim 16 of the '980 patent requires a formulation that is stable at 18 months.[34] Much of the parties' invalidity analysis centers

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[31] The asserted claims 1, 2, 3, 4, 5, and 16 of the '980 patent are:

> 1. A pharmaceutical single-use, unit-dose formulation for intravenous administration to a human to reduce the likelihood of cancer chemotherapy-induced nausea and vomiting, comprising a 5 mL sterile aqueous solution, said solution comprising: a) palonosetron hydrochloride in an amount of 0.25 mg based on the weight of its free base, b) optionally a chelating agent, and c) a tonicifying agent in an amount sufficient to make said solution isotonic, wherein said formulation is stable at 24 months when stored at room temperature.
>
> 2. The pharmaceutical formulation of claim 1, wherein said solution is buffered at a pH of 5.0. ±.0.5.
>
> 3. The pharmaceutical formulation of claim 1, wherein said tonicifying agent is mannitol.
>
> 4. The pharmaceutical formulation of claim 3, wherein said mannitol is in an amount from 10 mg/mL to 80 mg/mL.
>
> 5. The pharmaceutical formulation of claim 4, wherein said mannitol is in an amount of 41.5 mg/mL.
>
> […]
>
> 16. A pharmaceutical single-use, unit-dose formulation for intravenous administration to a human to reduce the likelihood of cancer chemotherapy-induced nausea and vomiting, comprising a 5 mL sterile aqueous solution, said solution comprising: a) palonosetron hydrochloride in an amount of 0.25 mg based on the weight of its free base, b) optionally a chelating agent, and c) a tonicifying agent in an amount sufficient to make said solution isotonic, wherein said formulation is stable at 18 months when stored at room temperature.

('980 patent at col. 9, line 47 to col. 10, line 12; id. at col. 10 lines 42–52.)

[32] In this invalidity section, we will refer to these ten claims collectively as the "asserted claims."

[33] The '094 and '980 patents were filed after September 16, 2012, and are governed by the Leahy-Smith America Invents Act, Pub. L. No. 112-29, 125 Stat. 284 (2011).

[34] As a preliminary matter, the parties ask us to construe the term "stability" as it appears in the asserted claims. DRL asks us to construe "stability" in accordance with its plain and ordinary meaning. (Dkt. 199 at 144–45; dkt. 217 at 18–19.) Specifically, DRL proposes that "stability" means a formulation "having no significant change in chemical or physical properties throughout the specified shelf life." (Dkt. 199 at 145.) Helsinn proposes that we construe "stability" to mean "less than 10 percent palonosetron degradation over the period of stability required by the asserted claims." (Dkt. 200 at 58; dkt. 216 at 42).

on the '351 Provisional Application, to which both patents claim priority. (Dkt. 168 at 8).

We accepted Dr. Joanne Broadhead as an expert for DRL in the field of pharmaceutical formulation and development.[35] (Dkt. 185 at 10–17.) We accepted Dr. Christian Schöneich as an expert for Helsinn in the field of pharmaceutical chemistry and stability. (Dkt. 228 at 5.)

For the following reasons, we find that DRL has failed to meet its burden of demonstrating, by clear and convincing evidence, the invalidity of the asserted claims for either lack of enablement or written description.

A. Enablement

1. Legal Standards

A patent specification must contain an adequate enabling disclosure. 35 U.S.C. § 112(a). The enablement requirement "prevents both inadequate disclosure of an invention and overbroad claiming that might otherwise attempt to cover more than was

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Both parties argue that the intrinsic and extrinsic evidence support their constructions. The parties presented expert testimony on the question at trial—Dr. Broadhead for DRL and Dr. Schöneich for Helsinn.

Although the parties provide differing constructions of the term "stability," the parties have not convinced us that either would have a tangible and practical effect on the invalidity challenges. See, e.g., dkt. 228 at 78. Under either construction, we conclude that DRL has not met its burden of demonstrating invalidity for lack of enablement or written description.

[35] We have considered the small portion of sealed testimony presented by Dr. Broadhead, and it does not impact our findings and conclusions. (Dkt. 185 at 81–83.)

actually invented." MagSil Corp. v. Hitachi Global Storage Techs., Inc., 687 F.3d 1377, 1381 (Fed. Cir. 2012).

"[T]o 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.'" In re Wright, 999 F.2d 1557, 1561 (Fed. Cir. 1993) (quotation omitted). "Undue experimentation" is not a statutory term, but our case law establishes that enablement requires that the specification teach a POSA to make and use the invention without undue experimentation. In re Wands, 858 F.2d 731, 737 (Fed. Cir. 1988). As the Federal Circuit has noted, "[t]he key word is 'undue,' not 'experimentation.'" Id. A specification does not lack adequate enablement if it requires a "reasonable amount of routine experimentation" to practice the claimed invention. ALZA Corp. v. Andrx Pharms., 603 F.3d 935, 940 (Fed. Cir. 2010).

The Federal Circuit has outlined factors for district courts to consider when weighing whether a specification would require undue experimentation, including:

> (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.

Wands, 858 F.2d at 737.

The Federal Circuit has advised district courts that these "Wands factors" are "illustrative, not mandatory." Streck, Inc. v. Research & Diagnostic Sys., 665 F.3d 1269, 1288 (Fed. Cir. 2012). Thus, we need not consider every factor in evaluating whether there is undue experimentation, and we will only consider the ones relevant to these facts.

Patents are presumed valid, and the challenging party bears the burden of showing by clear and convincing evidence that the specification lacks adequate enablement. ALZA Corp., 603 F.3d at 940.

2. Parties' Arguments

DRL argues that the asserted claims are invalid for lack of enablement. DRL contends that the claims are broad, containing thousands of possible formulations, and that the only way to practice the full scope of the claims—i.e., to know whether a specific formulation is stable—is by conducting an unreasonable amount of experimentation. (Dkt. 199 at 149–50, 157.)

DRL relies on the Wands factors to argue that the asserted claims require undue experimentation. Specifically, DRL says that the asserted claims have a substantial breadth because they potentially cover thousands of formulations (Wands factor 8). (Id. at 54, 150.) The asserted claims encompass formulations at varying levels of pH that include the option of using a chelating agent or a citrate buffer. (Id. at 149–50.) The nature of the invention is a fixed length of stability, and not a mere likelihood of stability (Wands factor 4). (Id. at 77, 150.) Yet, according to DRL, whether a specific formulation will achieve the 18-month or 24-month stability is uncertain without results from a substantial amount of real-time testing (Wands factor 1). (Id. at 150.) The nature of pharmaceutical arts, specifically developing the stability of a formulation, is complex and an unpredictable science (Wands factor 7). (Id. at 99, 150–51.) DRL contends that the '351 application provides only one example (Example 4) for a complete intravenous

formulation, and no further guidance is given on how to modify this example and still achieve the claimed stability (Wands factors 2 and 3). (Id. at 89, 152.)

Helsinn notes that the Wands factors are not mandatory for a district court to apply. (Dkt. 216 at 45.) Helsinn argues that DRL has not shown by clear and convincing evidence that the asserted claims fail to meet the enablement requirement by demanding undue experimentation to make and use the formulations. (Dkt. 200-1 at 33; dkt. 216 at 47–49.) According to Helsinn, the '351 application adequately discloses to a POSA how to practice each asserted claim. (Dkt. 200-1 at 26.) The specification teaches that formulations with 0.05 mg/mL palonosetron concentration (the optimal concentration) have the claimed 18-month and 24-months stability and that certain excipients can improve stability further. (Id. at 25.) Helsinn submits that routine experimentation would have allowed a POSA to confirm the requisite shelf stability. (Dkt. 200-1 at 29–30; dkt. 216 at 49.) A POSA would thus be able to practice the full scope of the claimed inventions without undue experimentation based on the '351 enabling disclosure. (Dkt. 200-1 at 25.)[36]

3. Summary of Evidence

(i) DRL's Evidence

DRL introduced Dr. Broadhead as an expert witness. DRL also submitted the designated testimony of seven witnesses: Dr. Gordon Amidon, Helsinn's formulation expert during the prior ANDA trial; Dr. Thomas Malefyt, an inventor and Chemistry,

[36] Helsinn also relies on extrinsic evidence to argue that DRL has failed to meet its burden. (Dkt. 200 at 71–79; dkt. 216 at 43–46.)

Manufacturing, and Controls ("CMC") leader for the palonosetron project at Syntex; Dr. Roberta Canella, an inventor responsible for ensuring a pharmaceutically stable palonosetron formulation; Dr. Kathleen Lee, an inventor and formulator for Syntex; Dr. Valentino Stella, professor of pharmaceutical chemistry and a declarant for Helsinn in the Patent Office; Daniele Bonadeo, an inventor and head of corporate technical affairs for Helsinn; and Dr. Giorgio Calderari, an inventor and Helsinn's witness from the prior ANDA trial.

Dr. Broadhead explained her understanding of the enablement requirement as the patent must enable a POSA[37] to make and use the full scope of the asserted claims without undue experimentation. (Dkt. 185 at 22–23.) Dr. Broadhead opined that the asserted claims lack enablement across the scope of the claims. (Id. at 22, 100–05.)

Dr. Broadhead testified that the '980 and '094 patents did not disclose any specific data regarding shelf-life stability. (Id. at 98.) Outside of the patent, Dr. Broadhead was only aware of two examples of data showing stability greater than 18 months for palonosetron formulations—Example 4 (the Aloxi® formulation) and DRL's 505(b)(2) acetate formulation. (Id.) The patents did not even disclose accelerated data. (Id.)

Dr. Broadhead argued that a POSA reading Example 4 would have believed that EDTA was important to the stability of the formulations. (Id. at 75.) Because Helsinn

[37] We apply the definition of POSA stated above. See supra note 4. Dr. Broadhead proposed to define a POSA as an individual with a Ph.D. in pharmaceutical sciences or a similar discipline with a year or two hands-on experience, or an individual with a lesser degree with more hands-on experience, about two to four years of experience. (Dkt. 185 at 17.) But on cross-examination, she indicated that her opinions would not change if a different definition was used (id. at 153–55). Dr. Schöneich set forth his definition of a POSA that he relied upon in giving his opinions, but he explained that applying Dr. Broadhead's definition of POSA would not impact his opinions. (Dkt. 228 at 6–7.)

included EDTA in Example 4, Dr. Broadhead concluded that EDTA was a necessary component for achieving the requisite 18-month or 24-month stability. (Id. at 85.) Dr. Broadhead also relied on statements by Dr. Malefyt for support that EDTA was an important component of the formulation. (Id. at 76.)

Dr. Broadhead further explained that buffers, tonicifying agents, the concentration of excipients, and the pH all impact the stability of the formulation. (Id. at 75–76.) Dr. Broadhead relied on the Formulation Book (DTX-73) to argue that all components of the formulation are important to its stability. (Id. at 77.) Dr. Broadhead explained that a POSA would avoid using unnecessary formulation components, and would only use a component when there was a reason for including it.[38] (Id. at 150.) DRL pointed to Notes For Guidance on Inclusion of Antioxidants and Antimicrobial Preservatives in Medicinal Products (DTX-77), prepared by the European Agency for the Evaluation of Medicinal Products, which states that antioxidants should only be used in situations where their use could not be avoided, and that accordingly the antioxidants in Helsinn's product (i.e., EDTA) were "necessary for stability." (Id. at 84–85.)

Dr. Broadhead explained that the prior art did not provide teachings regarding shelf stability of palonosetron to guide a POSA in making and using the claimed inventions. (Id. at 70.) DRL submitted testimony that evaluating drug stability in general is complicated and that palonosetron in particular is a very complex compound. DRL noted that Helsinn's formulation expert in another case, Dr. Amidon, called formulation

[38] Dr. Schöneich agreed that a POSA would not add anything to a formulation unless the addition was justified based on need. (Dkt. 228 at 160–61.)

development an "unpredictable science" and noted further that "the degradation of pharmaceutical compositions is highly complex and unstable." (DTX-098 at ¶¶ 24, 134.) Helsinn's declarant in the patent office, Dr. Stella, likewise explained that "drug stability . . . is a very complex process . . . ." (Dkt. 199 at 101.) Regarding the stability of palonosetron specifically, Dr. Amidon stated that "[t]he unusual properties of palonosetron . . . would have further enhanced the complex and unpredictable nature of any suspected oxidation." (DTX-098 at ¶ 123.) Other testimony, including that of Dr. Stella, Dr. Malefyt, and Dr. Bonadeo, echoed the sentiment that palonosetron has unusual properties that affect its stability. (Dkt. 199 at 103.)

DRL also contended that finding stable formulations of palonosetron is made more complicated by the need for extensive real-time stability testing. Dr. Broadhead explained that a POSA can only determine whether a formulation is stable by performing stability testing. (Dkt. 185 at 57.) And the only way to establish shelf-life stability with certainty is with real-time stability data. (Id. at 57–58.) DRL pointed to the report of Dr. Amidon (DTX-98) which noted that "a POSA could not have reasonably expected at least a two-year shelf life without performing adequate long-term, real-time stability testing." (Id. at 58–59.) Other testimony submitted by DRL supported the idea that real-time testing would be necessary to establish stability for a specific shelf life. For example, Dr. Malefyt testified that "[t]wo year data justifies two-year shelf life." (Dkt. 112 at 112–13.) DRL pointed to draft FDA guidance regarding stability testing in drugs (DTX-82), which Dr. Broadhead argued would indicate to a POSA that at least 12 months of stability testing data would be necessary to determine whether the product was

sufficiently stable. (Dkt. 185 at 61–63.) DRL also submitted testimony that accelerated testing data would be inadequate to establish a specified shelf life stability. Dr. Lee, for example, stated that it would be impossible to establish real-time stability from a particular accelerated stability study. (Dkt. 199 at 114.)

Dr. Broadhead identified two purposes for accelerated testing, which can involve testing at a higher temperature than the intended storage temperature in order to project the ultimate shelf life. (Dkt. 185 at 63, 65.) First, during the development phase, accelerated testing yields information in a faster time period than real-time testing. (Id. at 63–66.) Second, application for an NDA requires accelerated testing as part of the registration process. (Id. at 64.) Accelerated testing, on its own, would not have been sufficient for a POSA in 2003 to establish the actual shelf life, according to Dr. Broadhead, because real-time stability data is necessary for that purpose. (Id. at 66, 158–59.) After conducting accelerated testing and identifying promising formulations that might be sufficiently stable, a POSA would have to conduct real-time testing for 18 or 24 months. (Id. at 94–95.) Dr. Broadhead acknowledged that a POSA would run the accelerated studies in parallel to the real-time studies. (Id. at 156.)

Experimental design allows a POSA to test multiple variables across multiple formulations simultaneously, but, according to Dr. Broadhead, substantial work remains for a formulator because there would still be "a very, very large number" of formulations to test. (Id. at 87.) Dr. Broadhead explained that reducing the number of experiments would reduce the amount of information and data on how the different variables interact with each other in a formulation. (Id. at 88.)

Dr. Broadhead concluded that the asserted patents did not enable a POSA to make and use the full scope of the asserted claims without undue experimentation. (Id. at 22, 100–05.) Relying on the Wands factors, Dr. Broadhead concluded that the claims are "very broad"; that the patents provided very little guidance for a POSA on how to develop the formulation; that the patents disclosed some stability issues with palonosetron and thus it would be difficult to predict for a POSA which formulations achieve the requisite shelf life; that Example 4 is the only working example and final formulation within the claims; and that a POSA would need to engage in significant experimentation to ascertain which potential formulations would achieve the claimed stability. (Id. at 98–100.)

(ii) Helsinn's Evidence

Dr. Schöneich explained his understanding of the test for enablement as whether a POSA could have practiced the full scope of the claimed invention based on the specification disclosure, without undue experimentation. (Dkt. 228 at 52.) He added that the enablement requirement is still met even if a POSA has to undertake some experimentation because routine experimentation does not qualify as undue. (Id.)

Dr. Schöneich testified that, to establish the stability of a formulation, a POSA would engage in routine stability studies. (Id. at 9–10.) There are two types of studies a POSA could perform to test stability, according to Dr. Schöneich: real-time stability studies, usually for a period of 24 months, and accelerated stability studies.[39] (Id. at 10.)

[39] Dr. Broadhead agreed that a POSA would commonly be in the practice of running stability studies. (Dkt. 185 at 154.) She also acknowledged that physically setting up and performing the stability study

For a real-time study, a POSA would place a number of vials containing the formulation into an incubator. (Id. at 10–11.) To test whether a formulation remains stable at 24 months, the POSA would generally assess the samples "a couple of times" over a 24-month period, but Dr. Schöneich explained that to measure stability a POSA would only need to take two measurements—once at the beginning and once at the end of the 24-month period. (Id. at 11.) For claims of 24-month stability, the FDA requires 24 months of real-time stability testing data. (Id. at 171–72.)

Dr. Schöneich explained that an accelerated study tests the formulation at specific time periods at various temperatures, and the POSA can extrapolate the data to estimate the stability of the formulation at room temperature. (Id. at 12–15.) The purpose of accelerated stability studies is to run fewer experiments yet obtain more information on a larger set of formulations. (Id. at 16.) Dr. Schöneich explained that stability tests could be machine automated. (Id. at 86–87.)

In support of the contention that a POSA might rely on accelerated stability study data, Dr. Schöneich pointed to Chemical Stability of Pharmaceuticals (PTX-390). (Id. at 11–14.) In defending the value of accelerated testing data, Helsinn submitted a letter from DRL to the FDA (PTX-599) requesting a two-year stability label based in part on accelerated testing data. (Dkt. 185 at 162–64.)

Dr. Schöneich discussed accelerated studies that monitored the percent of palonosetron remaining in a formulation at a wide range of temperatures, including room

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is not difficult for a POSA, but said that designing the study and analyzing the samples requires a lot of work. (Id. at 154–55.)

temperature, and with various concentrations of palonosetron. (Dkt. 228 at 58–59, 72–73.) According to Dr. Schöneich, these studies demonstrated stable formulations. (Id. at 62–63, 71.) The studies indicated to Dr. Schöneich that EDTA was not critical to achieve stability because the studies demonstrated stable formulations that did not contain EDTA. (Id. at 67, 73.) Dr. Schöneich also pointed to pre-2003 Helsinn experimental real-time data (PTX-239; PDX-728) showing that 0.05 mg/mL palonosetron formulations showed relatively little degradation even at a pH of 7.4 and without EDTA. (Id. at 105–07.)[40]

Dr. Schöneich opined that a POSA would "readily" be able to practice the claimed inventions and make a stable palonosetron formulation based on the specification disclosures:

> The POSA would prepare the formulation starting with .25 milligrams of palonosetron in a 5-milliliter vial as asserted in the claims and identified in the specification. The POSA can then simply use pH adjusters and a buffer in an appropriate amount to maintain the claimed pH at pH 5. The POSA can then add a tonicity modifying agent such as mannitol in an appropriate amount, and, ultimately, sterilize the formulation.

(Id. at 78–80.) The POSA could use the optimal levels and concentration disclosed in the '351 application to achieve this. (Id. at 81.)

[40] Dr. Schöneich was asked on direct examination by Helsinn about the stability testing results of certain DRL formulations, including DRL's 505(b)(2) formulation. Counsel for DRL moved to strike that portion of testimony, arguing that the parties had agreed there would be no expert testimony on that topic during the invalidity trial, but the topic could be covered in post-trial submissions. The Court reserved on that motion to strike. (Dkt. 228 at 108–10.) We do not rely on the challenged testimony in reaching our conclusions on DRL's invalidity claims, so we will treat that motion to strike as moot.

According to Dr. Schöneich, a POSA would only choose from a limited amount of buffers and tonicity agents in preparing the formulation.[41] (Id. at 79–80.) The patent provides guidance that limits the number of excipients a POSA might choose. (Id. at 178.) Dr. Schöneich noted that the '351 application specified a citrate buffer as the preferred buffer, and mannitol as the preferred tonicity agent. (Id. at 79–80.) Replacing one buffer with another buffer would only require routine experimentation by a POSA, according to Dr. Schöneich. (Id. at 179.)

Dr. Schöneich stated that a POSA would easily be able test with routine experimentation whether a formulation that fell within the scope of the claims was stable at room temperature at 24 months. (Id. at 83.) Dr. Schöneich disagreed with Dr. Broadhead's assessment that a POSA would have needed to test thousands of samples to confirm 24-month stability of the claimed formulations. (Id. at 84.) Dr. Schöneich acknowledged that a POSA starting without the guidance of the '351 application would have needed to engage in more testing, but explained that the '351 application provided detailed information that reduced the need for broad experimentation. (Id. at 95.)

Dr. Schöneich explained that Example 4 of the '351 application referenced 18-month or 24-month stability at room temperature, and a POSA would have understood this to indicate that there was experimental data supporting the stability of the claimed formulations, even though the data was not explicitly detailed in the specification. (Id. at 96–97, 136.)

[41] Dr. Broadhead acknowledged that there is a relatively narrow range of excipients acceptable for use in an intravenous formulation. (Dkt. 185 at 128.)

Dr. Schöneich summarized his conclusions regarding enablement:

- "The specification enables a POSA to make and use the full scope of the claimed formulations."
- "The specification discloses stable 0.05 milligram per milliliter palonosetron formulations."
- "A POSA could make the full scope of the claimed formulations based on the teachings in the specification and common knowledge of pharmaceutical excipients."
- "A POSA could confirm the inherent stability of the claimed formulations with only routine experiments."

(Id. at 110–11.)

4. Findings of Fact and Conclusions of Law

Based on the evidence and testimony presented, we make the following findings of fact and conclusions of law regarding enablement.

The asserted claims (claims 22, 23, 24, and 25 of the '094 patent and claims 1, 2, 3, 4, 5, and 16 of the '980 patent) each require 0.05 mg/mL of palonosetron in a 5 mL sterile aqueous solution, with certain types of excipients, such as buffers and tonicifying agents. ('094 patent col. 11, line 18 to col. 12, line 15; '980 patent col. 9, line 47 to col. 10, line 12.) A POSA could have made a 5 mL aqueous solution containing 0.05 mg/mL of palonosetron. (Dkt. 228 at 78–80.) A POSA could also have made a 5 mL palonosetron formulation containing common buffers and tonicifying agents. (Id.)

To make the claimed formulations, a POSA would have begun by looking at the specification from the '351 application and what it taught. (Dkt. 185 at 139, 141–42.) To prepare the 18-month (claim 16 of the '980 patent) and the 24-month (claims 22, 23, 24, and 25 of the '094 patent and claims 1, 2, 3, 4, and 5 of the '980 patent) stable

palonosetron formulations, a POSA would have started with the claimed palonosetron concentration, preferred excipients, concentrations, and pH ranges from the '351 application's teachings. (Dkt. 228 at 81.)

The '351 application discloses: the optimal pH level (pH 5.0), the preferred chelating agent (0.5 mg/mL EDTA), the preferred buffering agent (20 mM citrate buffer), and the preferred tonicifying agent (41.5 mg/mL mannitol). (Id. at 81–82.) Example 4 discloses these preferred concentrations. (PTX-63 at 11.) A POSA could have made formulations with this pH and these excipients. (Dkt. 228 at 81–82.)

Based on the '351 application's disclosure, a POSA could have made other formulations with the requisite 18-month or 24-month stability. A POSA could have made a 5 mL sterile aqueous solution containing 0.05 mg/mL of palonosetron that met each requirement of the asserted claims. (Id. at 80–81.) Based on the '351 application, a POSA could have modified the optimal excipients and pH range to make other stable palonosetron formulations within the scope of the asserted claims. (Id. at 79–81.) To do so, a POSA would have used standard references to identify common pharmaceutical excipients, the universe of which that have a prior history of use in intravenous formulations is limited. (Dkt. 185 at 128, 150; dkt. 228 at 79–80.) A POSA would have chosen from a limited number of tonicifying agents as a replacement for mannitol that would comport with the scope of claim 1 of the '980 patent, which requires a tonicifying agent in an amount sufficient to make the solution isotonic. ('980 patent col. 10, lines 2–4; dkt. 228 at 80.) A POSA would have known to select an appropriate buffer to maintain an aqueous solution of palonosetron with a pH of about 5.0 to stay within the

scope of the asserted claims of the '094 patent and claim 2 of the '980 patent, which require the solution to be buffered at a pH of about 5.0 ± 0.5. ('094 patent col. 11, lines 18–23; '980 patent col. 10, lines 5–6; dkt. 228 at 79.)

Routine experiments would have allowed a POSA to confirm the stability of these formulations. (Dkt. 228 at 10–11.) Stability studies are done "commonly" and "quite regularly" and would be a routine task for a POSA. (Dkt. 185 at 154.) As Dr. Broadhead explained, the "physical execution of setting up and doing a stability study is not difficult, but there's a lot of work to do in designing the study and analyzing the samples from the study and analyzing the results of the study." (Id. at 154–55.)

Real-time stability testing involves storing a product under recommended storage conditions and monitoring the product over the course of its shelf life. (Dkt. 228 at 10.) A POSA would generally use 24 months as a common target shelf life, and 24 months therefore is the common length of a real-time stability study. (Dkt. 185 at 155; dkt. 228 at 10, 44.) A real-time study would not have been a labor-intensive or time-consuming task for a POSA. (Dkt. 185 at 155; dkt. 228 at 11, 83–87.) Stability studies can be machine automated. (Dkt. 228 at 11, 86–87.) A POSA would not have to repeatedly test samples of a formulation over the 24-month period. During this period, according to Dr. Broadhead, a POSA would have had to test samples seven or eight times. (Dkt. 185 at 155.) Dr. Schöneich testified that to learn about 24-month stability, only two measurements were required—at the initiation of the storage and at the 24-month period. (Dkt. 228 at 11, 86.)

A POSA would not have needed to make and test an unduly burdensome number of formulations in order to practice the claimed inventions. (Id. at 84–85.) The '351 application would have directed a POSA where to begin developing stable palonosetron formulations. (Id. at 78–85.) As Dr. Broadhead testified, a POSA would generally not use unnecessary excipients in a formulation. (Dkt. 185 at 150–51.)

Weighing the relevant Wands factors, we conclude that the totality of this evidence does not support a finding that undue experimentation would be necessary to practice the asserted claims. See Wands, 858 F.2d at 737. With respect to factor 4, the nature of the invention requires shelf-life stability at 18 months (claim 16 of the '980 patent) and 24 months (claims 22, 23, 24, and 25 of the '094 patent and claims 1, 2, 3, 4, and 5 of the '980 patent). The asserted claims are broad in scope as they cover a range of formulations (factor 8). But the '351 application and Example 4 provide sufficient direction and guidance to teach a POSA to practice the full scope of the formulations (factors 2 and 3). The '351 application discloses stable 0.05 mg/mL palonosetron formulations. The '351 application teaches that formulations with this optimal palonosetron concentration have the claimed 18-month and 24-month shelf stability. The '351 application also teaches that specific categories of excipients may be used to improve upon that stability. Thus, based on the '351 application, we find that a POSA would have been able to practice the full scope of the claimed inventions without extensive experimentation (factor 1). A POSA may need to perform routine stability studies to confirm that the formulations possessed the requisite 18-month or 24-month shelf-life stability but such testing does not rise to the level of undue experimentation.

See Cephalon, Inc. v. Watson Pharms., Inc., 707 F.3d 1330, 1338 (Fed. Cir. 2013) ("[E]xtensive experimentation does not necessarily render the experiments unduly extensive where the experiments involve repetition of known or commonly used techniques.").

We conclude that DRL has failed to meet its burden of demonstrating, by clear and convincing evidence, that the '351 application and the asserted patents do not adequately disclose to a POSA how to practice the asserted claims (claims 22, 23, 24, and 25 of the '094 patent and claims 1, 2, 3, 4, 5, and 16 of the '980 patent) without undue experimentation. See Alcon Research, 745 F.3d at 1189–90. Therefore, the asserted claims are not invalid for lack of enablement.

B. Written Description

1. Legal Standards

A patent specification must contain "a written description of the invention." 35 U.S.C. § 112(a). "[T]he specification must describe an invention understandable to [a POSA] and show that the inventor actually invented the invention claimed." Ariad Pharms., Inc. v. Eli Lilly & Co., 598 F.3d 1336, 1351 (Fed. Cir. 2010). "The purpose of the written description requirement is to prevent an applicant from later asserting that he invented that which he did not." Amgen Inc. v. Hoechst Marion Roussel, 314 F.3d 1313, 1330 (Fed. Cir. 2003). The requirement thus mandates that the applicant "recount his invention in such detail that his future claims can be determined to be encompassed within his original creation." Vas-Cath Inc. v. Mahurkar, 935 F.2d 1555, 1561 (Fed. Cir. 1991).

The "hallmark of written description is disclosure." Ariad, 598 F.3d at 1351. The disclosure must "allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described." Enzo Biochem, Inc. v. Gen-Probe Inc., 323 F.3d 956, 968 (Fed. Cir. 2002). "There is no rigid requirement that the disclosure contain 'either examples or an actual reduction to practice'; the proper inquiry is whether the patentee has provided an adequate description that 'in a definite way identifies the claimed invention' in sufficient detail such that a person of ordinary skill would understand that the inventor had made the invention at the time of filing." Allergan, Inc. v. Sandoz Inc., 796 F.3d 1293, 1308 (Fed. Cir. 2015) (quoting Ariad, 598 F.3d at 1352).

The analysis for adequate written description is an objective inquiry "into the four corners of the specification." Ariad, 598 F.3d at 1351.

The challenging party must show lack of adequate written description by clear and convincing evidence to rebut the patent's presumption of validity. Alcon Research, 745 F.3d at 1188.

2. Parties' Arguments

DRL argues that the asserted claims are invalid for lack of adequate written description because the narrow specifications in the patents do not show that the inventor was in possession of the broad scope of stable formulations in the asserted claims. According to DRL, the asserted claims have a broader scope than, and are not fully supported by, what is described in the narrow specifications of the '094 and '980 patents. (Dkt. 199 at 123, 163.) These specifications solely provide one optimized formulation, but do not teach what modifications, if any, would also yield 18-month or 24-month

stability in other formulations covered by the asserted claims. (Id. at 159–60.) DRL contends that the specifications fail to show that the inventor was in possession of a broad range of formulations—with a functional requirement of 18-month or 24-month stability—that parallel the scope of the claims. (Id. at 159.)

Per DRL, the claims require a specific shelf life of 18 or 24 months, but the patents do not describe to a POSA formulations across the full scope of the claims that have this level of stability. (Id. at 123.) The '980 and '094 patents do not show which formulations would be stable for 18 or 24 months and which would not be. (Id. at 123–24.) DRL's expert, Dr. Broadhead, testified that the '980 and '094 patents teach that EDTA and citrate, and their concentrations, are critical to the stability of the product. (Id. at 124.) But the patents do not teach a POSA how to obtain the 18-month or 24-month stability across all formulations that include various concentrations of those excipients covered by the asserted claims. (Id. at 125.)[42] Example 4 of the '351 application discloses one optimized intravenous formulation, but although the FDA has approved this formulation for more than 24 months of stability under specified conditions, the patents do not state the particular shelf life of this formulation. (Id. at 123.) Even though the asserted claims cover formulations beyond Example 4, DRL argues that the '980 and '094 patents do not show that the inventor possessed other formulations that modify or differ from the formulation in Example 4 while also retaining the 18-month or 24-month

[42] Helsinn argues that this Court should discount Dr. Broadhead's testimony because by her own admission, she did not apply the correct burden of proof ("clear and convincing evidence") when opining on written description and enablement. (Dkt. 200-1 at 14.) We, however, have applied that burden of proof, and have evaluated her expert testimony accordingly.

stability, nor do the patents describe what changes to the formulation in Example 4 would still yield 18-month or 24-month stability. (Id. at 123–24.)

Helsinn contends that DRL has failed to meet its burden of demonstrating that the challenged claims are invalid by clear and convincing evidence. (Dkt. 200-1 at 19–21.) According to Helsinn, the '351 application makes clear that the patents are directed at shelf-stable palonosetron formulations, and the '351 application explicitly disclose the stability of various formulations. Specifically, the '351 application discloses 0.05 mg/mL palonosetron formulations that have 18-month and 24-month stability at room temperature. (Id. at 22.) Because the '351 application can be relied upon to meet the written description requirements for the'094 and '980 patents, the specifications can support a POSA's understanding that 0.05 mg/mL palonosetron formulations are stable at room temperature for 18 and 24 months. (Id. at 23.)[43]

[43] Helsinn argues that the 18-month or 24-month stability is an inherent property of the formulation, and therefore, under Allergan, stability data does not need to be explicitly disclosed in the specification. (Dkt. 200-1 at 23.) According to Helsinn, this provides an independent basis for the Court to reject DRL's argument of invalidity for lack of written description. (Id.) Specifically, Helsinn relies on Allergan for the principle that "[a] claim that recites a property that is necessarily inherent in a formulation that is adequately described is not invalid as lacking written description merely because the property itself is not explicitly described." Allergan, 796 F.3d at 1309.

Dr. Schöneich, Helsinn's expert, testified that that when a vial is stored, "it will have a certain stability" and "[t]hat stability will be the same of the same vial that's made with the same ingredients and stored in the same conditions anywhere else." (Dkt. 228 at 8.) Further, in a prior ANDA action, DRL acknowledged that "[t]he stability of a formulation is an inherent property and/or characteristic of that formulation that is governed by the particular makeup of formulation components, concentrations, and conditions." (PTX-595 at 53.)

In Allergan, the Federal Circuit noted that the claims "recite clinical profile limitations and the specifications do not explicitly describe the clinical efficacy and hyperemia profile of the claimed formulation." 796 F.3d at 1309. With respect to the patent at issue, the challenging parties had acknowledged that the "inherent properties of [the] formulation" produced the clinical profile the patent-holder claimed and "the effects *necessarily* result[ed]" from the formulation. Id. DRL has made no such explicit concession here, and continues to dispute whether stability is an inherent property of the formulation. (Dkt. 217 at 36.)

3. Summary of Evidence

(i) DRL's Evidence

Dr. Broadhead stated that her understanding of the written description requirement is whether the disclosure allows "a POSA to recognize that the inventor invented what is claimed across the scope of the claim." (Dkt. 185 at 24.) Dr. Broadhead explained that, in her opinion, the asserted claims lack adequate written description. (Id. at 22.)

Dr. Broadhead identified that the '980 and '094 patents discussed discoveries that enable shelf-stable formulations for periods greater than 24 months. (Id. at 25.) But the summary of invention does not identify any specific formulation that had 24-month stability. (Id.) The original patent application discussed shelf-stability for periods greater than 18 months (which was later changed to 24 months), and Dr. Broadhead stated this would have indicated to a POSA the inventors did not at the time have stability data for greater than 24 months. (Id. at 25–28.)

Dr. Broadhead opined that the '980 patent would have indicated to a POSA that the pH and the excipient concentrations (the citrate, EDTA, and mannitol) influence the stability of a palonosetron formulation. (Id. at 29–32, 36.) Dr. Broadhead explained that

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The Federal Circuit suggested that a patent will not be invalid for lack of adequate written description if the specification does not explicitly describe a claimed property when that property is a necessary result of the described formulation. Because the question of whether the property was inherent was not factually disputed in Allergan, the Federal Circuit did not provide guidance on what qualifies as an inherent property of a formulation and what showing must be made to satisfy a court of the inherent property.

As discussed infra, we conclude that DRL has failed to show by clear and convincing evidence that the patents do not provide an adequate written description for the full scope of the claims. Thus, we do not address the factual question of whether stability is an inherent property of the formulation and the legal question of, if stability is an inherent property, whether that would provide an independent basis to reject DRL's challenge to the claims for lack of written description.

adding too much citrate buffer to a formulation could negatively impact the shelf-life stability of a formulation. (Id. at 78, 80.)

According to Dr. Broadhead, Example 2 of the '980 patent would have indicated to a POSA that EDTA and citrate were more important factors in stability than the palonosetron concentration and the pH level. (Id. at 32–33.) Dr. Broadhead testified that Example 2 is the only instance in the '980 patent where the concentration of palonosetron is discussed in connection with stability. (Id. at 33.) She opined that the patent identifying the optimal concentration of palonosetron relates to the dose, and not to stability. (Id. at 34.) According to Dr. Broadhead, palonosetron concentration is never mentioned in the patent as the only factor relevant to stability or as the most important factor. (Id. at 35.)

In Dr. Broadhead's opinion, there are conceivably thousands of different possible formulations that share the features of claim 1 of the '980 patent. (Id. at 55.) Dr. Broadhead said that a POSA would not have been able to tell from reading the '980 patent which of these broad range of possible formulations have either 18-month or 24-month stability. (Id. at 56.) The only formulation, according to Dr. Broadhead, with known stability is Example 4 of the '351 application, and even there, the patent does not explicitly list stability information.[44] (Id.) There is no indication, according to Dr. Broadhead, what the stability of the formulation in Example 4 would be if either the EDTA or citrate were removed. (Id. at 195.)

[44] Dr. Broadhead acknowledged that this formulation is known to be stable. (Dkt. 185 at 56.)

Dr. Broadhead concluded that the asserted claims lack adequate written description because each claim has a stated requisite shelf life but the patent does not show a POSA how to make a formulation that has that specific shelf life across the scope of the claims. (Id. at 106.) Thus, it would not have been clear to a POSA in 2003 that the inventors were in possession of formulations across the full scope of the claims. (Id. at 108–09.)

(ii) Helsinn's Evidence

Dr. Schöneich explained his understanding of the written description requirement as whether the specification reasonably conveys to a POSA that the inventors were in possession of the formulation as of January 30, 2003 (the priority date of the '351 application). (Dkt. 228 at 6, 22.) Dr. Schöneich noted that there were "some minor differences" between the disclosure in the '351 application and the specification of the '094 and '980 patents-as-issued, but the differences were not germane to his expert opinion. (Id. at 24.)

Dr. Schöneich opined that a POSA would have understood the '351 application as the inventors seeking to increase the shelf-life stability of a palonosetron formulation and actually achieving that goal for all formulations included in the specification. (Id. at 30–31.) The '351 application does not specifically state that a formulation is stable at 24 months when stored at room temperature. (Id. at 35.) Dr. Schöneich opined, however, that a POSA would have understood that the conclusions stated there—that the formulations of the invention were stable at room temperature for periods greater than 18 months but not exceeding 36 months—were supported by experimental data of stability

testing at room temperature for those time periods.[45] (Id. at 35–39.) Dr. Schöneich also agreed with Dr. Broadhead, who acknowledged that Helsinn had 36 months of actual real-time stability testing of the Example 4 formulation at room temperature in 2002 but did not disclose the data results in the '351 application. (Id. at 104.) Dr. Schöneich also referred to underlying experimental data, not set forth in the '351 application but documented in the inventors' pre-application formulation studies, showing stability of the claimed low concentration of palonosetron (0.05 mg/mL), with and without EDTA and citrate buffers. (Id. at 56–75.) Although that data was derived from standard accelerated testing procedures, Dr. Schöneich opined that a POSA would have concluded that the claimed formulations were stable at room temperature at 24 months. (Id.)

Dr. Schöneich testified that all of the ingredients for the formulation in the claims of the '094 parent were disclosed in the '351 application. (Id. at 25.) According to Dr. Schöneich, Dr. Broadhead believed that the 24-month stability in the '094 patent lacks

[45] Dr. Schöneich testified:

Q. Do you also recall Dr. Broadhead testifying that the '351 specification does not disclose any numerical stability data?

A. Yes, I recall that.

Q. And what is your reaction to Dr. Broadhead's testimony?

A. Well, the '351 application includes conclusions which in my opinion are based on experimental data; otherwise, there wouldn't be conclusions in that application.

Q. And, specifically, what type of experimental data would a POSA understand to have been performed to support the conclusions you're referring to?

A. Stability experiments at room temperature.

Q. And for what duration of time?

A. For greater than 18 months and up to 36 months.

(Dkt. 228 at 37–38.)

support in the '351 application. (Id. at 27.) Dr. Schöneich disagreed with Dr. Broadhead because the abstract of the '351 application states that the invention related to shelf-stable liquid formulations of palonosetron, which according to Dr. Schöneich, would have indicated to a POSA that the inventors made shelf-stable liquid formulations of palonosetron. (Id. at 20–21.) Dr. Schöneich disagreed with Dr. Broadhead's assessment that formulating palonosetron in liquid formulations is not easily accomplished because of shelf-stability issues. (Id. at 29.) Instead, Dr. Schöneich opined that the claimed formulations would have given sufficient guidance to the POSA to achieve the requisite stability. (Id.)

Example 2 of the '351 application, according to Dr. Schöneich, would have disclosed to a POSA that the palonosetron concentration is a "critical factor" for stability and that concentrations of citrate buffers and EDTA can affect the stability of the formulation.[46] (Id. at 39–40.) Dr. Schöneich did not agree with Dr. Broadhead that the '351 application disclosed EDTA and citrate buffer to be "critical" for achieving the claimed levels of stability. (Id. at 41, 132–33.) Dr. Schöneich relied on Claim 4 of the '351 application, which required 0.05 mg/mL of palonosetron and no other buffer, as evidence that the inventors achieved the requisite stability without EDTA and citrate buffer. (Id. at 41–42, 48–49.) Dr. Schöneich noted that citric buffer could improve stability without being a necessary "critical" factor for stability, for example, by adding

[46] Dr. Broadhead acknowledged that Example 2 referred to palonosetron concentration as a "critical factor in chemical stability." (Dkt. 185 at 126.)

citric buffer to a formulation that was already stable in order to further increase the existing stability. (Id. at 138, 185.)

Dr. Schöneich explained that the inventors further disclosed in the '351 application that it was possible to increase the stability of the palonosetron formulations by adjusting the pH and/or the excipient concentrations of the formulations. (Id. at 45.) For example, according to Dr. Schöneich, the '351 application discloses that the optimal pH is 5.0, but the formulation could be stable within a pH range of 4.5 to 5.5. (Id. at 46.) Additionally, Dr. Schöneich explained that the '351 application discloses that mannitol, in an amount between 40 and 45 mg/mL, could further increase the stability of the formulation. (Id. at 47–48.)

Dr. Schöneich testified that a POSA would have understood Example 4, the Aloxi® formulation, to be the formulation with the most optimal concentrations of palonosetron and excipients. (Id. at 49.) Dr. Schöneich believed that the asserted claims in patents '094 and '980 covered Example 4. (Id. at 50.)

Dr. Schöneich explained that "stability is an inherent property of a formulation." (Id. at 7–8.) He reasoned that the stability of the formulation—made with the same ingredients and stored in the same conditions—would always be the same. (Id. at 8.)

Dr. Schöneich made the following conclusions regarding written description:

- "The specification reasonably conveys possession of .05 milligram per milliliter formulations having 24-month stability."
- "All the components of the claimed formulations are sufficiently disclosed."
- "The '351 application adequately supports the 18- and 24-month stability limitation of the asserted claims."

- "The '351 application discloses .05 milligram per milliliter palonosetron formulations with pharmaceutically acceptable carriers having the required stability."

- "[T]he '351 application discloses optionally adjusting pH and excipients to further increase stability."

(Id. at 51–52.)

4. Findings of Fact and Conclusions of Law

Having considered all the evidence and testimony presented by the parties, the Court makes the following findings of fact and conclusions of law regarding written description.

The specification of the '351 application discloses each component of the formulations set forth in the asserted claims (i.e., claims 22, 23, 24, and 25 of the '094 and claims 1, 2, 3, 4, 5, and 16 of the '980 patent). (PTX-63 at 7–8; dkt. 228 at 25–27)

The asserted claims of the '094 and '980 patents cover formulations with a 0.05 mg/mL palonosetron concentration.

Each asserted claim of the '094 patent is directed to a method of administering intravenously a single-use, unit dose formulation containing 0.05 mg/mL palonosetron hydrochloride in a 5 mL sterile aqueous isotonic solution, buffered at a pH of about 5.0 ± 0.5, and with a tonicifying amount of mannitol. ('094 patent col. 11, line 18 to col. 12, line 15; dkt. 228 at 25.) Each asserted claim of the '094 patent requires a formulation that "is stable at 24 months when stored at room temperature." ('094 patent col. 12, lines 3–4.)

The asserted claims of the '980 patent require a pharmaceutical single-use, unit dose formulation for intravenous administration containing 0.05 mg/mL palonosetron

hydrochloride in a 5 mL sterile aqueous solution and a tonicifying agent in an amount to make the solution isotonic. ('980 patent col. 9, line 47 to col. 10, line 12; dkt. 228 at 26) The dependent claims of the '980 patent (claims 2, 3, 4, and 5) additionally require that the solution be buffered at a pH of about 5.0 ± 0.5, and that the tonicifying agent be mannitol (specifically 41.5 mg/mL of mannitol). ('980 patent col. 10, lines 5–12; dkt. 228 at 27.) Claims 1 through 5 of the '980 patent require a formulation that "is stable at 24 months when stored at room temperature." ('980 patent col. 10, lines 3–4.) Claim 16 of the '980 patent requires a formulation that "is stable at 18 months when stored at room temperature." ('980 patent col. 10, lines 51–52.)

The '351 application explains that "formulating palonosetron in liquid formulations has not proven an easy task, typically due to shelf-stability issues." (PTX-63 at 2; dkt. 228 at 29.) A stated objective of the '351 application was thus disclosure of stable palonosetron formulations. (PTX-63 at 3; dkt. 228 at 30–31.) ("[T]here exists a need for a palonosetron formulation with increased stability and thereby increased shelf life.") The abstract of the '351 application states that the invention relates to achieving "shelf-stable liquid formulations of palonosetron." (PTX-63 at 20; dkt. 228 at 27–28.) Another stated objective was to identify "an acceptable range of concentrations," including the concentration of palonosetron, which would stabilize palonosetron formulations. (PTX-63 at 3; dkt. 228 at 38–39.)

The "Summary of the Invention" section of the '351 application states, in part: "The inventors have made a series of discoveries that support a surprisingly effective and versatile formulation for the treatment and prevention of emesis using palonosetron.

These formulations are shelf stable for periods greater than 18 months at room temperature, and thus can be stored without refrigeration . . . ." (PTX-63 at 4.) This would indicate to a POSA that the inventors achieved the disclosed stability objective, and that the formulations are shelf stable at room temperature at 18 and 24 months. (Dkt. 228 at 31–32.) A POSA would have recognized that "[t]hese formulations," which the summary discusses, refers to all the formulations in the '351 application. (Id.)

The '351 application discloses that "the inventors have discovered that formulations of the present invention allow storage of the product for extended periods at room temperature," including for "one month, 3 months, 6 months, one year, 18 months, or more (but preferably not exceeding 36 months)." (PTX-63 at 9; dkt. 228 at 33–35.) A POSA would have known that the formulations would have shelf stability during these time periods of storage, and that there would be no reason to store a formulation for a period up to 36 months unless that formulation was stable for that entire period. (Dkt. 228 at 35.)

The '351 application further discloses that formulations with a 0.05 mg/mL palonosetron concentration are stable at room temperature for 18 and 24 months. (PTX-63 at 7, 10, 13; dkt. 228 at 38–43.) The application indicates that "most optimally" for stability, the concentration of palonosetron is about 0.05 mg/mL. (PTX-63 at 7; dkt. 228 at 37–38.) "[O]ne particular embodiment" identified by the '351 application was 0.25 mg of palonosetron supplied in a vial comprising 5 mL of solution. (PTX-63 at 7; dkt. 228 at 43.)

Example 2 of the '351 application discloses that a "critical factor" for stability is the palonosetron concentration of the formulation. (PTX-63 at 10; dkt. 228 at 39–40.) The "greatest stability" was "seen at the lowest palonosetron concentrations." (Id.) 0.05 mg/mL was the lowest concentration tested in Example 2. (PTX-63 at 10.) The '351 application discloses that for stability, the most optimal palonosetron concentration is the lowest one, which DRL's expert Dr. Broadhead acknowledged. (Dkt. 185 at 126.)

Claim 4 of the '351 application discloses a formulation that requires a 0.05 mg/mL palonosetron concentration, in a pharmaceutically acceptable carrier, and no additional ingredients. (PTX-63 at 13; dkt. 228 at 42–43.) A POSA would recognize that this would be stable at room temperature at 18 and 24 months. (Dkt. 228 at 42–44.)

The '351 application demonstrates that a range of stable formulations with differing concentrations of excipients and embodiments was envisioned. (Id. at 37–38.)

The '351 application discloses stable formulations where adjustments to the pH and/or the excipient concentrations increase the stability of the palonosetron formulations. (PTX-63 at 7) ("The inventors have further discovered that by adjusting the formulation's pH and/or excipient concentrations it is possible to increase the stability of palonosetron formulations.") A POSA would have understood from this disclosure that the stability of formulations containing optimal palonosetron concentrations could be increased further by modifying other aspects of the formulation. (Dkt. 228 at 45.) Dr. Broadhead acknowledged that a POSA would have understood that the stability could be influenced by pH and certain excipients, such as citrate buffer. (Dkt. 185 at 36–37.)

The ’351 application discloses “alternative embodiments” leading to stable palonosetron formulations with an “optimal[]” pH at 5.0, but within the range of 4.5 to 5.5. (PTX-63 at 7; dkt. 228 at 46.)

Citrate buffer and specific pH ranges are set forth as alternate embodiments that increase stability further. (PTX-63 at 7–8; dkt. 208 at 45, 49.) A POSA would have understood these as not necessary for obtaining the claimed stability of 18 months and 24 months. (Dkt. 228 at 45, 49.)

The ’351 application teaches that adding mannitol and a chelating agent could increase the stability of the palonosetron formulations. (PTX-63 at 8; dkt. 228 at 47–48.) A POSA would have recognized that a 0.05 mg/mL palonosetron formulation with mannitol is an embodiment with increased stability over a concentration without mannitol. (Dkt. 228 at 48.)

We have considered the arguments and evidence presented by DRL and the countervailing arguments and evidence by Helsinn, and find that Helsinn’s evidence is more persuasive on the matter of written description. The ’351 application discloses to a POSA a range of 0.05 mg/mL palonosetron formulations that are stable at room temperature for 18 and 24 months. These formulations include stable embodiments containing 0.05 mg/mL palonosetron and a tonicifying agent, and 0.05 mg/mL palonosetron and mannitol with the formulation adjusted to the optimal pH range. We conclude that DRL has failed to meet its burden of demonstrating, by clear and convincing evidence, that the asserted claims lack adequate written description of the claimed stability limitation. See Enzo Biochem, 323 F.3d at 963 (“Compliance with the

written description requirement is essentially a fact-based inquiry that will necessarily vary depending on the nature of the invention claimed." (internal quotation marks omitted)).

IV. Conclusion

For the reasons discussed in Section II, we find that DRL's Accused Product infringes claim 9 of the '724 patent, claim 27 of the '980 patent, and claim 6 of the '980 patent. For the reasons discussed in Section III, we also find that claims 22, 23, 24, and 25 of the '094 patent and claims 1, 2, 3, 4, 5 and 16 of the '980 patent are not invalid for lack of enablement or lack of written description.

s/ Mary L. Cooper
MARY L. COOPER
United States District Judge

Dated: February 14, 2017