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Paper 7
Entered: November 28, 2017

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

TARO PHARMACEUTICALS U.S.A., INC.,
Petitioner,

v.

APOTEX TECHNOLOGIES, INC.,
Patent Owner.

Case IPR2017-01446
Patent 7,049,328 B2

Before LORA M. GREEN, JEFFREY N. FREDMAN, and ZHENYU YANG, *Administrative Patent Judges.*

FREDMAN, *Administrative Patent Judge*.

DECISION
Institution of *Inter Partes* Review
37 C.F.R. § 42.108

I. INTRODUCTION

A. Background

Taro Pharmaceuticals U.S.A., Inc. ("Petitioner") filed a Petition (Paper 2, "Pet.") requesting an *inter partes* review of claims 1–17 and 19 (the "challenged claims") of U.S. Patent No. 7,049,328 B2 (Ex. 1001, "the '328 patent"). *See* 35 U.S.C. §§ 311–319. Apotex Technologies, Inc. ("Patent Owner") filed a Preliminary Response. Paper 6 ("Prelim. Resp.").

Institution of an *inter partes* review is authorized by statute when "the information presented in the petition . . . and any response . . . shows that there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. § 314; *see* 37 C.F.R. §§ 42.4, 42.108. For the reasons set forth below, we conclude that Petitioner has established a reasonable likelihood that it would prevail in showing the unpatentability of at least one of the challenged claims of the '328 patent. Therefore, we institute an *inter partes* review for claims 1, 2, and 4–17 and 19 of the '328 patent. [1]

B. Related Proceedings

Petitioner indicates that the '328 patent was asserted in *ApoPharma Inc. v. Taro Pharmaceutical Industries, Ltd.*, No. 2:16-cv-00528 (E.D.Tx.) Pet. 2.

[1] We note that "Apotex has filed a Statutory Disclaimer under 35 U.S.C. § 253(a) in compliance with 37 C.F.R. § 1.321(a) with the United States Patent and Trademark Office for the '328 patent to statutorily disclaim claim 3." Prelim Resp. 8. Therefore, because claim 3 is disclaimed, we dismiss the Petition for *inter partes* review as to claim 3 pursuant to 37 C.F.R. § 42.107(e).

C. The ’328 Patent (Ex. 1001)

The ’328 patent addresses patients who require “regular transfusions of red blood cells” that can result in “widespread iron overload in the patient.” Ex. 1001, 1:27–30. “Iron overload is dangerous since the excessive iron can cause toxic degenerative changes in the heart, liver and endocrine organs.” *Id.* at 1:30–32.

The ’328 patent teaches: “Iron chelators are drugs that enhance the iron excretion. Iron overload is most often treated by the use of the iron chelator desferrioxamine.” *Id.* at 1:52–54. “Recently another iron chelator, deferiprone by oral administration, has been used successfully for removal of iron in thalassemia patients who could not comply with desferrioxamine.” *Id.* at 1:63–66.

The ’328 patent teaches

> data now reveal that iron-induced heart disease occurs even in patients who are compliant with desferrioxamine, and even some of those who do not have high levels of total body iron as assessed by serum ferritin or liver iron concentrations. It has thus become evident that lowering of the total body iron alone is insufficient to protect against iron-induced heart damage.

Id. at 2:48–54. The ’328 patent teaches: “Nowhere is there taught the cardio selective/preferred function of deferiprone in relation to desferrioxamine and/or other chelating agents when administered to patients having iron overload.” *Id*. at 9:40–43.

The ’328 patent teaches the inventors “unexpectedly discovered that deferiprone has a cardio selective/preferred function when compared to desferrioxamine or alternative chelating agents utilized in patients suffering iron overload.” *Id*. at 10:2–5.

D. Illustrative Claims

Of the challenged claims, claims 1, 2, and 4–10 are independent claims of the '328 patent. The remaining challenged claims 11–17 and 19 depend directly from claims 1, 2, and 4–10.[2] Claims 1 and 15 are illustrative of the challenged claims and recite:

> 1. A method of treating iron induced cardiac disease in a blood transfusion dependent patient experiencing an iron overload condition of the heart, said method comprising administering to the patient a therapeutically effective amount of deferiprone or a physiologically acceptable salt thereof sufficient to stabilize/reduce iron accumulation in the heart resulting from being transfusion dependent.
>
> 15. The method of claims **1**, **2**, **3**, **4**, **5**, **6**, **7**, **8**, **9** or **10** wherein the administration frequency to the patient of a dosage amount of deferiprone or a physiologically acceptable salt thereof is daily in the range of 25 mg to 75 mg per kilogram of body weight.

Ex. 1001, 27:3–9, 28:33–37.

E. The Asserted Grounds of Unpatentability

Petitioner contends that the challenged claims are unpatentable based on the following grounds. Pet. 9–10.

Reference	Basis	Claims Challenged
MIMS 1998[3]	§ 102(b)	1, 2, 4–11, 13–17, 19

[2] Claims 18 and 20 were not challenged in this proceeding.
[3] *Monthly Index of Medical Specialties*, Vol. 18, No. 12, December 1998 ("MIMS 1998," Ex. 1009).

Hoffbrand 1998[4]	§ 102(b)	1, 2, 4–11, 13–17, 19
Olivieri Abstract 1995[5]	§ 102(b)	1, 2, 4–11, 13–17, 19
Agarwal 2000[6]	§ 102(b)	1, 2, 4–11, 13–17, 19
Olivieri 1995[7]	§ 102(b)	1, 2, 4–11, 13–17, 19
MIMS 1998	§ 103(a)	1, 2, 4–17, 19
Hoffbrand 1998	§ 103(a)	1, 2, 4–17, 19
Olivieri Abstract 1995	§ 103(a)	1, 2, 4–17, 19
Agarwal 2000	§ 103(a)	1, 2, 4–17, 19
Olivieri 1995	§ 103(a)	1, 2, 4–17, 19

Petitioner relies on the Declaration of Jayesh Mehta, M.D. Ex. 1002. Patent Owner relies upon two Declarations, that of Dr. Thomas D. Coates, M.D., Ex. 2001, and of Dr. Dudley J. Pennell, M.D., Ex. 2003.

II. ANALYSIS

A. Claim Interpretation

In an *inter partes* review, claim terms in an unexpired patent are given their broadest reasonable construction in light of the specification of the patent in which they appear. 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs.*,

[4] Hoffbrand et al., *Long-Term Trial of Deferiprone in 51 Transfusion-Dependent Iron Overloaded Patients*, BLOOD, 91(1):295–300, 1998 ("Hoffbrand 1998," Ex. 1007).
[5] Olivieri et al., *First Prospective Randomized Trial of the Iron Chelators Deferiprone (L1) And Deferoxamine*, Abstract 983: Hemoglobinopathies and Thalassemias II, 249a, PROGRAM OF THE 37TH ANNUAL MEETING OF THE AMERICAN SOCIETY OF HEMATOLOGY, December 1995 ("Olivieri Abstract 1995," Ex. 1010).
[6] Agarwal, *Deferiprone (Kelfer): A Report of 22 Patients Who Have Taken It for over a Decade*, 10TH INTERNATIONAL CONFERENCE ON ORAL CHELATORS IN THE TREATMENT OF THALASSEMIA AND OTHER DISEASES AND BIOMED MEETING, March 2000 ("Agarwal 2000," Ex. 1011).
[7] Olivieri et al., *Iron-Chelation Therapy with Oral Deferiprone in Patients with Thalassemia Major*, N. ENGL. J. MED., 332:918–22, 1995 ("Olivieri 1995," Ex. 1012).

LLC v. Lee, 136 S. Ct. 2131, 2144–46 (2016). Under the broadest reasonable interpretation approach, claim terms are given their ordinary and customary meaning as would be understood by one of ordinary skill in the art in the context of the entire disclosure. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). We determine that the following claim language needs to be discussed.

1. "*a blood transfusion dependent patient experiencing an iron overload condition of the heart*"

Petitioner offers an interpretation of the preamble as limiting "the patient who is to be treated" "as patients with a condition on the spectrum of cardiac disease that includes patients with minor cardiac dysfunction due to iron overload on one end, and patients with severe congestive heart failure due to iron overload on the other." Pet. 20, 23 (citing Ex. 1002 ¶ 60). Patent Owner agrees "the preambles of claims 1–10 should be considered limitations of the claims." Prelim. Resp. 11.

We agree with the parties that the preamble language gives life and meaning to the claims by limiting the patient population being treated to patients dependent on blood transfusions who are "experiencing an iron overload condition of the heart" (Ex. 1001 27:4–5, claim 1). *See Griffin v. Bertina*, 285 F.3d 1029, 1033 (Fed. Cir. 2002) ("Diagnosis is thus the essence of this invention; its appearance in the [claim] gives 'life and meaning' to the manipulative steps."). In both *Griffin* and the instant claims, the manipulative steps are directly related to the preamble limitations.

2. "*therapeutically effective amount*"

Petitioner interprets "'therapeutically effective amount' recited in each of claims 1–10 . . . [to] necessarily include the ranges recited in each of

claims 13, 14, and 15. Claims 1–10 therefore each include a daily dose of, for example, 75 mg of deferiprone per kg of body weight." Pet. 24.

Patent Owner disagrees, and contends "the 'therapeutically effective amount of deferiprone' required by claims 1, 2, and 4–10 varies depending on the desired result." Prelim. Resp. 13. Patent Owner contends the "dosages required by claims 1, 2, and 4–10 can necessarily be broader than those required by claims 13–15. For at least this reason, the disputed limitations are material to their respective claims, and without them there would be no way to assess what amount of deferiprone is required by these claims." *Id*. at 14.

We agree with both Petitioner and Patent Owner's proposed constructions, which overlap in scope and are therefore not mutually exclusive, at this stage of the proceeding on the record before us. The independent claims 1, 2, and 4–10 do not recite a specific "therapeutically effective amount" as noted by Patent Owner and, therefore, reasonably encompass any amounts that are "therapeutically effective" consistent with the remaining limitations of the claims. We also agree with Petitioner, however, that because dependent claims cannot be broader than the claims from which they depend under 35 U.S.C. § 112, fourth paragraph, the recitation of 75 mg per kilogram of body weight in claim 15 necessarily constitutes a value that is a "therapeutically effective amount" as recited in claims 1, 2, and 4–10.

3. *Intended results*

Petitioner contends the "recitations that the administration of deferiprone is 'sufficient' to treat the conditions stated in the preambles (claims 1, 2, 4, and 5) or is intended to produce a particular result (claims 6–

10) do not have patentable weight because they do not alter the steps of the method." Pet. 24. Petitioner relies on *Bristol-Myers* for the proposition "that a recitation of an intended result, 'reduced hematologic toxicity,' was not limiting because the expression 'does not result in a manipulative difference in the steps of the claim.'" Pet. 25, citing *Bristol-Myers Squibb Co. v. Ben Venue Labs.*, 246 F.3d 1368, 1376 (Fed. Cir. 2001). Petitioner contends: "Neither the doctrine of claim differentiation, nor an alleged newly discovered result of a known process, directed to the same purpose as taught by the prior art— to treat iron-overload conditions—render these intended results limitations of the claims." Pet. 27.

Patent Owner contends "the claimed invention is not the mere administration of deferiprone to blood transfusion-dependent patients, but instead the discovery of methods for using deferiprone to *selectively reduce the iron burden on the hearts* of blood transfusion patients, in particular compared to other available iron chelators (*e.g.*, desferrioxamine)." Prelim. Resp. 14–15. Patent Owner contends they "overcame prior art and enablement rejections by explaining at length how the specific results required by claims 1, 2, 4–10, and 19 distinguished the invention over the prior art." *Id*. Patent Owner contends

> the disputed phrase in *Bristol-Myers* was unnecessary to patentability and was only voluntarily added to the claims after the Examiner allowed the claims. ([citing *Bristol-Myers*, 246 F.3d at 1375]) This stands in direct contrast to the allegedly "intended results" of the challenged claims, which, as discussed above, were essential for the claims of the '328 patent to distinguish over the cited prior art.

Id. at 18. Patent Owner contends "under the "new *use* of a known process" standard in *Bristol-Myers*, the disputed claim terms are properly limitations of the claims." *Id*. at 18.

We agree with Petitioner's proposed interpretation that claim language reciting intended results are not limiting at this stage of the proceeding based on the preliminary record currently before us. In particular, claim 1 of the '328 patent recites the intended result of treatment of blood transfusion dependent patients with therapeutically effective amounts of deferiprone "sufficient to stabilize/reduce iron accumulation in the heart." Ex. 1001, 27:8–9.

We compare these facts to the simpler hypothetical in *Catalina*, where the Federal Circuit explained:

> Inventor A receives a patent having composition claims for shoe polish. . . . Suppose Inventor B discovers that the polish also repels water when rubbed onto shoes. Inventor B could not likely claim a method of using the polish to repel water on shoes because repelling water is inherent in the normal use of the polish to shine shoes. . . . In other words, Inventor B has not invented a "new" use by rubbing polish on shoes to repel water.

Catalina Mktg., Int'l v. Coolsavings.com, 289 F.3d 801, 809–10 (Fed. Cir. 2002). Just as the intended result of repelling water is not a new limiting use of shoe polish on shoes in Catalina, the intended results recited in claims 1–10 of treating or reducing iron burden in the heart do not, based on the record currently before us, appear to impose limitations on methods of treatment of blood transfusion patients with deferiprone relative to prior art methods of treatment of the same patient population with the same drug in the same amounts.

B. Principles of Law

A claim is unpatentable under 35 U.S.C. § 102 if a single prior art reference expressly or inherently describes each and every limitation as set forth in the claim. *See Perricone v. Medicis Pharm. Corp.*, 432 F.3d 1368, 1375 (Fed. Cir. 2005); *Verdegaal Bros., Inc. v. Union Oil Co.*, 814 F.2d 628, 631 (Fed. Cir. 1987). "A single prior art reference may anticipate without disclosing a feature of the claimed invention if such feature is necessarily present, or inherent, in that reference." *Allergan, Inc. v. Apotex Inc.*, 754 F.3d 952, 958 (Fed. Cir. 2014) (citing *Schering Corp. v. Geneva Pharm.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003)).

A patent claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the claimed subject matter and the prior art are such that the subject matter, as a whole, would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

In that regard, an obviousness analysis "need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *KSR*, 550 U.S. at 418. In *KSR*, the Supreme Court also stated that an invention may be found obvious if trying a

course of conduct would have been obvious to a person having ordinary skill:

> When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103.

KSR, 550 U.S. at 421. "*KSR* affirmed the logical inverse of this statement by stating that § 103 bars patentability unless 'the improvement is more than the predictable use of prior art elements according to their established functions.'" *In re Kubin*, 561 F.3d 1351, 1359–60 (Fed. Cir. 2009) (citing *KSR*, 550 U.S. at 417).

We are mindful that the level of ordinary skill in the art also is reflected by the prior art of record.[8] *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001); *See In re GPAC Inc*., 57 F.3d at 1579; *In re Oelrich*, 579 F.2d 86, 91 (CCPA 1978).

[8] Patent Owner states that the level of skill in the art at the time of the invention "would include physicians who treated iron overload in patients requiring chronic blood transfusions. . . . Such a person would have had a medical degree and some experience in hematology, cardiology, or a related field." Prelim. Resp. 10, citing Ex. 2001 ¶ 26, Ex. 2003 ¶ 29. Petitioner also states person with ordinary skill in the art "would have had an M.D. and several years of clinical work experience in hematology, and would have had research, clinical, and/or testing experience with iron chelators to treat iron overload in the body, including iron overload of the heart." Pet. 11, citing Ex. 1002 ¶ 41. We, therefore, agree with both parties that the level of ordinary skill in the art includes M.D.'s with clinical experience with iron chelators in treatment of transfusion patients with iron overload. *See* Prelim. Resp. 10, Pet. 11. *In re GPAC Inc.*, 57 F.3d 1573, 1579 (Fed. Cir. 1995).

We analyze the asserted grounds of unpatentability in accordance with the above-stated principles.

C. Anticipation over Mims 1998

Petitioner contends that claims 1, 2, 4–11, 13–17 and 19 are unpatentable under 35 U.S.C. § 102(b) as anticipated by MIMS 1998. Pet. 32–33.

Petitioner asserts that "MIMS 1998 discloses that deferiprone is used to treat transfusion haemosiderosis (Ex. 1009 (MIMS 1998) at 256), which, as Dr. Mehta explains, is iron overload due to blood transfusions"; that "MIMS 1998 also discloses that deferiprone is administered at a dose of 75 mg/kg per day"; and that "MIMS 1998 discloses that deferiprone is used to treat 'iron-storage disease' . . . a broad term that includes iron overload due to transfusion dependency and also includes the entire spectrum of cardiac disease caused by iron overload." Pet. 33–34.

Patent Owner asserts that this ground fails, among other reasons, because "a POSA would have understood 'iron-storage disease' to mean excess total body iron, or excess hepatic iron—not excess iron in the heart." Prelim. Resp. 34 (citing Ex. 2001 ¶ 46). Patent Owner asserts:

> Ex. 1017 refers to cardiac disease (among numerous other conditions) as a "sequelae of iron overload" []—meaning that cardiac disease may result from iron overload, not that cardiac disease *is* an iron storage disease. Further, when discussing haemochromatosis, which is synonymous with "iron storage disease," Ex. 1017 refers to total body iron or hepatic iron, and what, at the time, were general upper limits of hepatic iron that could result in "an increased risk of cardiac disease and early death." (Ex. 1017 at 565.) Thus, while an "iron-storage disease" may eventually lead to excess iron in the heart, the

> treatment of "iron-storage disease" does not inevitably result in treating a patient having an iron overload condition of the heart.

Id. at 34–35. Patent Owner asserts "Taro has not provided any evidence that administering 75 mg/kg of deferiprone yields the claimed results (*i.e.*, is a 'therapeutically effective amount') or that MIMS discloses *any* dose of deferiprone that necessarily yields the claimed results." *Id*. at 36.

1. *MIMS 1998 (Ex. 1009)*

MIMS 1998 teaches, in the context of a pharmacopeia, treatment of diseases including: "Transfusion haemosiderosis, acute iron poisoning, iron overload in liver cirrhosis, diagnosis of iron-storage disease" with deferiprone at doses of "50–100mg/kg body wt. Daily in 2-4 divided doses." Ex. 1009 3, col. 2.

Petitioner's Declarant, Dr. Mehta, states, relying on Exhibit 1017, that a "person of ordinary skill in the art would have known that cardiac disease is an iron storage disease, and is the most common cause of death for untreated iron overload." Ex. 1002 ¶ 73 (citing Ex. 1017, 557–58). Specifically, Exhibit 1017 states:

> The sequelae of iron overload include hepatic fibrosis and cirrhosis, multiple endocrinopathies (diabetes mellitus, hypogonadism, hypoparathyroidism, hypothyroidism), immunological dysfunction, growth and bone abnormalities, short stature, cardiac disease (congestive heart failure, arrhythmias), pulmonary dysfunction and hyperpigmentation of the skin. Progressive organ dysfunction, affecting the heart, liver and endocrine system in particular, ultimately leads to death in the second or third decade of life if left untreated.

Ex. 1017, 557.

Patent Owner's Declarant, Dr. Coates, "disagree[s] with Dr. Mehta that a POSA would understand the terms 'iron-storage disease' and 'cardiac disease' (or iron overload condition of the heart) to be synonymous." Ex. 2001 ¶ 46. Dr. Coates explains "Ex. 1017 teaches that cardiac disease is one of many different conditions that *may* result from iron overload. (Ex. 1017, 557–58.) Therefore, a POSA would not understand Ex. 1017 to teach that a patient with iron-storage disease necessarily has an iron overload condition of the heart." Ex. 2001 ¶ 47. Patent Owner's Declarant, Dr. Pennell, states "a POSA would have understood the term iron-storage disease to refer to liver disease resulting from excess iron." Ex. 2003 ¶ 35.

2. *Analysis*

We find, based on the current evidence of record, MIMS 1998, as supported by Drs. Coates and Pennell, better supports Patent Owner's position that MIMS 1988 does not anticipate claims 1, 2, 4–11, 13–17, and 19 because the evidence does not support Petitioner's position that patients with "iron-storage disease" as discussed in MIMS 1988 necessarily encompasses patients with "an iron overload condition of the heart" or "iron-induced cardiac disease" as required by independent claims 1, 2, and 4–10. "Inherency . . . may not be established by probabilities or possibilities. The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient." *MEHL/Biophile Int'l. Corp. v. Milgraum*, 192 F.3d 1362, 1365 (Fed. Cir. 1999).

Exhibit 1017 identifies a number of different diseases associated with iron storage, and the evidence of record does not demonstrate that any particular patient <u>*necessarily*</u> experiences iron overload of the heart rather than liver, endocrine or other tissues. *See* Ex. 1017, 557. Moreover, both of

Patent Owner's Declarants persuasively explain that the term "iron-storage disease" as used by MIMS 1998 is not necessarily coextensive with cardiac disease. *See* Ex. 2001 ¶ 47, Ex. 2003 ¶ 35. Even Petitioner's Declarant, Dr. Mehta, states that cardiac disease "is the most common cause of death for untreated iron overload," reasonably supporting the position that other, less common, causes of death based on overload of other tissues are encompassed by the phrase "iron-storage disease" in MIMS 1998. *See* Ex. 1002 ¶ 73.

Accordingly, we find that Petitioner has not sufficiently demonstrated a reasonable likelihood that it would prevail on one of claims 1, 2, 4–11, 13–17, and 19 as anticipated by MIMS 1998.

D. Anticipation over Hoffbrand 1998

Petitioner contends that claims 1, 2, 4–11, 13–17 and 19 are unpatentable under 35 U.S.C. § 102(b) as anticipated by Hoffbrand 1998. Pet. 34–36. *See* Prelim Resp. 38–41.

Petitioner asserts "Hoffbrand 1998 discloses the treatment of 'fifty-one iron-overloaded regularly transfused patients' with deferiprone" and "Hoffbrand 1998 discloses administration of deferiprone at a dose of 75 mg/kg per day." Pet. 35 (citing Ex. 1007, 296 and Ex. 1002 ¶ 74). Petitioner further states "Hoffbrand 1998 discloses that ten patients had a liver iron content above 15.0 mg/g dry weight, due to iron overload." *Id*. at 35–36 (citing Ex. 1007, 297 and Ex. 1002 ¶¶ 74–75).

Patent Owner asserts that this ground fails, among other reasons, because "there is a discordance between liver iron content and heart iron content—indeed, heart iron content cannot be predicted from liver iron concentration and heart function (*e.g.*, left-ventricular ejection fraction) is

unrelated to liver iron or serum ferritin concentrations." Prelim. Resp. 39 (citing Ex. 2003 ¶ 51). Patent Owner asserts that:

> Hoffbrand 1998 states that the death of four patients due to cardiac disease implies that "deferiprone is inappropriate therapy for patients with iron-induced cardiomyopathy in whom continuous intravenous DFX [deferoxamine] is needed to cause continuous removal of toxic, nontransferrin-bound iron from plasma." (Ex. 1007 at 299.) A POSA reading this statement would understand that Hoffbrand 1998 is teaching the use of intravenous DFX (not deferiprone) for patients having an iron overload condition of the heart (*e.g.*, iron-induced cardiomyopathy).

Id. at 39–40. Patent Owner further notes Hoffbrand 1988 "was not designed to assess whether deferiprone could reduce cardiac iron levels." *Id*. at 40.

Patent Owner also contends "Hoffbrand 1998 was expressly considered, on numerous occasions, by the Examiner during prosecution of the '328 Patent" and, therefore, "the Office has fully considered the patentability of the '328 patent in view of Hoffbrand 1998." *Id*. at 42.

1. *Hoffbrand 1998 (Ex. 1007)*

Hoffbrand 1998 teaches: "Fifty-one iron-overloaded regularly transfused patients who were unable to take DFX or not compliant with DFX were included in the trial." Ex. 1007, 295. Hoffbrand 1998 teaches "Deferiprone was administered orally in a total daily dose of 75 mg/kg/body weight (range, 50 to 79 mg/kg) at least an hour before food every 8 to 12 hours." *Id*.

Hoffbrand 1998 identifies three types of patients, i) "*Patients withdrawn from long-term therapy*," "*Fatalities during the study*," and "*Patients continuing to take deferiprone*." Regarding fatalities, Hoffbrand 1998 teaches:

> Five patients died, but in none could this be attributed a toxic effect of the drug. In four previously, poorly chelated patients, death was due to cardiac disease induced by iron overload. However, these findings imply that deferiprone is inappropriate therapy for patients with iron-induced cardiomyopathy in whom continuous intravenous DFX is needed to cause continuous removal of toxic, nontransferrin-bound iron from plasma.

Id. at 299.

Regarding patients continuing to take deferiprone, Hoffbrand 1998 teaches: "Five patients had liver iron content between 7.9 and 14.1 mg/g dry weight and the remaining 10 patients had a liver iron content above 15.0 mg/g dry weight, ie, falling within the range that has been associated with cardiac disease." *Id*. at 297.

Petitioner's Declarant, Dr. Mehta, states "Hoffbrand 1998 discloses that ten patients had a liver iron content above 15.0 mg/g dry weight, which falls in the range of iron content that has been associated with cardiac disease due to iron overload," thereby anticipating claims 1, 2, 4–11, 13–17, and 19. Ex. 1002 ¶ 74.

Patent Owner's Declarant, Dr. Coates, states "Hoffbrand 1998 could not have assessed whether 75 mg/kg/day of deferiprone is a therapeutically effective amount . . . because Hoffbrand did not measure cardiac iron levels." Ex. 2001 ¶ 55. Dr. Coates states because "patients died of iron-induced cardiac disease despite deferiprone treatment . . . a POSA would have viewed Hoffbrand 1998 as disparaging the use of deferiprone to stabilize, reduce, or treat iron overload in the heart, including iron-induced heart disease." *Id*. ¶ 56.

Patent Owner's Declarant, Dr. Pennell, states "Hoffbrand 1998 did not measure cardiac iron levels" and "four deaths occurred as a result of

congestive heart failure—despite treatment with 75 mg/kg/day of deferiprone." Ex. 2003 ¶ 36. Dr. Pennell concludes "a POSA would understand that Hoffbrand 1998 teaches the use of desferrioxamine as opposed to deferiprone in patients with cardiac disease." *Id*.

2. Section 325(d) – Discretion to Decline to Institute

Patent Owner urges us to decline to institute this asserted ground under 35 U.S.C. § 325(d) because "Hoffbrand 1998 was expressly considered, on numerous occasions, by the Examiner during prosecution of the '328 Patent" and, therefore, "the Office has fully considered the patentability of the '328 patent in view of Hoffbrand 1998." Prelim. Resp. 42.

Under § 325(d), we have discretion to "reject the petition or request because[] the same or substantially the same prior art or arguments previously were presented to the Office." 35 U.S.C. § 325(d). Considering all of the relevant facts and circumstances, Patent Owner's argument is insufficient to persuade us to exercise our discretion to deny the Petition. Petitioner relies on a declaration from Dr. Mehta, which Patent Owner does not allege is duplicative of evidence previously presented to the Office. *See Tandus Flooring, Inc. v. Interface, Inc*., Case IPR2013-00333, 2013 WL 8595289, at *2 (PTAB Dec. 9, 2013) (Paper 16) (declining to deny petition under § 325(d) where petitioner presented new declaration evidence).

3. Analysis

We find that the current evidence of record in Hoffbrand 1998, as supported by Dr. Mehta, provides a reasonable likelihood that Hoffbrand 1998 anticipates claims 1, 2, 4–11, 13–17, and 19 because the evidence currently of record supports Petitioner's position that at least ten patients

discussed in Hoffbrand 1988 necessarily satisfy the requirement for patients treated with a therapeutically effective amount of deferiprone who had "an iron overload condition of the heart" or "iron-induced cardiac disease" as required by independent claims 1, 2, and 4–10.

In particular, Hoffbrand 1998 teaches patients who continued deferiprone treatment including "10 patients [who] had a liver iron content above 15.0 mg/g dry weight, ie, falling within the range that has been associated with cardiac disease." Ex. 1007, 297. This disclosure evidences that the patients in Hoffbrand 1998 necessarily had iron levels sufficient for iron overload conditions of the heart. *Id*. Hoffbrand 1998 further teaches treatment of those patients with 75 mg/kg of body weight, a dose directly falling within the therapeutically effective range required by dependent claims 13–15. *Id*. at 295, Ex. 1001, 28:23–37. Dr. Mehta affirms that "a liver iron content above 15.0 mg/g dry weight . . . falls in the range of iron content that has been associated with cardiac disease due to iron overload." Ex. 1002 ¶ 74.

These facts align with *Montgomery*, where the Federal Circuit found that a claim to a method for treatment of stroke to a diagnosed patient by administration of ramipril was found anticipated by prior art that taught administration of ramipril to the same patient population. *In re Montgomery* 677 F.3d 1375, 1381–82 (Fed. Cir. 2012). Indeed, because Hoffbrand 1998 actually administered 75 mg/kg of deferiprone to ten patients with iron content "within the range that has been associated with cardiac disease," Ex. 1007, 297, Hoffbrand 1998 would inherently anticipate even under a requirement "that the claimed method have been actually performed." *Montgomery*, 677 F.3d at 1382. At most, Patent Owner's claims appear to

be directed to a newly discovered benefit of deferiprone treatment of patients with iron content in a range associated with cardiac disease, but "[n]ewly discovered results of known processes directed to the same purpose are not patentable because such results are inherent." *Bristol–Myers Squibb Co. v. Ben Venue Laboratories, Inc.*, 246 F.3d 1368, 1376 (Fed. Cir. 2001).

We note that the facts here also differ from the concerns expressed by Judge Lourie's dissent in *Montgomery*, that "there is no evidence in the record to prove that HOPE discloses administration sufficient to inevitably treat or prevent stroke." *Montgomery*, 677 F.3d at 1385. Unlike *Montgomery*, Hoffbrand 1998 provides evidence of the inevitability of treatment success by teaching administration of an amount of deferiprone, 75 mg/kg, that represents a deferiprone dosage at the high end of the range of claim 15 of the '328 patent, to at least ten patients with iron content "within the range that has been associated with cardiac disease." Ex. 1007, 297. Thus, Hoffbrand 1998 provides evidence the prior art disclosure of Hoffbrand 1998 inevitably and necessarily inherently anticipates.

We have considered the evidence and argument as to all the claims, and Petitioner establishes a reasonable likelihood as to all the claims. Moreover, Patent Owner does not address any particular claim in the Preliminary Response.

Accordingly, we find that Petitioner has sufficiently shown that it has a reasonable likelihood that it would prevail in demonstrating claims 1, 2, 4–11, 13–17, and 19 as anticipated by Hoffbrand 1998.

E. Anticipation over Olivieri Abstract 1995

Petitioner contends that claims 1, 2, 4–11, 13–17 and 19 are unpatentable under 35 U.S.C. § 102(b) as anticipated by Olivieri Abstract 1995. Pet. 36–39. *See* Prelim Resp. 38–45.

Petitioner asserts the "Olivieri Abstract 1995 discloses treatment of "thalassemia major" patients who, by definition, are transfusion-dependent, with 75 mg/kg deferiprone per day" Pet. 37. Petitioner asserts the

> Olivieri Abstract 1995 discloses that prior to treatment, the patients had an average T2 relaxation time ("TRT") of 23.9±6.4 msec. (Ex. 1010 (Olivieri Abstract 1995); Ex. 1002 (Mehta Dec.) at ¶ 75.) TRT, measured by MRI, is an indicator of the extent of iron overload in the heart. . . . Thus, the patients who were treated with deferiprone in Olivieri Abstract 1995 had conditions on the spectrum of cardiac disease due to iron overload.

Id. at 38.

Patent Owner asserts that as "discussed by Dr. Pennell, the TRT MRI method described in Olivieri Abstract 1995 was an inaccurate method for assessing cardiac iron concentration. . . . Further, the presence of cardiac iron does not definitively signal an iron overload condition of the heart." Prelim. Resp. 43, citing Ex. 2003 ¶¶ 55–56. Patent Owner asserts "POSA would not have understood this reference as disclosing the use of deferiprone to treat a patient *having* an iron overload condition of the heart." *Id*. ¶ 44. Patent Owner asserts "the 'therapeutically effective amount' of deferiprone required by claims 1, 2, and 4–10 is the amount necessary to produce the claimed results. Taro has not provided any evidence that the 75 mg/kg/day administered in Olivieri Abstract 1995 yielded the results of claims 1, 2, 4–10, and 19." *Id*. at 44–45.

1. *Olivieri Abstract 1995 (Ex. 1010)*

Olivieri Abstract 1995 teaches in "thalassemia major (TM), the orally active iron chelator deferiprone (L1) has demonstrated encouraging results in early, non-randomized trials." Ex. 1010, 983. Olivieri Abstract 1995 teaches "we began in the first trial to compare the effectiveness and safety of, and compliance with, L1 [deferiprone] 75 mg/kg/day, and subcutaneous deferoxamine (DFO) 50mg/kg/day, in TM [thalassemia major] pts matched for age and body iron." *Id*. Olivieri Abstract 1995 teaches "54 pts have been randomized . . . . MRI demonstrates changes consistent with reduction in cardiac iron in L1-treated pts, in whom baseline T2 relaxation time (TRT) of 23.9±6.4msec (normal>32) has increased to 32.4±9.3msec, $p<0.0005$, while initial TRT in DFO-treated pts [21.4±7.9msec] remains unchanged [21.7±6.9msec, $p>0.67$]." *Id*. Olivieri Abstract 1995 teaches: "Changes consistent with reduction of cardiac iron in L1-treated pts suggest early evidence that L1 induces reduction in extra-hepatic at least equal to that achieved by DFO." *Id*.

Petitioner's Declarant, Dr. Mehta, states "[p]rior to treatment, the patients had an average T2 relaxation time ('TRT') of 23.9±6.4 msec, as measured by MRI." Ex. 1002 ¶ 75. Dr. Mehta states "TRT is an indicator of the extent of iron overload in the heart. Normal TRT is greater than 32 msec, as disclosed in Olivieri Abstract 1995, and lower TRT values indicate cardiac disease due to iron overload." *Id*.

Patent Owner's Declarant, Dr. Pennell, states "in 1995, MRI T2 quantification was unreliable and was not useful as a means for measuring cardiac iron. This is because scanning techniques available in 1995 were very limited." Ex. 2003 ¶ 55. Dr. Pennell states "it was not until my lab

developed T2* CMR in late 2000 that myocardial iron could be reliably assessed. Thus, it would be inappropriate to suggest that a patient had cardiac disease purely on the MRI T2 relaxation time in the heart."

Id. Dr. Pennell states

> in 1998, Dr. Olivieri and colleagues associated the use of deferiprone with a greatly increased risk of cardiac disease. (Ex. 2011 at 420–21.) These conclusions from the 1998 publications are grossly inconsistent with the conclusions drawn by Dr. Olivieri in 1995 when she stated that deferiprone is a "promising agent" capable of reducing cardiac iron (Ex. 1010).

Id. ¶ 57.

Patent Owner's Declarant, Dr. Coates, states "I agree with Dr. Pennell that even if iron were present in the heart, this does not conclusively establish that a patient has cardiac disease." Ex. 2001 ¶ 59. Dr. Coates also agrees with Dr. Pennell that "a POSA would not have considered the data in Olivieri's 1995 publications to be reliable in view of the conclusions drawn in her subsequent 1998 publications." *Id*. ¶ 65.

2. *Analysis*

We find that the current evidence of record in Olivieri Abstract 1995, as supported by Dr. Mehta, provides a reasonable likelihood that Olivieri Abstract 1995 anticipates claims 1, 2, 4–11, 13–17, and 19 because the evidence sufficiently demonstrates that at least some of the patients discussed in Olivieri Abstract 1995 necessarily satisfy the requirement for patients treated with a therapeutically effective amount of deferiprone who had "an iron overload condition of the heart" or "iron-induced cardiac disease" as required by independent claims 1, 2, and 4–10.

In particular, Olivieri Abstract 1995 teaches patients treated with deferiprone at 75 mg/kg/day, who were also shown by MRI testing using T2 relaxation time, to have initially high cardiac iron levels that were reduced by administration of deferiprone. Ex. 1010.

We recognize the concerns of Drs. Pennell and Coates regarding the accuracy of the MRI data in Olivieri Abstract 1995, but although the Declarants criticize the data, they provide no evidence rebutting the finding in Olivieri Abstract 1995 that particular patients being treated with deferiprone at the 75 mg/kg/day level consistent with claim 15 of the '328 patent were not experiencing an iron overload condition of the heart. By contrast, the reduced T2 relaxation time data in Olivieri Abstract 1995 is evidence that patients were experiencing an iron overload condition of the heart as supported by Dr. Mehta. Ex. 1010, Ex. 1002 ¶ 75.

"The keystone of the inherency doctrine is inevitability. For anticipation by inherency, a later-claimed invention must have necessarily resulted from the practice of a prior art reference. Our precedent has been steadfast in this strict requirement of inevitability." *Montgomery*, 677 F.3d at 1384.

Based on that standard, Olivieri Abstract 1995 inherently anticipates even under a requirement "that the claimed method have been actually performed." *Montgomery*, 677 F.3d at 1382, because deferiprone was administered in amounts claimed by the '328 patent as "therapeutically effective" to patients with evidence of iron overload of the heart. Ex. 1010. To the extent that the later Olivieri publications disagree with Olivieri Abstract 1995, those publications may impact the obviousness analysis. Those publications, however, do not address the issue of inherent

anticipation by Olivieri abstract 1995 because, based on the evidence currently before us, it appears that Olivieri Abstract 1995 performed the claimed method and, therefore, anticipates the requirements of the claimed method.

We have considered the evidence and argument as to all the claims, and Petitioner establishes a reasonable likelihood as to all the claims. Moreover, Patent Owner does not address any particular claim in the Preliminary Response.

Accordingly, we find that Petitioner has sufficiently shown a reasonable likelihood that it would prevail on demonstrating that claims 1, 2, 4–11, 13–17, and 19 are anticipated by Olivieri Abstract 1995.

F. Anticipation over Agarwal 2000

Petitioner contends that claims 1, 2, 4–11, 13–17 and 19 are unpatentable under 35 U.S.C. § 102(b) as anticipated by Agarwal 2000. Pet. 39–41. *See* Prelim Resp. 46–49.

Petitioner asserts the "Agarwal 2000 discloses continuous treatment of 22 patients who had blood-transfusion-dependent thalassemia with 75 mg/kg deferiprone for over a decade." Pet. 40. Petitioner asserts "healthy, non-iron overloaded people have a serum ferritin levels of 30–300 ng/mL for men and 10 to 200 ng/mL for women, and levels of 5000 ng/mL indicate iron overload." *Id*. Petitioner asserts "two of the patients had mild diastolic dysfunction (Ex. 1011 (Agarwal 2000)), a condition which is on the spectrum of cardiac disease due to iron overload." *Id*. at 41.

Patent Owner asserts "Agarwal does not disclose: (i) administering deferiprone to a patient having an iron overload condition of the heart . . . or (ii) the use of a therapeutically effective amount of deferiprone" Prelim.

Resp. 46–47. Patent Owner asserts "it is unclear whether the 'mild diastolic dysfunction' observed in these two patients in Agarwal was identified before or after deferiprone treatment." *Id.* at 47. Patent Owner also asserts "it is unclear whether the 'mild diastolic dysfunction' was iron-induced, as required by the claims." *Id.* at 48.

1. Agarwal 2000 (Ex. 1011)

Agarwal 2000 teaches "216 transfusion dependent thalassaemia major patients have received Deferiprone (Ll, Kelfer) as an iron chelator . . . . Twenty two of these have continued to take Deferiprone until now except for a brief period in 1994-95, when the clinical trials were over and the drug was yet not licensed for marketing." Ex. 1011. Agarwal 2000 teaches the "dose varied between 75 and 120 mg/kg/day with a mean of 86±12 mg/kg/day. The efficacy was excellent with S. ferritin dropping from a mean of 5820 ± 2660 ng/ml to 2130 ± 1680 ng/ml." *Id.* Agarwal 2000 teaches: "Assessment of cardiac function shows normal ejection fraction in all with mild diastolic dysfunction in two [patients]." *Id.*

Petitioner's Declarant, Dr. Mehta, states "[n]on-iron-overloaded patients have serum ferritin levels of 30–300 ng/mL for men and 10 to 200 ng/mL for women; a serum ferritin level of 5000 ng/mL or higher indicates iron overload." Ex. 1002 ¶ 76. Dr. Mehta states "Agarwal 2000 discloses that two of the patients had mild diastolic dysfunction, a condition which is on the spectrum of iron overload conditions of the heart, e.g., cardiac disease due to iron overload." Ex. 1002 ¶ 76.

Patent Owner's Declarant, Dr. Pennell, states

> the disclosure of two patients with mild diastolic dysfunction, in the absence of any additional information, does not teach a patient having or experiencing iron-induced cardiac disease.

> For example, Agarwal does not disclose whether the cardiac dysfunction in these two individuals was related to the presence of cardiac iron, a requirement of claims 1, 2, and 6–9. (Ex. 1011.) Further, I note that Agarwal does not disclose whether this cardiac dysfunction was identified before or after initiation of treatment with deferiprone.

Ex. 2003 ¶ 61.

Patent Owner's Declarant, Dr. Coates, states "cardiac disease can have an etiology other than iron overload, thus the cardiac abnormalities observed in Agarwal cannot necessarily be attributed to iron overload." Ex. 2001 ¶ 68. Dr. Coates states "Agarwal does not disclose a dose of deferiprone that yields the claimed results, *i.e.*, the stabilization, reduction, or treatment of iron overload in the heart, including iron-induced heart disease." *Id*. ¶ 71.

2. Analysis

We find that the current evidence of record in Agarwal 2000, as supported by Drs. Coates and Pennell, better supports Patent Owner's position that Agarwal 2000 does not anticipate claims 1, 2, 4–11, 13–17, and 19 because the evidence does not support Petitioner's position that the two patients with "mild diastolic dysfunction" discussed in Agarwal 2000 necessarily encompasses patients with "an iron overload condition of the heart" or "iron-induced cardiac disease" as required by independent claims 1, 2, and 4–10. "Inherency . . . may not be established by probabilities or possibilities. The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient." *MEHL*, 192 F.3d at 1365.

As Dr. Coates points out, Ex. 1011 does not demonstrate that the diastolic dysfunction is due to iron overload, rather than another etiology.

Ex. 2001 ¶ 68. Also, as Dr. Pennell states, and Dr. Coates concurs, Agarwal 2000 is silent on whether the patients had the diastolic dysfunction prior to treatment with deferiprone or whether the condition manifested itself during or after treatment. Ex. 2003 ¶ 61; Ex. 2001 ¶ 68. Dr. Mehta does not identify a teaching in Agarwal 2000 addressing these concerns. Therefore, the evidence of record does not demonstrate that the treatment Agarwal 2000 inevitably resulted in treatment of patients with iron overload of the heart.

Accordingly, we find that Petitioner has not sufficiently shown a reasonable likelihood that it would prevail in demonstrating that claims 1, 2, 4–11, 13–17, and 19 are anticipated by Agarwal 2000.

G. Anticipation over Olivieri 1995

Petitioner contends that claims 1, 2, 4–11, 13–17 and 19 are unpatentable under 35 U.S.C. § 102(b) as anticipated by Olivieri 1995. Pet. 42–43. *See* Prelim Resp. 46–49.

Petitioner asserts "Olivieri 1995 discloses treatment of blood-transfusion-dependent thalassemia patients who have 'complications with iron overload' with 75 mg/kg deferiprone per day." Pet. 42–43. Petitioner asserts "[a]t least two of the patients treated in Olivieri 1995 had established cardiac disease and were medicated for cardiac disease." *Id*. at 43.

Patent Owner asserts though "Olivieri 1995 discloses two patients with cardiac disease, Olivieri 1995 does not state that the cardiac disease observed in these two patients was *iron induced*. . . . it is entirely possible that the cardiac disease in these two individuals was a result of diabetes, and not iron overload." Prelim. Resp. 50–51, citing Ex. 2001 ¶ 74. Patent Owner asserts "Taro has not provided any evidence that the administration

of 75 mg/kg/day of deferiprone in Olivieri 1995 leads to the claimed results." Id. at 51.

1. Olivieri 1995 (Ex. 1012)

Olivieri 1995 teaches "[p]atients with thalassemia major who were unwilling or unable to use deferoxamine . . . were enrolled in the trial. . . . Two patients with insulin-dependent diabetes had cardiac disease requiring medication." Ex. 1012, 918. Olivieri 1995 teaches "[p]atients were given a total daily dose of 75 mg of deferiprone per kilogram of body weight, to be taken orally every eight hours." *Id*. at 919. Olivieri 1995 teaches in "10 patients in whom deferoxamine had failed to reduce hepatic iron stores to a level below 80 μmol of iron per gram (levels associated with an increased risk of cardiac disease and early death), the body iron load was uniformly reduced with deferiprone ($P<0.005$)." *Id*. at 921. Olivieri 1995 teaches "Our data provide direct evidence of the efficacy of deferiprone for the treatment of iron overload in patients with thalassemia major." *Id*. at 922.

Petitioner's Declarant, Dr. Mehta, states a "person of ordinary skill in the art would have understood that the most common 'complication of iron overload' is cardiac disease." Ex. 1002 ¶ 77.

Patent Owner's Declarant, Dr. Pennell, states "there is no evidence that the cardiac disease observed in [Olivieri 1995's] two patients resulted from excess cardiac iron." Ex. 2003 ¶ 64. Dr. Pennell states "There was no assessment of cardiac iron levels. . . . Thus, it is my opinion that Olivieri 1995 did not, and could not have disclosed that the 'cardiac disease' observed in 2 patients was due to the presence of cardiac iron." *Id*. ¶ 65.

Patent Owner's Declarant, Dr. Coates, states "it is entirely possible that the cardiac disease observed in these patients was a result of their

diabetic condition." Ex. 2001 ¶ 74. Dr. Coates agrees "with Dr. Pennell that the measurements of hepatic iron and serum ferritin in Olivieri 1995 do not substitute for measurements of cardiac iron." *Id*. ¶ 75.

2. Analysis

We find that the current evidence of record in Olivieri 1995, as supported by Dr. Mehta, provides a reasonable likelihood that that Olivieri 1995 anticipates claims 1, 2, 4–11, 13–17, and 19 because the evidence supports Petitioner's position that at least the ten patients discussed in Olivieri 1995 with iron levels "associated with an increased risk of cardiac disease and early death" who, when treated with a therapeutically effective amount of deferiprone, showed reduced iron load, necessarily satisfy the requirements for having "an iron overload condition of the heart" or "iron-induced cardiac disease" as required by independent claims 1, 2, and 4–10.

In particular, Olivieri 1995 teaches patients who, "after deferoxamine had failed to reduce hepatic iron stores to a level below 80 μmol of iron per gram (levels associated with an increased risk of cardiac disease and early death), the body iron load was uniformly reduced with deferiprone." Ex. 1012, 921. Olivieri 1995 further teaches treatment of these patients with 75 mg/kg of body weight, a dose directly falling within the therapeutically effective range required by dependent claims 13–15.
Id. at 919, Ex. 1001 28:23–37.

Olivieri 1995, therefore, provides sufficient evidence of treatment success by teaching administration of an amount of deferiprone, 75 mg/kg, that represents a deferiprone dosage at the high end of the range of claim 15 of the '328 patent, to at least ten patients with iron content at "levels

associated with an increased risk of cardiac disease" and showing reduced iron levels in these patients after treatment. Ex. 1012, 919, 921.

As discussed above with respect to Hoffbrand 1998, these facts are consistent with *Montgomery*, and because Olivieri 1995 actually treated and showed successful iron reduction in ten patients, the evidence would inherently anticipate even under a requirement "that the claimed method have been actually performed." *Montgomery*, 677 F.3d at 1382. At most, Patent Owner's claims appear to be directed to a newly discovered benefit of deferiprone treatment of patients with iron content in a range associated with cardiac disease. *Bristol–Myers.*, 246 F.3d at 1376.

We have considered the evidence and argument as to all the claims, and Petitioner establishes a reasonable likelihood as to all the claims. Moreover, Patent Owner does not address any particular claim in the Preliminary Response.

Accordingly, we find that Petitioner has sufficiently shown a reasonable likelihood that claims 1, 2, 4–11, 13–17, and 19 are anticipated by Olivieri 1995.

H. Obviousness

Petitioner contends that claims 1, 2, 4–11, 13–17 and 19 are unpatentable under 35 U.S.C. § 103(a) as obvious over each of MIMS 1998, Hoffbrand 1998, Olivieri abstract 1995, Agarwal 2000, and Olivieri 1995 in view of the knowledge of a person of ordinary skill in the art. Pet. 43–52.

Petitioner asserts the "prior art as a whole, and each of the Primary References individually, teaches that deferiprone is an orally active iron chelator used to treat transfusion-dependent iron-overloaded patients by oral

administration at a dose of 75 mg/kg per day." Pet. 44 (citing Ex. 1002 ¶ 79).

Petitioner asserts that "the prior art as a whole also teaches, and a person of ordinary skill in the art would have known, that deferiprone was used successfully to chelate iron from an iron-overloaded patient." Pet. 45 (citing Ex. 1002 ¶ 79; Ex. 1001 9:35–37). Petitioner asserts the "prior art provides a motivation and a reasonable expectation of success in using deferiprone to treat iron-overload conditions of the heart, and a person of ordinary skill in the art would have known as much." Pet. 45–46 (citing Ex. 1002 ¶¶ 82–83). In particular, Petitioner asserts

> Statements in the prior art regarding the "excellent" efficacy of deferiprone to treat iron-overload conditions (*e.g.*, Ex. 1011 (Agarwal 2000)) and to reduce cardiac iron levels (*e.g.*, Ex. 1012 (Olivieri 1995)) provide both a motivation and a reasonable expectation of success that deferiprone could be used successfully to treat iron-overload conditions of the heart. . . . The prior art studies with deferiprone include direct and indirect measurements of iron in the heart. (*See, e.g.*, Ex. 1006 (Hoffbrand 1997); Ex. 1007 (Hoffbrand 1998); Ex. 1010 (Olivieri Abstract 1995); Ex. 1012 (Olivieri 1995).) These studies measured the level of iron in the heart <u>because</u> that level is directly correlated with the incidence of iron-induced heart disease, evidencing that a POSA understood that a reduction of the level of iron in the heart is correlated with a reduction in iron-induced heart disease.

Pet. 46 (citing Ex. 1002 ¶¶ 82–83).

Petitioner asserts that they are "unaware of any secondary considerations such as unexpected results, commercial success, long-felt but unmet need or industry praise that may support the non-obviousness of the claims." Pet. 51.

Patent Owner asserts that Petitioner "has failed to articulate any differences between the prior art and the claims at issue. Accordingly, for the same reasons as discussed in *Johns Manville*,[9] the Board should deny institution of the obviousness grounds." Prelim. Resp. 55. Patent Owner contends that Petitioner "advances these obviousness grounds without ever articulating a single difference between any of the Primary References and the challenged claims. Not only does this render the obviousness analysis improper, it also renders Ground 6-10 redundant of the anticipation arguments." *Id*. at 55.

Patent Owner asserts "the prior art taught away from using deferiprone to treat iron-induced heart disease. Specifically, the prior art taught that not only could deferiprone not control total body iron but also that deferiprone was toxic to the heart." Prelim. Resp. 56 (citing Exs. 2011–2013). Patent Owner specifically relies upon teachings of Olivieri 1998 abstract[10], Olivieri 1998 A[11], and Olivieri 1998 B[12] for teachings that "deferiprone treatment in patients with TM may be associated with . . . increased cardiac iron deposition at lower body iron burdens, and (ii) an

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[9] *Johns Manville Corp. v. Knauf Insulation, Inc.*, Case IPR2015-01402, slip. op at 12–14 (PTAB Oct. 21, 2015) (Paper 18).

[10] Olivieri et al., *Cardiac Failure And Myocardial Fibrosis In A Patient With Thalassemia Major ™ Treated With Long-Term Deferiprone*, BLOOD 92(10):532A (1998) ("Olivieri 1998 abstract", Ex. 2012).

[11] Olivieri et al., *Long-Term Safety And Effectiveness Of Iron-Chelation Therapy With Deferiprone For Thalassemia Major*, NEW ENGL. J. MED. 339(7):417–423 (1998) ("Olivieri 1998 A", Ex. 2011).

[12] Olivieri et al., *Long-Term Trials of Deferiprone in Cooley's Anemia*, ANNALS OF THE NEW YORK ACADEMY OF SCIENCES, 850:217–222 (1998) ("Olivieri 1998 B", Ex. 2013).

exacerbation or acceleration of cardiac fibrosis," that after "deferiprone therapy, body iron burden was at concentrations associated with a greatly increased risk of cardiac disease and early death in 7 of 18 patients," and that "deferiprone may not provide adequate control of body iron in a substantial portion of patients with thalassemia major." Prelim. Resp. 56–57 (citing Ex. 2012, Ex. 2011 420–421, Ex. 2013 420).

> Patent Owner asserts secondary considerations, including that
>
> it was wholly unexpected when clinical trials comparing the efficacy of deferiprone and deferoxamine revealed a preferential effect in the deferiprone treated patents in protecting the heart, both from iron induced cardiac disease as well as survival, which could not be explained by the removal of iron from the body alone.

Prelim. Resp. 58 (citing Ex. 2001 ¶¶ 82–84). Patent Owner asserts "there was a long-felt, unmet need for a therapeutically effective, orally administered, treatment for iron-overload conditions of the heart." Prelim. Resp. 58 (citing Ex. 2001 ¶ 85). Patent Owner asserts "the non-obviousness of the '328 patent is established by the praise of others." Prelim. Resp. 59 (citing Ex. 2014).

1. Analysis

Both Petitioner and Patent Owner address the prior art in the entirety, rather than separately addressing combinations of particular references, so we will do likewise. We find that the current evidence of record better supports Petitioner's position that each of Hoffbrand 1998, Olivieri abstract 1995, and Olivieri 1995, in combination with the knowledge of the ordinary artisan, would have rendered claims 1, 2, 4–11, 13–17, and 19 obvious.

To the extent that Petitioner is not addressing the references individually, it does not explain how the obviousness analysis overcomes the deficiency in the anticipation analysis for MIMS 1998 and Agarwal 2000.

Each of the references cited by Petitioner, as well as Olivieri 1998 A, Olivieri 1998 B, and Olivieri 1998 abstract cited by Patent Owner, teach treatment of thalassemia patients with 75 mg of deferiprone to address iron overload conditions. Ex. 1009, Ex. 1007, 295, Ex. 1010, Ex. 1011, Ex. 1012, 919, Ex. 2011, 418, Ex. 2013, 218, and Ex. 2012.

Petitioner's references teach treatment of patients identified as having iron content "within the range that has been associated with cardiac disease." Ex. 1007 297. Olivieri 1995 specifically teaches that "[i]n 10 patients in whom deferoxamine had failed to reduce hepatic iron stores to a level below 80 μmol of iron per gram (levels associated with an increased risk of cardiac disease and early death), the body iron load was uniformly reduced with deferiprone ($P<0.005$)." Ex. 1012, 921. Moreover, the Olivieri 1995 abstract teaches that "MRI demonstrates changes consistent with reduction in cardiac iron in L1[deferiprone]-treated [patients]." Ex. 1010, 983

Thus, these three references identify patients with levels of iron consistent with iron overload conditions of the heart and treat those patients with deferiprone in amounts identified by the '328 claims themselves as therapeutically effective amounts and Olivieri 1995 and Olivieri 1995 abstract demonstrate reductions in body iron load and cardiac iron in particular patient populations. Ex. 1012, 921, Ex. 1010.

As discussed with regard to the anticipation issue, we recognize the concerns of Drs. Pennell and Coates regarding the accuracy of the MRI data in Olivieri Abstract 1995, but while the Declarants criticize the data, but at

this stage of the proceeding, the declarants have not provided any evidence rebutting the finding in Olivieri Abstract 1995 that particular patients being treated with deferiprone at the 75 mg/kg/day level consistent with claim 15 of the '328 patent were not experiencing an iron overload condition of the heart. By contrast, the reduced T2 relaxation time data in Olivieri Abstract 1995 is evidence that patients were experiencing an iron overload condition of the heart as supported by Dr. Mehta. Ex. 1010, Ex. 1002 ¶ 75.

Dr. Mehta concludes, based on this evidence, that

> a person of ordinary skill in the art would have had a motivation to treat a transfusion-dependent patient with deferiprone, including those experiencing a heart condition due to iron overload, and would have had a reasonable expectation of success. In other words, it is my opinion that the methods described in claims 1–17 and 19 of the '328 Patent are obvious over the prior art.

Ex. 1002 ¶ 84.

We recognize Patent Owner's assertions that Hoffbrand, Olivieri 1998 A, Olivieri 1998 B, and Olivieri 1998 abstract teach away from the use of deferiprone for reduction in cardiac iron, as supported by Dr. Coates contention that "a POSA would not have expected that administering a therapeutically effective amount of deferiprone, as claimed in the '328 patent, would provide a cardio protective effect." Ex. 2001 ¶ 84. Dr. Pennell also states a "POSA would have understood the prior art to teach away from the claimed invention." Ex. 2003 ¶ 74.

We find these arguments unpersuasive on the current record because while Hoffbrand teaches away from patients with iron-induced cardiomyopathy and each of Olivieri 1998 A, Olivieri 1998 B, and Olivieri 1998 abstract address concerns with long term administration of deferiprone,

the claims themselves do not include any limitation requiring patients' long term administration and therefore encompass short term administration of deferiprone.

Hoffbrand teaches "deferiprone is inappropriate therapy for patients with iron-induced cardiomyopathy in whom continuous intravenous DFX is needed to cause continuous removal of toxic, nontransferrin-bound iron from plasma." Ex. 1007, 299. However, claim 1 is not limited to patients with iron-induced cardiomyopathy, but rather any patient with "an iron overload condition of the heart." Ex. 1001 27:4–5. The Specification of the '328 patent states "iron induced cardiac disease (such as heart failure, and iron induced cardiac complications)." Ex. 1001 10:11–13. Thus, "iron overload condition of the heart" as interpreted in light of the Specification and current evidence, is not reasonably interpreted as limited to patients with cardiomyopathy, but broadly encompasses patients with increased levels of cardiac iron associated with cardiac disease.

Olivieri 1998 A teaches "a direct quantitative assessment of body iron burden demonstrated a favorable effect of deferiprone on iron balance." Ex. 2011, 417. Olivieri 1998 A does not dispute that deferiprone functions in short term treatment, but addresses "whether the effects of deferiprone are sustained during long-term therapy." Ex. 2011, 418. Olivieri 1998 A teaches "the mean (±SE) hepatic iron concentration decreased from 88.7±12.1 to 65.5±7.9 μmol per gram of liver, wet weight (normal value, about 1.6), after a mean of 4.6±0.3 years of therapy (range, 2 to 7)" though this result was not identified as significant. Ex. 2011, 419. Olivieri 1998 A does conclude that "[a]fter a mean of 4.6 years of deferiprone therapy, body

iron burden was at concentrations associated with a greatly increased risk of cardiac disease and early death in 7 of 18 patients." Ex 2011, 420–421.

Olivieri 1998 B similarly teaches "short-term deferiprone treatment was shown to reduce hepatic storage iron in many patients over three years. As emphasized at the time of that report, the long-term effectiveness of this agent remained undetermined." Ex. 2013, 218. Olivieri 1998 B recognizes that "Patients who sustain hepatic storage iron concentrations exceeding 15 milligrams iron per gram liver, dry weight have a greatly heightened risk of cardiac disease and early death." Ex. 20013, 219. Olivieri 1998 B concludes "long-term deferiprone may not provide adequate sustained control of body iron in a substantial proportion of patients with Cooley's anemia." Ex. 2013, 219.

Therefore, the Olivieri 1998 A and Olivieri 1998 B references both recognize the short term efficacy of deferiprone on reducing iron levels, but contend that deferiprone may not function in long term treatment. Claim 1 encompasses both the acknowledged effective short term treatment with deferiprone as well as long term treatment that the references disparage. However, "[e]vidence concerning whether the prior art teaches away from a given invention must relate to and be commensurate in scope with the ultimate claims at issue." *Idemitsu Kosan Co., Ltd. V. SFC Co. Ltd*., 870 F.3d 1376, 1381 (Fed. Cir. 2017). This instant teaching away argument is not commensurate in scope with the breadth of claim 1 encompassing both long term and short term deferiprone treatment. Thus, even if the prior art, when considered as a whole, teaches away from long term treatment of "iron overload of the heart" with deferiprone, on this record the prior art equally

teaches deferiprone is effective in short term treatments to reduce iron levels, including cardiac iron levels. Ex. 1010.

We also find the current evidence of record insufficient to establish secondary considerations such as unexpected results, long-felt need, and praise of others. *See* Prelim. Resp. 57–60.

"[W]hen unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art." *In re Baxter Travenol Labs*., 952 F.2d 388, 392 (Fed. Cir. 1991), here the references cited by Petitioner, and "objective evidence of non-obviousness must be commensurate in scope with the claims which the evidence is offered to support." *In re Tiffin*, 448 F.2d 791, 792 (CCPA 1971). No evidence of such a comparison with the prior art appears to be currently of record, and to the extent that the results in the Specification are drawn to long term treatment with deferiprone, the claims encompass both short term and long term treatments. *See* Ex. 1001, 22:7–12.

To establish a long-felt need, three elements must be proven: First, the need must have been a persistent one that was recognized by ordinarily skilled artisans. *In re Gershon*, 372 F.2d 535, 538 (CCPA 1967). Second, the long-felt need must not have been satisfied by another before Appellant's invention. *See Newell Companies, Inc. v. Kenney Mfg. Co*., 864 F.2d 757, 768 (Fed. Cir. 1988) ("[O]nce another supplied the key element, there was no long-felt need or, indeed, a problem to be solved . . . ."). Third, the invention must, in fact, satisfy the long-felt need. *In re Cavanagh*, 436 F.2d 491, 496 (CCPA 1971).

In this case, Dr. Coates states "there was a need for a new oral treatment option for iron-induced cardiac disease that was met by the

method recited in the claims of the '328 patent." Ex. 2001 ¶ 85. This provides some evidence supporting the first and third elements for long-felt need. However, Dr. Mehta states "deferiprone was well-known before the '328 Patent and it filled an important need, as explained above. The claims of the '328 Patent add nothing new to the prior art methods." Ex. 1002 ¶ 85. Thus, Dr. Mehta supports a finding under the "reasonable likelihood" standard that the long-felt need had already been satisfied prior to Patent Owner's invention. *See* 37 C.F.R. § 42.108(c) Consequently, the evidence currently of record does not establish the secondary consideration of long felt need.

We have considered the evidence of "praise of others", specifically the *Humanitarian of the Year Award* from the Cooley's Anemia Foundation. Ex 2014. However, the press release, dated June 8, 2017, states that the award was for "their work on deferiprone (Ferriprox™), the first oral medication used to treat . . . certain hereditary red blood cell disorders" and that "Ferriprox™ has been used to treat patients for almost 30 years and was first approved in Europe almost 20 years ago". Ex. 2014 1, 4. The "praise" was for the use of deferiprone generally, and was not specifically directed to the improved use of deferiprone for treatment of patients "experiencing an iron overload condition of the heart," the limitation argued by Patent Owner as an essential limitation distinguishing the instant claim 1 from the prior art. Prelim. Resp. 14. While the "praise" does mention "cardiac mortality" there is no specific connection with "an iron overload condition of the heart". Ex. 2014, 5. Thus, the evidence is not commensurate in scope with the claims. In addition, to the extent that the press release is relevant, it specifically states that deferiprone was approved for use in Europe 20 years

ago, *i.e*. prior to 1999, and, therefore, suggests that the use of deferiprone for treatment of thalassemia patients was used prior to the filing of the instant claims.

III. CONCLUSION

After reviewing the information presented in the Petition and the Preliminary Response, as well as the evidence of record, we determine that Petitioner has established a reasonable likelihood that it will prevail in showing that claims 1, 2, 4–17, 19 of the '328 patent are unpatentable.

IV. ORDER

Accordingly, it is

ORDERED that Pursuant to 35 U.S.C. § 314(a), an *inter partes* review is hereby instituted on the following grounds;

References	Basis	Claims Challenged
Hoffbrand 1998	§ 102(b)	1, 2, 4–11, 13–17, 19
Olivieri Abstract 1995	§ 102(b)	1, 2, 4–11, 13–17, 19
Olivieri 1995	§ 102(b)	1, 2, 4–11, 13–17, 19
Hoffbrand 1998	§ 103(a)	1, 2, 4–17, 19
Olivieri Abstract 1995	§ 103(a)	1, 2, 4–17, 19
Olivieri 1995	§ 103(a)	1, 2, 4–17, 19

FURTHER ORDERED that no other ground of unpatentability asserted in the Petition is authorized for this *inter partes* review; and

FURTHER ORDERED that pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, notice is hereby given of the institution of a trial; the trial will commence on the entry date of this Decision.

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