UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Taro Pharmaceuticals U.S.A., Inc.,

v.

Apotex Technologies, Inc.

Patent No. 7,049,328 B2

Title: USE FOR DEFERIPRONE

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 7,049,328 B2

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TABLE OF CONTENTS

TABLE OF AUTHORITIES

Page(s)

Cases

Statutes

Other Authorities

List of Exhibits for U.S. Patent No. 7,049,328 Petition for *Inter Partes* Review

Exhibit No.	Description
1001	U.S. Patent No. 7,049,328, Spino et al., *Use for Deferiprone*, issued on May 23, 2006 ("the '328 Patent")
1002	Declaration of Jayesh Mehta, M.D. ("Mehta Dec.")
1003	Curriculum Vitae of Jayesh Mehta, M.D.
1004	Prosecution History of U.S. Patent No. 7,049,328
1005	Olivieri et al., *Reduction of Tissue Iron Stores and Normalization of Serum Ferritin During Treatment with the Oral Iron Chelator L1 in Thalassemia Intermedia*, BLOOD, 79(10):2741–48, 1992 ("Olivieri 1992")
1006	Hoffbrand & Wonke, *Iron Chelation Therapy*, JOURNAL OF INTERNAL MEDICINE, 242 (Supplement 740): 37–41, 1997 ("Hoffbrand 1997")
1007	Hoffbrand et al., *Long-Term Trial of Deferiprone in 51 Transfusion-Dependent Iron Overloaded Patients*, BLOOD, 91(1):295–300, 1998 ("Hoffbrand 1998")
1008	U.S. Patent No. 5,922,761, Lai, *Methods for In Vivo Reduction of Iron Levels and Compositions Useful Therefor*, Issued on July 13, 1999 ("Lai '761")
1009	Monthly Index of Medical Specialties, Vol. 18, No. 12, December 1998 ("MIMS 1998")
1010	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")

Exhibit No.	Description
1011	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")
1012	Olivieri et al., *Iron-Chelation Therapy with Oral Deferiprone in Patients with Thalassemia Major*, N. ENGL. J. MED., 332:918–22, 1995 ("Olivieri 1995")
1013	Intentionally Left Blank
1014	Olivieri et al., *Survival in Medically Treated Patients with Homozygous β-Thalassemia*, N. ENGL. J. MED., 331:547–78, 1994 ("Olivieri 1994")
1015	Nathan & Gunn, *Thalassemia: The Consequences of Unbalanced Hemoglobin Synthesis*, AMERICAN JOURNAL OF MEDICINE, 41:815–30, 1966 ("Nathan 1966")
1016	Bannerman et al., *Thalassemia Intermedia, with Iron Overload, Cardiac Failure, Diabetes Mellitus, Hypopituitarism and Porphyrinuia*, AMERICAN JOURNAL OF MEDICINE, 476–86, 1967 ("Bannerman 1967")
1017	Barman Balfour & Foster, *Deferiprone: A Review of its Clinical Potential in Iron Overload in β-Thalassemia Major and Other Transfusion-Dependent Diseases*, DRUGS 58(3):553–78, 1999 ("Barman Balfour 1999")
1018	Barry et al., *Long-Term Chelation Therapy in Thalassemia Major: Effect on Liver Iron Concentration, Liver Histology, and Clinical Progress*, BMJ, 2:16–20, 1974 ("Barry 1974")
1019	Kontoghiorghes, *Oral Iron Chelation Is Here*, BMJ, 303:1279–80, 1991 ("Kontoghiorghes 1991")
1020	Nathan, *An Orally Active Iron Chelator*, N. ENGL. J. MED., 332(14):953–54, 1995 ("Nathan 1995")

Exhibit No.	Description
1021	GB 2 118 176, *Pharmaceutically Active 3-Hydroxypyrid-2-and-4-ones*, published on October 1983 ("Hider Patent")
1022	Diav-Citrin & Koren, *Oral Iron Chelation with Deferiprone*, NEW FRONTIERS IN PEDIATRIC DRUG THERAPY, 44(1):235–47, 1997 ("Diav-Citrin 1997")
1023	Prescribing Information for Ferriprox® (deferiprone) tablets, for oral use (Revised 10/2011) ("Deferiprone Label 2011")
1024	Olson et al., *Endomyocardial Biopsy in Hemochromatosis: Clinicopathologic Correlates in Six Cases*, JACC, 13(1):116–20, 1989 ("Olson 1989")
1025	Kontoghiorghes et al., *L1-Deferiprone Worldwide Update and New Strategies for Improving its Therapeutic Efficiency*, 10TH INTERNATIONAL CONFERENCE ON ORAL CHELATORS IN THE TREATMENT OF THALASSEMIA AND OTHER DISEASES AND BIOMED MEETING, March 2000 ("Kontoghiorghes 2000")
1026	Faa & Crisponi, *Iron Chelating Agents in Clinical Practice*, COORDINATION CHEMISTRY REVIEWS, 184:291–310, 1999 ("Faa 1999")
1027	Borgna-Pignatti, *Survival and Disease Complications in Thalassemia Major*, ANNALS NEW YORK ACADEMY OF SCIENCES, 227–31, 1998 ("Borgna-Pignatti 1998")
1028	McDonald, *Deferoxamine and Diethylenetriaminepentaacetic Acid (DTPA) in Thalassemia*, THE JOURNAL OF PEDIATRICS 69(4):563–71, 1966 ("McDonald 1966")
1029	Cerami, *Propper"Use of Desferrioxamine*, N. ENGL. J. MED, 294(26): 1456-57, 1976 ("Cerami 1976")
1030	Matsui, *Effective Iron Chelation /using the Oral Iron Chelator 1,2,-dimethyl-3-hydroxypyrid-4-one (L1), in Homozygous b-Thalassemia Major (HBT) Patients*, Abstract P1-43, Clinical Pharmacology & Therapeutics, 53(2) (1993). ("Matsui")

Exhibit No.	Description
1031	Mehta J. et al., *Autoantibodies in Thalassaemia Major: Relationship with Oral Iron Chelator L1*, J. ASSOC. PHYSICIANS INDIA, 41(6):339–41, 1993
1032	Kratz, *Normal Reference Laboratory Values*, NEW ENGLAND JOURNAL OF MEDICINE, Vol. 339, No. 15, 1998 ("Kratz")
1033	Mehta et al., *Deaths in Patients Receiving Oral Iron Chelator L1*, BR. J. HAEMATOL., 85:430–31, 1993
1034	Mehta et al., *Deferiprone in Iron Overload,* N. ENGL. J. MED., 333:597–99, 1995
1035	Mehta et al., *Oral Iron Chelator L1 and Autoimmunity*, BLOOD, 81:1970–71, 1993

I. INTRODUCTION

Taro Pharmaceuticals USA, Inc. ("Taro" or "Petitioner") petitions for *inter partes* review ("IPR") under 35 U.S.C. §§ 311–319 and 37 C.F.R. § 42 et seq. of claims 1-17 and 19 of U.S. Patent 7,049,328 (Ex. 1001 ("the '328 Patent")).

II. PRELIMINARY STATEMENT

The '328 Patent is directed to an old method of administering deferiprone to transfusion-dependent patients with iron overload. Deferiprone is an oral iron chelator that was first approved for use in treating iron overload diseases in India in 1995, years prior to the earliest filing date of the '328 Patent. As explained in more detail below and as acknowledged in the patent specification, every element of the claims, including the target patient population, the oral dosage amount of 75 mg/kg per day, and the goal of treating iron overload and related heart conditions, was explicitly disclosed in many prior art references.

According to the specification, prosecution history, and statements the Patent Owner made during an opposition to the European counterpart to the '328 Patent, the alleged inventive aspect of the claimed method is the discovery that deferiprone preferentially reduces iron in the heart. According to the Patent Owner, deferiprone targets iron found in the heart in preference to iron found in other organs, such as the liver. Regardless of the merits of this alleged discovery, the claimed methods are identical to previously known methods of administering

deferiprone, including the target patient population (transfusion-dependent patients), the dosage form and amount (oral, at least 75 mg/kg per day), and the goal of the treatment (to treat iron-overload conditions, including overload conditions of the heart). Claims drawn to a newly discovered benefit of an old method are not patentable. Therefore, the claims of the '328 Patent are anticipated and rendered obvious by each of many prior art references, including the five representative references selected by Petitioner and its expert, and discussed in detail below.

III. MANDATORY NOTICES

A. Real Parties-in-Interest (37 C.F.R. § 42.8(b)(1))

The real parties-in-interest are Taro, Taro Pharmaceutical Industries, Ltd., and Sun Pharmaceuticals, Ltd.

B. Related Matters (37 C.F.R. § 42.8(B)(2))

The '328 Patent is at issue in *ApoPharma Inc. v. Taro Pharmaceutical Industries, Ltd.*, No. 2:16-cv-00528, currently pending in the District Court for the Eastern District of Texas – Marshall Division. Taro Pharmaceutical Industries Ltd. was served with a complaint in that case on June 2, 2016.

C. Lead and Back-Up Counsel (37 C.F.R. § 42.8(b)(3))

Lead counsel is Huiya Wu, Reg. No. 44,411. Backup counsel are Robert V. Cerwinski (to seek *pro hac* vice admission) and Sarah Fink, Reg. No. 64,886. All counsel are with Goodwin Procter LLP at 620 Eighth Avenue, New York, NY

10018, tel. 212-813-8800, fax 212-355-3333. Email addresses for counsel are hwu@goodwinlaw.com, rcerwinski@goodwinlaw.com, and sfink@goodwinlaw.com.

D. Service Information (37 C.F.R. § 42.8(b)(4))

Please direct all correspondence to counsel at the contact information above. Petitioner consents to service by electronic mail at hwu@goodwinlaw.com, rcerwinski@goodwinlaw.com, and sfink@goodwinlaw.com.

IV. CERTIFICATION OF GROUNDS FOR STANDING

Petitioner certifies pursuant to 37 C.F.R. § 42.104(a) that the patent for which review is sought is available for *inter partes* review and that Petitioner is not barred or estopped from requesting an *inter partes* review challenging the patent claims on the grounds identified in this petition.

V. FEES

The Commissioner is hereby authorized to charge all fees due in connection with this matter to Attorney Deposit Account 506989.

VI. SUMMARY OF THE '328 PATENT AND PROSECUTION HISTORY

The '328 Patent (Ex. 1001) issued on May 23, 2006, from Application Ser. No. 10/311,814 ("the '814 application"), which entered the U.S. national stage on April 4, 2003, and claims priority to a foreign application that was filed on June 30, 2000. The earliest possible priority date associated with the '328 Patent is June 30, 2000.

A. The Claims of the ’328 Patent

The ’328 Patent has 20 claims. Claims 1–10 are each independent, and claims 11–20 are each multiply dependent on claims 1–10. The claims are generally drawn to a method of treating a transfusion-dependent patient who has an iron overload condition comprising administering an effective amount of deferiprone. The claims also include recitations of alleged intended results of treatment with deferiprone, such as the reduction of iron in the heart or the preferential reduction of iron in the heart as compared to iron in other parts of the body.[1]

The dependent claims further specify the mode of administration of deferiprone (claims 11, 16, and 17), that deferiprone is in a dosage form with excipients (claim 12), the dosage amount (claims 13, 14, and 15), and the property

[1] Petitioner and its expert Dr. Mehta offer no opinion as to the merits of the alleged intended results or discovery of the cardio-selectivity of deferiprone that is suggested in the patent. It is Petitioner’s position that the behavior of deferiprone in the human body as set forth in the ’328 Patent is identical to the behavior of deferiprone in the human body prior to the filing of the ’328 Patent, and there is no patentable invention here. Any and all references to the “discovery” described in the ’328 Patent should be understood to mean the *alleged* “discovery” disclosed therein.

that deferiprone is more cardio-selective in its reduction of iron than another iron chelator, desferrioxamine (claim 19).

B. Specification of the ’328 Patent

The ’328 Patent is directed to a “method of treating iron induced cardiac disease in a patient with iron overload, such as in thalassemia patients or the like comprising administering to the patient a therapeutically effective amount of deferiprone.” (Ex. 1001 (’328 Patent) at Abstract.) The patent discloses that patients with thalassemia must be treated with regular transfusions of red blood cells, and that the transfusions create “a wide-spread iron overload in the patient.” (*Id*. at col. 1, ll. 27–29.) This iron overload may cause toxic degenerative changes in organs, in particular, to the heart. (*Id.*)

The patent states that iron overload has been treated with two iron chelators known in the art. Iron overload is most often treated with desferrioxamine, which must be subcutaneously infused daily with the use of an infusion pump for a period of 8–12 hours, as long as the patient continues to receive regular blood transfusions. (*Id*. at col. 1, ll. 52–62; col. 2, ll. 26–30.) Alternatively, “another iron chelator, deferiprone by oral administration,” has “been used successfully for removal of iron in thalassemia patients.” (*Id*. at col. 1, ll. 63–65.)

Thalassemia patients who receive regular transfusions generally die from heart failure in their teens “if iron overload is not treated.” (*Id*. at col. 2, ll. 9–13.)

Treatment with desferrioxamine often prolongs life only through age 30, with many treated patients still dying prematurely from heart failure. (*Id.*) The specification states that the high rate of premature death despite treatment with desferrioxamine is because "patients do not take adequate amounts of the injectable chelator," and notes that patient compliance is poor with the difficult treatment regimen. (*Id*. at col. 2, ll. 26–34.) The specification further hypothesizes, without providing a basis, that while desferrioxamine "removes iron from the liver and possibly the blood, its effects on the heart are secondary, not specific for this organ." (*Id*. at col. 2, ll. 18–26.) Further, according to the specification, "[i]t has thus become evident that lowering of the total body iron alone is insufficient to protect against iron-induced heart damage." (*Id*. at col. 2, ll. 53–55.) The patent states that there is therefore a "long felt need to improve the life expectancy" of these patients. (*Id*. at col. 2, ll. 55–60.)

The patent then provides a list of 62 prior art references, characterizes them as "technical literature which discusses the clinical use of chelating agents in conditions of chronic iron overload" (*id*. at col. 2, l. 63–col. 6, l. 56), and further states, "[t]here are more than 250 articles in the peer-reviewed literature which refer to deferiprone and 48 of these (at the time of writing) present data on the use of deferiprone in patients with iron overload." (*Id*. at col. 6, ll. 57–60.)

According to the patent, however, "there is no literature that demonstrates that deferiprone has a greater cardio-protective effect than desferrioxamine, or that it might have such activity beyond its general ability to reduce the total body iron load." (*Id*. at col. 7, ll. 6–10.)

The "Summary of the Invention" section provides the patentees' description of the alleged invention in the '328 Patent: "Applicants have now discovered that the use of deferiprone in effective amounts as an iron chelating agent for patients suffering from an iron overload condition … provides for unexpected prevention/stabilization/reduction of the risk of heart disease such as heart failure and iron-induced cardiac complications." (*Id*. at col. 9, l. 60–col. 10, l. 1.)

C. Prosecution History of the '328 Patent

The '814 application entered the U.S. national stage on April 4, 2004, and was filed with a preliminary amendment. The patent was allowed following several rounds of rejections by the examiner, each of which was met with a response and amendment, and two examiner interviews. The examiner rejected the pending claims as anticipated by or obvious over Olivieri 1992[2] (Ex. 1005),

[2] Olivieri et al., *Reduction of Tissue Iron Stores and Normalization of Serum Ferritin During Treatment with the Oral Iron Chelator L1 in Thalassemia Intermedia,* BLOOD, 79(10):2741–48, 1992 ("Olivieri 1992," Ex. 1005).

Hoffbrand 1997[3] (Ex. 1006), Hoffbrand 1998[4] (Ex. 1007), and Lai '761[5] (Ex. 1008). The examiner also made rejections based on indefiniteness and lack of enablement under 35 U.S.C. § 112.

In an Office Action Response dated July 30, 2004, the applicants provided "the Examiner with further general discussion and perspective information." (Ex. 1004 (Response to Office Action, July 30, 2004[6]) at 9.) This "general discussion" largely mirrors the discussion of the prior art provided in the patent specification and discussed above. Applicants argued that Olivieri 1992, Hoffbrand 1997, and Hoffbrand 1998, are not anticipatory and do not render the claims obvious, *inter alia*, because they do not disclose the cardio-protective effect of deferiprone. Applicants purported to differentiate the alleged invention from the prior art identified in the patent specification as follows: "However, in Applicant's opinion

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[3] Hoffbrand & Wonke, *Iron Chelation Therapy*, JOURNAL OF INTERNAL MEDICINE, 242 (Supplement 740): 37–41, 1997 ("Hoffbrand 1997," Ex. 1006).

[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] U.S. Patent No. 5,922,761, Lai, *Methods for In Vivo Reduction of Iron Levels and Compositions Useful Therefor*, issued on July 13, 1999 ("Lai '761," Ex. 1008).

[6] Prosecution History, U.S. Patent Application No. 10/311,814.

there is no literature that demonstrates that deferiprone has a greater cardio protective effect than desferrioxamine or that it might have activity beyond its general ability to reduce the total body iron load, and benefit to heart function." (*Id*. at 19–20.) Applicants made similar statements throughout the prosecution history.

The application was allowed on December 23, 2005.

VII. OVERVIEW OF CHALLENGE AND PRECISE RELIEF REQUESTED

In Grounds 1-5, Petitioner challenges claims 1–11, 13–17 and 19 of the '328 Patent as anticipated by each of MIMS 1998[7] (Ex. 1009), Hoffbrand 1998 (Ex. 1007), Olivieri Abstract 1995 (Ex. 1010), Agarwal 2000[8] (Ex. 1011), and Olivieri

[7] *Monthly Index of Medical Specialties*, Vol. 18, No. 12, December 1998 ("MIMS 1998," Ex. 1009).

[8] 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. 1010).

1995[9] (Ex. 1012) (collectively, "the Primary References").

In Grounds 6–10, Petitioner challenges claims 1–17 and 19 of the '328 Patent as obvious over each of the Primary References in view of the knowledge of a person of ordinary skill in the art.

Petitioner's challenge to the claims of the '328 patent are based on the bedrock principle that a patent may not be supported by a mere discovery of an alleged new benefit of an old process, when that process was used in the same way and for the same reason as disclosed in the prior art. *See, e.g.*, *King Pharmaceuticals, Inc. v. Eon Labs, Inc.*, 616 F.3d 1267, 1276 (Fed. Cir. 2010), discussed in detail *infra*.

This petition is supported by the Expert Declaration of Dr. Jayesh Mehta, M.D. (Ex. 1002.) Dr. Mehta is Professor of Medicine and Director of the Hematopoietic Stem Cell Transplant Program at the Northwestern University Feinberg School of Medicine. He has extensive experience treating thalassemia patients for iron overload using chelators including those described in the '328 Patent. In particular, he has administered deferiprone to thalassemia patients as early as 1989.

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[9] 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. 1011).

The petition and supporting declaration show that there is at least a reasonable likelihood that Petitioner will prevail with respect to at least one of the challenged claims. *See* 35 U.S.C. § 314(a). Petitioner respectfully requests that the Board institute IPR and find claims 1–17 and 19 unpatentable.

VIII. LEVEL OF ORDINARY SKILL IN THE ART

As Dr. Mehta explains, as of June 2000, the priority date of the '328 Patent, physicians had been treating iron overload in blood-transfusion-dependent patients with iron chelators for decades. The art of treating iron overload using iron chelators was very mature, and the level of ordinary skill in the art was relatively high in 2000. A person of 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. The skilled person would have been familiar with blood disorders such as thalassemia or hemochromatosis[10], including their causes and treatments. (Ex. 1002 (Mehta Dec.) at ¶ 41.)

[10] Hemochromatosis is a genetic disorder which causes the body to load too much iron. (Ex. 1002 (Mehta Dec.) at ¶ 41.)

IX. BACKGROUND ON DEFERIPRONE AND IRON OVERLOAD

As conceded by the Patent Owner, at least 250 articles discuss the use of deferiprone as an orally administered iron chelator by transfusion-dependent patients in order to reduce iron overload, and 48 of these articles provide data on this use. (Ex. 1001 ('328 Patent) at col. 6, ll. 57–61.) The patent specification also says that deferiprone was "commonly" administered at a dose of 75 mg/kg per day. (*Id*. at col. 7, ll. 2–3.) Indeed, the prior art shows that deferiprone is an old drug, was known at the time that the patent was filed, and was "commonly" used to treat transfusion-dependent patients in order to reduce iron overload. Petitioner further agrees with Patent Owner that "a general review of the literature reveals that deferiprone is effective in removing iron from patients who are iron loaded." (*Id*. at col. 9, ll. 34–36.)

A. "Iron-Overload Conditions of the Heart" in Transfusion-Dependent Patients

Thalassemia is a type of anemia, a disorder in which a person's blood cells are not able to hold and transport oxygen sufficiently to the body tissues. ((Ex. 1002 (Mehta Dec.) at ¶ 27; Ex. 1001 ('328 Patent) at col. 1, ll. 27–32.) Left untreated, a patient with thalassemia has a life expectancy of less than 20–30 years.

(Ex. 1002 (Mehta Dec.) at ¶ 26; Ex. 1014 (Olivieri 1994[11]) at 574; Ex. 1001 ('328 Patent) at col. 2, ll. 16–17.) A regimen of regular blood transfusions is effective at treating thalassemia. (Ex. 1002 (Mehta Dec.) at ¶ 27.) This treatment has been known and used since at least the 1960s. (Ex. 1015 (Nathan 1966[12]) at 828; Ex. 1001 ('328 Patent) at col. 1, ll. 27–29.) A thalassemia patient is therefore characterized as "transfusion-dependent." The '328 Patent recognizes that thalassemia causes a patient to be transfusion-dependent, and its claims are drawn to treating a "transfusion dependent patient."[13]

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[11] Olivieri et al., *Survival in Medically Treated Patients with Homozygous β-Thalassemia*, N. ENGL. J. MED., 331:547–78, 1994 ("Olivieri 1994," Ex. 1014.)

[12] Nathan & Gunn, *Thalassemia: The Consequences of Unbalanced Hemoglobin Synthesis*, AMERICAN JOURNAL OF MEDICINE, 41:815–30, 1966 ("Nathan 1966," Ex. 1015.)

[13] Two sub-types of thalassemia are described in the literature. Patients with "Thalassemia Major" are always transfusion dependent, while patients with "Thalassemia Intermedia" may or may not be transfusion dependent. *See* Bannerman et al., *Thalassemia Intermedia, with Iron Overload, Cardiac Failure, Diabetes Mellitus*, *Hypopituitarism and Porphyrinuia*, AMERICAN JOURNAL OF MEDICINE, 476–86, 1967 ("Bannerman 1967," Ex. 1016.)

The frequent blood transfusions received by a patient with thalassemia, while providing the patient with a life-saving mechanism to hold and transport oxygen to the body tissues, also delivers other blood components, including iron, to the patient. (Ex. 1002 (Mehta Dec.) at ¶ 28.) While humans require a low level of iron in their bodies, there is no natural mechanism by which the human body eliminates excess iron, and patients who receive regular blood transfusions therefore build up an excess of iron in their bodies. (*Id*.) The build-up of excess iron in the body resulting from blood transfusions leads to a condition called "iron overload," which, left untreated, causes cardiac disease, dysfunction in other organs and premature death, most commonly due to cardiac failure. (*Id*. at ¶¶ 28-29; Ex. 1017 (Barman Balfour 1999[14]) at 557–58.)

As Dr. Mehta explains, all transfusion-dependent patients must be treated for iron overload. The objective of this treatment is to treat iron overload in general, and to reduce the risk of developing dysfunction in any organ affected by iron

[14] Barman Balfour & Foster, *Deferiprone: A Review of its Clinical Potential in Iron Overload in β-Thalassemia Major and Other Transfusion-Dependent Diseases*, DRUGS 58(3):553–78, 1999 ("Barman Balfour 1999," Ex. 1017.)

overload including the heart and the liver. (Ex. 1002 (Mehta Dec.) at ¶ 30; *see also* Ex. 1027 (Borgna-Pignatti 1998[15]).)

B. Iron Chelators Treat Iron-Overload Conditions

A "chelator" is an agent that binds metal ions. (Ex. 1002 (Mehta Dec.) at ¶ 30; Ex. 1026 (Faa 1999[16]) at 292.) When taken as a drug, an iron chelator binds to "free" iron, forming a complex. (Ex. 1026 (Faa 1999) at 293.) This complex is excreted as waste, thereby removing toxic free iron from the body. (*Id*.) Iron ions have six electrochemical coordination sites and an iron chelator acts by binding to these six sites to inactivate the free iron, preventing unwanted reactions within the body. (Ex. 1002 (Mehta Dec.) at ¶ 36; Ex. 1017 (Barman Balfour) at 558; Ex. 1001 ('328 patent) at col. 13, ll. 41-50.)

1. Desferrioxamine

Introduced in 1960, desferrioxamine was the first iron chelator widely used to treat iron overload in transfusion-dependent patients. (Ex. 1002 (Mehta Dec.) at

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[15] Borgna-Pignatti, *Survival and Disease Complications in Thalassemia Major*, ANNALS NEW YORK ACADEMY OF SCIENCES, 227–31, 1998 ("Borgna-Pignatti 1998," Ex. 1027.)

[16] Faa & Crisponi, *Iron Chelating Agents in Clinical Practice*, COORDINATION CHEMISTRY REVIEWS, 184:291–310, 1999 ("Faa 1999," Ex. 1026.)

¶ 32; Ex. 1018 (Barry 1974[17]) at 17; Ex. 1026 (Faa 1999) at 294; Ex. 1001 ('328 Patent) at col. 13, ll. 41–46.) Desferrioxamine is "hexadentate," which means that one molecule of desferrioxamine binds to all six coordination sites of an iron ion. (Ex. 1002 (Mehta Dec.) at ¶ 36.) Desferrioxamine is not orally active and must be administered either intramuscularly or subcutaneously via an infusion that takes 8–12 hours. (*Id*. at ¶ 32; Ex. 1019 (Kontoghiorghes 1991[18]) at 1279; Ex. 1001 ('328 Patent) at col. 1, ll. 54–59.) The infusion must be given between five and seven times per week to be effective, and is usually done overnight. (Ex. 1002 (Mehta Dec.) at ¶ 32; Ex. 1006 (Hoffbrand 1997) at 37; Ex. 1001 ('328 Patent) at col. 2, ll. 26–30.) Desferrioxamine is expensive and, coupled with the need for prolonged, overnight transfusions, often results in poor patient compliance. (Ex. 1002 (Mehta Dec.) at ¶ 33; Ex. 1017 (Barman Balfour) at 554; Ex. 1001 ('328 Patent) at col. 1, ll. 59–62.)

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[17] Barry et al., *Long-Term Chelation Therapy in Thalassemia Major: Effect on Liver Iron Concentration, Liver Histology, and Clinical Progress*, BMJ, 2:16–20, 1974 ("Barry 1974," Ex. 1018.)

[18] Kontoghiorghes, *Oral Iron Chelation Is Here*, BMJ, 303:1279–80, 1991 ("Kontoghiorghes 1991," Ex. 1019.)

2. Deferiprone

Because of the compliance and expense problems associated with desferrioxamine treatment, researchers worked on developing alternate chelators in the years following the introduction of desferrioxamine. (Ex. 1020 (Nathan 1995[19]) at 954; Ex. 1001 ('328 Patent) at col. 1, ll. 59–62.) In 1982, Robert Charles Hider of King's College, London, successfully developed deferiprone, which is an orally active iron chelator. (*See* Ex. 1021 (Hider Patent[20]).) Deferiprone was approved in India in 1995 and in European, South American, and other Asian countries in 1999. (Ex. 1002 (Mehta Dec.) at ¶ 35; Ex. 1009 (MIMS 1998); Ex. 1022 (Diav-Citrin[21]) at 243; Ex. 1025 (Kontogiorghes 2000[22]).)

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[19] Nathan, *An Orally Active Iron Chelator*, N. ENGL. J. MED., 332(14):953–54, 1995 ("Nathan 1995," Ex. 1020.)

[20] GB 2 118 176, *Pharmaceutically Active 3-Hydroxypyrid-2-and-4-ones*, published in October 1983 ("Hider Patent," Ex. 1021.)

[21] Diav-Citrin & Koren, *Oral Iron Chelation with Deferiprone*, NEW FRONTIERS IN PEDIATRIC DRUG THERAPY, 44(1):235–47, 1997 ("Diav-Citrin 1997," Ex. 1022.)

[22] Kontoghiorghes et al., *L1-Deferiprone Worldwide Update and New Strategies for Improving Its Therapeutic Efficiency*, 10TH INTERNATIONAL CONFERENCE ON ORAL CHELATORS IN THE TREATMENT OF THALASSEMIA AND OTHER DISEASES AND BIOMED MEETING, March 2000 ("Kontoghiorghes 2000," Ex. 1025.)

Deferiprone is "bidentate," which means that three molecules of deferiprone are necessary to chelate a single ion of iron. As compared to desferrioxamine, three times as many molecules of deferiprone are necessary to chelate one iron ion. (Ex. 1002 (Mehta Dec.) at ¶ 36; Ex. 1020 (Nathan 1995) at 953.) Further, the half-life of deferiprone is a mere 1.9 hours; patients therefore need to take multiple doses of deferiprone throughout the day. (Ex. 1002 (Mehta Dec.) at ¶ 36; Ex. 1017 (Barman Balfour) at 555.) Early trials with deferiprone revealed that the drug was successful in chelating iron, as measured by urinary iron excretion, blood iron levels or liver iron content, but some patients developed severe neutropenia/agranulocytosis, a potentially serious side effect, upon treatment with deferiprone. (Ex. 1002 (Mehta Dec.) at ¶ 36; Ex. 1017 (Barman Balfour) at 559; Ex. 1001 ('328 Patent) at col. 1, ll. 63–col. 2, ll. 8.) Because of the possibility of these severe side effects and the short half-life of deferiprone, some physicians and researchers recommend deferiprone for use only in patients who are unable to adhere to the difficult desferrioxamine regimen. (Ex. 1002 (Mehta Dec.) at ¶ 36; Ex. 1022 (Diav Citrin) at 244; Ex. 1001 ('328 Patent) at col. 2, ll. 1–8.)

Despite the need for multiple doses daily and the potential side effects of deferiprone, by 2000, more than 6000 patients in 40 countries had been using deferiprone for more than 12 years. (Ex. 1002 (Mehta Dec.) at ¶ 36; Ex. 1025 (Kontoghiorghes 2000).) In 2011, the FDA approved deferiprone in the United

States for "the treatment of patients with transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate." (Ex. 1023 (Deferiprone Label 2011)[23]. Deferiprone is marketed under the trade name FERRIPROX, and the label provides "a total daily dose of 75 mg/kg to 99 mg/kg body weight." (Ex. 1023 (FERRIPROX Label) at 1.)

X. CLAIM CONSTRUCTION

Because the '328 Patent has not yet expired, and will not expire during the pendency of this proceeding, the challenged claims should be given their broadest reasonable construction in light of the patent specification. 37 C.F.R. § 42.100(b); *see also Cuozzo Speed Techs. LLC v. Lee*, 136 S. Ct. 2131, 2142 (2016). "Under a broadest reasonable interpretation, words of the claim must be given their plain meaning, unless such meaning is inconsistent with the specification and prosecution history." *Trivascular, Inc. v. Samuels*, 812 F.3d 1056, 1062 (Fed. Cir. 2016).

Independent claims 1–10 of the '328 Patent, except claim 3, each have three parts: (1) a preamble identifying a transfusion-dependent patient with an iron overload condition; (2) the administration of a therapeutically effective amount of deferiprone or a physiologically acceptable salt thereof to the patient; and (3) an

[23] Prescribing Information for Ferriprox® (deferiprone) tablets, for oral use (Revised 10/2011) ("Deferiprone Label 2011," Ex. 1023.)

intended result that the "therapeutically effective amount" is "sufficient" to treat the condition stated in the preamble (claims 1, 2, 4, and 5), or that it preferentially reduces the iron in the heart (claims 6–10). Claim 3 does not contain a third clause stating an intended result or a property of administering deferiprone.

1. Preamble – Identification of "the Patient"

Although preamble language in a claim is generally not limiting, the preambles of claims 1–10 are limiting to the extent they provide information that is necessary to understand the remainder of the claims: the preambles provide information on (1) the patient who is to be treated, i.e., they provide antecedent basis for the recited "patient" in the second clause of the claim, and (2) the medical condition of the patient for which a "therapeutically effective amount" of deferiprone must be administered. *See Catalina Mktg. Int'l, Inc. v. Coolsavings.com, Inc.*, 289 F.3d 801, 808 (Fed. Cir. 2002) (holding that a preamble may be limiting when the body of the claim relies on the preamble for antecedent basis and when the preamble "is essential to understand limitations or terms in the claim body").

The preambles of claims 1–10 are as follows:

- Claim 1: "A method of treating iron induced cardiac disease in a blood transfusion dependent patient experiencing an iron overload condition of the heart"

- Claim 2: “A method of treating iron loading in the heart of a blood transfusion dependent patient experiencing an iron overload condition of the heart”
- Claim 3: “A method of treating iron loading in the heart of a blood transfusion dependent patient risking iron overload of the heart”
- Claim 4: “A method of stabilizing iron induced heart disease in blood transfusion dependent patients having iron overload”
- Claim 5: “A method of reducing the iron burden in the heart associated with iron induced heart disease in blood transfusion dependent patients having iron overload”
- Claim 6: “A method of treating iron induced heart disease in a blood transfusion dependent patient having an iron overload condition of the heart”
- Claim 7: “A method of treating iron loading in the heart of blood transfusion dependent patient having an iron overload condition of the heart”
- Claim 8: “A method of treating iron loading in the heart of blood transfusion dependent patient having an iron overload condition of the heart”

- Claim 9: "A method of treatment of iron induced heart disease in a blood transfusion dependent patient having an iron overload condition of the heart"
- Claim 10: "a method to reduce the occurrence of iron-induced cardiac disease in a blood transfusion dependent patient with an iron overload condition"

According to the plain meaning of the terms, each of these preambles describes a blood-transfusion-dependent patient with iron overload. Some claims further require that the patient has an "iron overload condition of the heart."

Claims 4, 5, and 10 identify a blood-transfusion dependent patient "**having iron overload**" (claims 4 and 5) or "**with an iron overload condition**" (claim 10), in general. All patients who are blood-transfusion dependent, i.e. thalassemia major patients, have iron overload. (*See* Ex. 1002 (Mehta Dec.) at ¶ 59; Ex. 1001 at 1:27–32 ("transfusions create a widespread iron overload in the patient").)

Claim 3 identifies a blood-transfusion dependent patient "**risking iron overload of the heart**" (claim 3). All blood-transfusion dependent patients, i.e. thalassemia major patients, risk iron overload of the heart. (*See* Ex. 1002 (Mehta Dec.) at ¶ 59; Ex. 1001 ('328 Patent) at 29–31 ("iron overload is dangerous since the excessive iron can cause toxic degenerative changes in the heart, liver and

endocrine organs"); *id*. at Abstract ("iron induced cardiac disease [is] normally associated with iron overload.").)

Claims 1, 2, and 6–9 identify a patient who is "**experiencing an iron overload condition of the heart**" (claims 1 and 2) or who is "**having an iron overload condition of the heart**" (claims 6, 7, 8, and 9). Patients who have an "iron overload condition of the heart" are best understood 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. (Ex. 1002 (Mehta Dec.) at ¶ 60.) And as stated during the prosecution history of the '328 Patent, "regular blood transfusions cause an increase in overall body iron load in transfusion dependent patients, including iron loading of the heart." *Id.*; *see also* Ex. 1004 (Prosecution History of the '328 Patent) September 29, 2005 Response at 7.

2. Administration of a "Therapeutically Effective Amount"

Each of independent claims 1–10 describes only one step: the administration of a "therapeutically effective amount" of deferiprone. A therapeutically effective amount is one that causes adequate chelation. For example, the prior art teaches that a daily dose of 75 mg of deferiprone per kg of body weight is a therapeutically effective amount. (*See, e.g.,* Ex. 1012 (Olivieri 1995); Ex. 1010 (Olivieri Abstract 1995); Ex. 1011 (Agarwal 2000); Ex. 1007 (Hoffbrand 1998).)

The administered amount of deferiprone is further defined in dependent claims 13, 14 and 15. Dependent claim 13 depends from any of claims 1–10, and further requires that the daily dose of deferiprone is "in the range of up to 150 mg per kilogram of body weight;" dependent claim 14 depends from any of claims 1–10 and further requires that the daily dose of deferiprone is "in the range of up to 125 mg per kilogram of body weight;" and dependent claim 15 depends from any of claims 1–10, and further requires that the daily dose is "in the range of 25 to 75 mg per kilogram of body weight." Because claims 13, 14, and 15 depend from each of claims 1–10, claims 13, 14, and 15 must each be narrower in scope than any of claims 1–10. *See* M.P.E.P § 608.01(i), explaining that dependent claims must further limit the independent claims on which they depend; *see also* 35 U.S.C. § 112(d). Therefore, the "therapeutically effective amount" recited in each of claims 1–10 must 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.

3. Recitation of Intended Results

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. Instead, these clauses, which merely

recite the intended result of the method, are non-limiting. *See Syntex (U.S.A.) LLC v. Apotex, Inc.*, 407 F.3d 1371, 1378 (Fed. Cir. 2005) (holding that the phrase "in a stabilizing amount" recited in the body of the claim was not limiting because it "simply describes the intended result of using the weight to volume ratios recited in the claims"); *Endo Pharm. Inc. v. Watson Labs., Inc.*, No. 2:13-cv-192, 2014 WL 2859349, at *6, *8 (E.D. Tex. Jun. 23, 2014) (holding that the claim term "thereby administering a topically or systemically active agent with increased penetration" recited in the body of the claim was non-limiting because it was "simply a statement of intended result or purpose, to be accorded no weight"); *In re Copaxone*, Civil Action No. 14–1171-GMS, 2016 WL 873062, at *2 n.1–2 (D. Del. Mar. 7, 2016) (finding language such as "regimen being *sufficient to* alleviate the symptom of the patient" to be non-limiting). (*See also* Ex. 1002 (Mehta Dec.) at ¶¶ 55–56, 66 (explaining that the statements of intended results do not change or alter the steps of the claimed methods.)

In a case with strikingly similar claims and facts to those presented here, the Federal Circuit held 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." *Bristol-Myers Squibb Co. v. Ben Venue Labs.*, 246 F.3d 1368, 1376 (Fed. Cir. 2001). In that case, the claims were drawn to an old method, treating a patient suffering from a taxol-sensitive

tumor with a taxol, and also recited intended results, "reduced hematologic toxicity." As a matter of claim construction, and over patent owner's assertions that the recitation of intended results must be limiting so as to differentiate one claim from another under the doctrine of claim differentiation, the court held that the expressions of intended results were not limiting: claims with recitations of different intended results are co-extensive and are each limited to practicing the actual steps of the claims, "without regard to the result of performing the claimed steps." *Id*.

The Federal Circuit in that case also rejected an argument that the recitation of intended results must be a limitation so as to preserve the validity of the claims, which differed from the prior art only in the intended results: "Finally, we address Bristol's argument that new uses of old processes are patentable, that we should treat the expressions of efficacy as limitations because they distinguish the new use of the process over the prior art, and that claims should be read to preserve their validity. Bristol is correct that new uses of known processes may be patentable . . . However, the claimed process here is not directed to a new use; it is the same use, and it consists of the same steps as described by [the prior art]. Newly discovered results of known processes directed to the same purpose are not patentable because such results are inherent." *Id*. at 1376.

In this case, the statements of intended results are similarly not limiting. 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. Here, Patent Owner had expressly admitted that the entirety of the "invention" is the "discovery" of an alleged result of the claimed process:

> Applicant's [sic] have discovered that the administration of effective amounts of deferiprone results in patients being at less risk of developing cardiac disease than a patient treated with desferroxamine. Deferiprone preferentially reduces the iron stores in the heart in comparison to the iron stores in less critical organ/tissue in the body. Deferiprone's efficacy is cardio preferential when compared with its ability to lower total iron stores in the body.

(Ex. 1004 (Prosecution History) at 238.) But, as explained, these "newly discovered results" of a known method of treating iron overload with deferiprone are not patentable. Because the actual steps of the claimed methods may be practiced without regard to the result of performing the claimed methods, the recitations of intended results are therefore not properly claim limitations.

Independent claims 1–10 are therefore each drawn to the single step of administrating an effective amount of deferiprone to a blood-transfusion-dependent patient. All of the patients identified in the claims have iron overload, and some of the claims further require that the has an "iron overload condition of the heart,"

i.e., a condition on the spectrum of cardiac disease due to iron overload. And an amount of 75 mg of deferiprone per kg of body weight per day is a "therapeutically effective amount" within the scope of all of the claims.

Petitioner reserves the right to propose different claim constructions in different proceedings where the claim construction standard may be different.

XI. Grounds 1–5: Anticipation of Claims 1–11, 13–17, and 19 by Each of MIMS 1998, Hoffbrand 1998, Olivieri Abstract 1995, Agarwal 2000, and Olivieri 1995

As explained above in the section on claim construction, claims 1–10 are each drawn to the single step of administering an effective amount of deferiprone to blood-transfusion-dependent patients who, by definition, are iron overloaded, and for some of the claims, to patients who have an "iron overload condition of the heart." As discussed below, each of the Primary References (MIMS 1998, Hoffbrand 1998, Olivieri Abstract 1995, Agarwal 2000, and Olivieri 1995) discloses this single step and therefore anticipates claims 1–10.

Claims 11, 16, and 17 each depend from any of claims 1–10. These claims specify the mode of administration, and each includes oral administration. Claims 11, 16, and 17 are therefore anticipated by a reference that, in addition to disclosing the single claimed method step, also discloses that deferiprone is administered orally.

Claims 13, 14, and 15 each depend from any of claims 1–10. These claims specify a dosage amount for administration, and each includes a dosage of 75 mg/kg per day. Claims 13, 14, and 15 are therefore anticipated by a reference that, in addition to disclosing the single claimed method step, also discloses that deferiprone is administered at a dose of 75 mg/kg per day.

Claim 19 depends from any of claims 1–10 and further states that deferiprone "has a cardio preferred/selective function when compared to desferrioxamine or other alternative chelating agents utilized in patients suffering iron overload." As discussed in detail below, this function, if true, is merely an inherent property of deferiprone, and not limiting, and therefore, claim 19 is anticipated by a reference that anticipates any of claims 1–10.

A. The Intended Results Stated in Claims 1, 2, 4–10 and 19 Are Not Limiting, But Nonetheless Are Inherently Anticipated by the Primary References

In *Bristol Myers Squibb v. Ben Venue*, discussed above with respect to claim construction, the Federal Circuit held that the claims were anticipated by prior art that disclosed each of the manipulative steps of the claims. As explained above, the recitations of intended results were construed to be non-limiting, and so the prior art did not need to disclose these results in order to anticipate. Moreover, in *Bristol*, the anticipatory prior art did not disclose any efficacy of the claimed method, but was still found to anticipate

since the prior art disclosed the identical method recited in the claims, and use of the method for the same purpose. Noting the inherent unpredictability in treating patients with complicated diseases, the court further explained that the lack of disclosed efficacy in the prior art "does not mean that the protocol he used would never result in an antitumor response." *Bristol*, 246 F.3d at 1378. The prior art disclosed the performance of the steps of the method for the same purpose as recited in the claims (i.e., to treat taxol-sensitive tumors), thereby enabled the method, and anticipated the claims.

In this case, the intended results specified in claims 1, 2, 4–10, and 19 are not limiting, just as the claimed intended results were not limiting in *Bristol.* Therefore, whether the prior art identically discloses the claimed intended results is irrelevant. In this case, the prior art discloses the identical method of the claims, and use of the method for the identical purpose (i.e., to treat iron overload and its associated conditions), and therefore enables and anticipates the claims. "[O]ne cannot obtain a valid patent on a known use of a known process that has been described in the literature more than one year prior to the date of one's invention. Such processes are old, regardless of the relative success of the prior and later participants." *Bristol*, 246 F.3d at 1380; *see also Verdegaal Bros., Inc. v. Union Oil Co. of California*, 814 F. 2d 628, 633 (Fed. Cir. 1987) (explaining that the burden to proven

anticipation of a method is "limited to establishing that [the prior art] disclosed the same process," and the burden does not include establishing that the prior art "recognized the…capabilities" of the process).

Even if, contrary to Federal Circuit precedent, the recitation of intended results in claims 1, 2, 4–10 and 19 are construed to be limitations, each of the Primary References inherently anticipates these claims because the recited results of administering an effective amount of deferiprone to a transfusion-dependent patient is the "natural result flowing from the prior art's explicitly explicated limitations." *King Pharmaceuticals,* 616 F.3d at 1276. Petitioner takes no position on whether deferiprone sufficiently treats cardiac disease, iron overload, or preferentially removes iron from the heart, but taking the claims at face value, such intended results are simply the natural property or behavior of deferiprone when administered to a blood-transfusion-dependent patient. (Ex. 1002 (Mehta Dec.) at ¶¶ 67, 77.)

The Federal Circuit has long held that a patentee cannot prevent the public from using a known method simply by claiming some previously unknown property, effect, or result of the prior art method. In *King Pharmaceuticals*, quoted above, the Federal Circuit held that claims to a method of increasing metaxalone's bioavailability by taking that drug while ingesting food was inherently anticipated by prior art that disclosed (1)

taking metaxalone (2) while ingesting food. *King Pharmaceuticals*, 616 F.3d at 1276. Because the two steps were "undeniably disclosed by the prior art," and because of the patent-in-suit's teachings that an increase in metaxalone's bioavailability resulted upon taking the drug while ingesting food, "an increase in metaxalone's bioavailability is, therefore, an inherent aspect of the prior art." *Id*. Here, to the extent that deferiprone is capable of directly or preferentially removing iron from the heart, these properties are the inherent and natural results of treatment of an appropriate patient with an effective amount of deferiprone. Therefore, each of the Primary References, which discloses treatment with deferiprone of a blood-transfusion-dependent patient who has iron overload or is "an iron-overload condition of the heart," i.e., a condition on the spectrum of cardiac disease due to iron overload, inherently anticipates claims 1, 2, 4–10, and 19.

B. Ground 1: Anticipation by MIMS 1998 (Ex. 1009)

- MIMS 1998 is the Monthly Index of Medical Specialties that was published in December 1998, as stated on its face. As Dr. Mehta explains, MIMS is an Indian publication that is akin to the Physician's Desk Reference ("PDR") in the United States, in that it lists approved drugs in India, along with information about those drugs. (Ex. 1002 (Mehta Dec.) at ¶ 72.) Dr. Mehta further explains that as of 2000,

MIMS was well known to POSAs as a reference book. (*Id.* at ¶ 72.) MIMS 1998 is therefore a printed publication and prior art to the '328 Patent under 35 U.S.C. § 102(b).

- As explained above, claims 3, 4, 5, 10, and 19 are directed to treating a transfusion-dependent patient, who necessarily has iron overload and risks an iron overload condition of the heart, with an effective amount of deferiprone, which may be 75 mg/kg/day. Claims 13, 14, and 15, each multiply dependent on any of claims 1-10, are directed to dosage ranges of deferiprone, and each includes a dose of 75 mg/kg/day. 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. (Ex. 1002 (Mehta Dec.) at ¶ 73.) MIMS 1998 also discloses that deferiprone is administered at a dose of 75 mg/kg per day. (Ex. 1009 (MIMS 1998) at 296.) MIMS 1998 therefore anticipates claims 3, 4, 5, 10, 13, 14, 15, and 19. (Ex. 1002 (Mehta Dec.) at ¶ 73.)
- Claims 1, 2, 6, 7, 8, and 9 require that the treated patient has "an iron-overload condition of the heart," i.e., a condition on the spectrum of cardiac disease due to iron overload. MIMS 1998 discloses that deferiprone is used to treat "iron-storage disease." (Ex. 1009 (MIMS

1998) at 256.) As Dr. Mehta explains, "iron-storage disease" is a broad term that includes iron overload due to transfusion dependency and also includes the entire spectrum of cardiac disease caused by iron overload. MIMS 1998 therefore anticipates claims 1, 2, 6, 7, 8, and 9. (Ex. 1002 (Mehta Dec.) at ¶ 73; s*ee also* Ex. 1026 (Faa 1999) at 293.)

- Claims 11, 16, and 17 are each multiply dependent on any of claims 1-10, are directed to the mode of administration, and includes oral administration. MIMS 1998 discloses that deferiprone is an oral agent, and therefore anticipates claims 11, 16, and 17. (*See* Ex. 1009 (MIMS 1998) at 296; *see also* Ex. 1002 (Mehta Dec.) at ¶ 73.)

C. Ground 2: Anticipation by Hoffbrand 1998 (Ex. 1007)

- Hoffbrand 1998 published in 1998 in the *Blood* journal. As Dr. Mehta declares, *Blood* was a prestigious journal as of 2000 and was well-known by POSAs. (Ex. 1002 (Mehta Dec.) at ¶ 74.) Hoffbrand 1998 is listed in the '328 Patent specification as "technical literature" of which the patent applicants were aware. (Ex. 1001 ('328 Patent) at 2:63–67, 4:47–50.) This confirms Dr. Mehta's statement that POSAs were familiar with the *Blood* journal, and had access to and were aware of Hoffbrand 1998. Hoffbrand 1998 is therefore a printed publication and prior art to the '328 Patent under 35 U.S.C. § 102(b).

- As explained above, claims 3, 4, 5, 10, and 19 are directed to treating a transfusion-dependent patient, who necessarily has iron overload and risks an iron overload condition of the heart, with an effective amount of deferiprone, which may be 75 mg/kg/day. Claims 13, 14, and 15, each multiply dependent on any of claims 1-10, are directed to dosage ranges of deferiprone, and each include a dose of 75 mg/kg/day. Hoffbrand 1998 discloses the treatment of "fifty-one iron-overloaded regularly transfused patients" with deferiprone. Thirty-eight of these patients were transfusion dependent and, since they were iron-overloaded, they risked an iron overload condition of the heart. (Ex. 1007 at 296; Ex. 1002 (Mehta Dec.) at ¶ 74.) Hoffbrand 1998 discloses administration of deferiprone at a dose of 75 mg/kg per day. (*Id*. at 295; *see* Ex. 1002 (Mehta Dec.) at ¶ 74.) Hoffbrand 1998 therefore anticipates claims 3, 4, 5, 10, 13, 14, 15, and 19. (Ex. 1002 (Mehta Dec.) at ¶ 74.)
- Claims 1, 2, 6, 7, 8, and 9 require that the treated patient has "an iron-overload condition of the heart," i.e., a condition on the spectrum of cardiac disease due to iron overload. Hoffbrand 1998 discloses that ten patients had a liver iron content above 15.0 mg/g dry weight, which falls in the range that has been associated with heart disease

due to iron overload. (Ex. 1007 (Hoffbrand 1998) at 297; Ex. 1002 (Mehta Dec.) at ¶¶ 74, 75.) Hoffbrand 1998 therefore anticipates claims 1, 2, 6, 7, 8, and 9.

- Claims 11, 16, and 17 are each multiply dependent on any of claims 1-10, are directed to the mode of administration, and includes oral administration. Hoffbrand 1998 discloses that deferiprone is an oral agent, and therefore anticipates claims 11, 16, and 17. (*Id*. at 295; *see* Ex. 1002 (Mehta Dec.) at ¶ 74.)

D. Ground 3: Anticipation by Olivieri Abstract 1995 (Ex. 1010)

- Olivieri Abstract 1995 published in the Program Book that was printed in conjunction with the 37th Annual Meeting of The American Society for Hematology ("ASH"), which took place in December 1995, in Seattle, Washington. As Dr. Mehta explains, the Annual Meeting of ASH was, and continues to be, a popular meeting and was well attended by POSAs in the1990s. (Ex. 1002 (Mehta Dec.) at ¶ 75.) The Program Book was distributed before or during the meeting to all meeting attendees. (*Id*. at 75.) Dr. Mehta attended the meeting in 1995, presented his own research at that meeting, and received a copy of the Program book in conjunction with that meeting. (*Id*. at 75.) In fact, Dr. Mehta authored abstracts that were printed in

the 1995 Program Book. (*Id*. at 75.) Further, Olivieri Abstract 1995 is listed in the '328 Patent specification as "technical literature" of which the patent applicants were aware. (Ex. 1001 ('328 Patent) at 2:63–67, 3:38–42.) This confirms Dr. Mehta's statement that POSAs were familiar with the ASH meetings, and had access to and were aware of Olivieri Abstract 1995. Olivieri Abstract 1995 is therefore a printed publication and prior art to the '328 Patent under 35 U.S.C. § 102(b).

- As explained above, claims 3, 4, 5, 10, and 19 are directed to treating a transfusion-dependent patient, who necessarily has iron overload and risks an iron overload condition of the heart, with an effective amount of deferiprone, which may be 75 mg/kg/day. Claims 13, 14, and 15, each multiply dependent on any of claims 1-10, are directed to dosage ranges of deferiprone, and each include a dose of 75 mg/kg/day. The Olivieri Abstract 1995 discloses treatment of "thalassemia major" patients who, by definition, are transfusion-dependent, with 75 mg/kg deferiprone per day. (Ex. 1010 (Olivieri Abstract 1995); Ex. 1002 (Mehta Dec.) at ¶ 75.) The initial average hepatic iron concentration ("HIC"), a measure of the iron in a patient's liver, for the patients was 9.1±5.4 mg/g dry weight. (Ex.

1010 (Olivieri Abstract 1995).) As Dr. Mehta explains, healthy, non-iron overloaded people have a low HIC, and the patients treated with deferiprone in Olivieri Abstract 1995 have high HIC levels, and thus either had iron overload or risked having iron overload of the heart. (Ex. 1002 (Mehta Dec.) at ¶ 75.) Olivieri Abstract 1995 therefore anticipates claims 3, 4, 5, 10, 13, 14, 15, and 19.

- Claims 1, 2, 6, 7, 8, and 9 require that the treated patient has "an iron-overload condition of the heart," i.e., a condition on the spectrum of cardiac disease due to iron overload. 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. (Ex. 1002 (Mehta Dec.) at ¶ 75.) Normal TRT is greater than 32 msec, as disclosed in Olivieri Abstract 1995. (Ex. 1010 (Olivieri Abstract 1995).) Thus, the patients who were treated with deferiprone in Olivieri Abstract 1995 had conditions on the spectrum of cardiac disease due to iron overload. Olivieri Abstract 1995 therefore anticipates claims 1, 2, 6, 7, 8, and 9. (Ex. 1002 (Mehta Dec.) at ¶ 75.)

- Claims 11, 16, and 17 are each multiply dependent on any of claims 1-10, are directed to the mode of administration, and includes oral administration. The Olivieri Abstract 1995 discloses that deferiprone is an oral agent, anticipating claims 11, 16, and 17. (*See* Ex. 1010 (Olivieri Abstract 1995); Ex. 1002 (Mehta Dec.) at ¶ 75.)

E. Ground 4: Anticipation by Agarwal 2000 (Ex. 1011)

- Agarwal 2000 published in the Program Book that was printed in conjunction with the 10th International Conference on Oral Chelators, which took place in March 2000, in Cyprus. As Dr. Mehta explains, the International Conference on Oral Chelators was a popular meeting and was well attended by doctors who treated blood-transfusion-dependent patients in early 2000s. (Ex. 1002 (Mehta Dec.) at ¶ 76.) Dr. Mehta is familiar with the meeting that took place in Cyprus, but did not attend that meeting. (*Id*. at ¶ 34.) Agarwal 2000 is listed in the '328 Patent specification as "technical literature" of which the patent applicants were aware. (Ex. 1001 ('328 Patent) at 2:63–67, 4:59–64.) Patent Owner also listed Agarwal 2000 on an information disclosure statement dated December 8, 2004. (Ex. 1004 (Prosecution History) at 283.) The identification of Agarwal 2000 during the prosecution of the application leading to the '328 Patent confirms Dr.

Mehta's statement that POSAs were familiar with the Oral Chelators meetings, and had access to and were aware of Agarwal 2000. Agarwal 2000 is therefore a printed publication and prior art to the '328 Patent under 35 U.S.C. § 102(a).

- As explained above, claims 3, 4, 5, 10, and 19 are directed to treating a transfusion-dependent patient, who necessarily has iron overload and risks an iron overload condition of the heart, with an effective amount of deferiprone, which may be 75 mg/kg/day. Claims 13, 14, and 15, each multiply dependent on any of claims 1-10, are directed to dosage ranges of deferiprone, and each include a dose of 75 mg/kg/day. Agarwal 2000 discloses continuous treatment of 22 patients who had blood-transfusion-dependent thalassemia with 75 mg/kg deferiprone for over a decade. (Ex. 1011 (Agarwal 2000).) The patients' average serum ferritin levels, a measure of iron in the blood, at the start of treatment was 5820±2660 ng/ml. (*Id*.) As Dr. Mehta explains, 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. (Ex. 1002

(Mehta Dec.) at ¶ 76; *see also* Ex. 1032 (Kratz[24]) at 1070.) Thus, many of the patients in Agarwal 2000 had iron overload. Agarwal 2000 thus anticipates claims 3, 4, 5, 10, 13, 14, 15, and 19. (Ex. 1002 (Mehta Dec.) at ¶ 76.)

- Claims 1, 2, 6, 7, 8, and 9 require that the treated patient has "an iron-overload condition of the heart," i.e., a condition on the spectrum of cardiac disease due to iron overload. Agarwal 2000 discloses that 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. Agarwal 2000 therefore anticipates claims 1, 2, 6, 7, 8, and 9. (Ex. 1002 (Mehta Dec.) at ¶ 76.)
- Claims 11, 16, and 17 are each multiply dependent on any of claims 1-10, are directed to the mode of administration, and includes oral administration. Agarwal 2000 discloses that deferiprone is orally administered. (*See* Ex. 1011 (Agarwal 2000).) Agarwal 2000 therefore anticipates claims 11, 16, and 17. (Ex. 1002 (Mehta Dec.) at ¶ 76.)

[24] Kratz, *Normal Reference Laboratory Values*, NEW ENGLAND JOURNAL OF MEDICINE, Vol. 339, No. 15 (1998) ("Kratz," Ex. 1032).

F. Ground 5: Anticipation by Olivieri 1995 (Ex. 1012)

- Olivieri 1995 was published in April 1995 in *The New England Journal of Medicine*. As Dr. Mehta states, *The New England Journal of Medicine* was a prestigious journal as of 2000 and was well known to POSAs. (Ex. 1002 (Mehta Dec.) at ¶ 77.) Olivieri 1995 is listed in the '328 Patent specification as "technical literature" of which the patent applicants were aware. (Ex. 1001 ('328 Patent) at 2:63–67, 6:10–14.) This identification of Olivieri 1995 in the '328 Patent confirms Dr. Mehta's statement that POSAs were familiar with the *New England Journal of Medicine*, and had access to and were aware of Olivieri 1995. Olivieri 1995 is therefore a printed publication and prior art to the '328 Patent under 35 U.S.C. § 102(b).
- As explained above, claims 3, 4, 5, 10, and 19 are directed to treating a transfusion-dependent patient, who necessarily has iron overload and risks an iron overload condition of the heart, with an effective amount of deferiprone, which may be 75 mg/kg/day. Claims 13, 14, and 15, each multiply dependent on any of claims 1-10, are directed to dosage ranges of deferiprone, and each include a dose of 75 mg/kg/day. Olivieri 1995 discloses treatment of blood-transfusion-dependent thalassemia patients who have "complications with iron

overload" with 75 mg/kg deferiprone per day. (Ex. 1012 (Olivieri 1995) at 918-19). Olivieri 1995 therefore anticipates claims 3, 4, 5, 10, 13, 14, 15, and 19. (Ex. 1002 (Mehta Dec.) at ¶ 77.)

- Claims 1, 2, 6, 7, 8, and 9 require that the treated patient has "an iron-overload condition of the heart," i.e., a condition on the spectrum of cardiac disease due to iron overload. At least two of the patients treated in Olivieri 1995 had established cardiac disease and were medicated for cardiac disease. Olivieri 1995 therefore anticipates claims 1, 2, 6, 7, 8, and 9. (Ex. 1012 (Olivieri 1995) at 918; Ex. 1002 (Mehta Dec.) at ¶ 77.)
- Claims 11, 16, and 17 are each multiply dependent on any of claims 1-10, are directed to the mode of administration, and includes oral administration. Olivieri 1995 discloses that deferiprone is orally administered. (Ex. 1012 (Olivieri 1995) at 918.) Olivieri 1995 therefore anticipates claims 11, 16, and 17. (Ex. 1002 (Mehta Dec.) at ¶ 77.)

XII. Grounds 6–10: Obviousness of Claims 1–17 and 19 over Each of MIMS 1998, Hoffbrand 1998, Olivieri Abstract 1995, Agarwal 2000, and Olivieri 1995

To the extent that the Board finds that any of claims 1–11, 13–17 and 19 are not anticipated, these claims are rendered obvious by each of the Primary

References in view of the knowledge of a person of ordinary skill in the art. Claim 12 is also rendered obvious by each of the Primary References in view of the knowledge of a person of ordinary skill in the art. (Ex. 1002 (Mehta Dec.) at ¶ 78.) A finding of obviousness requires factual inquiries into four areas: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claims and the prior art; and (4) secondary considerations of non-obviousness. *See e.g.*, *Redline Detection, LLC v. Star Envirotech, Inc.*, 811 F.3d 435, 449 (Fed. Cir. 2015) (citing *Graham v. John Deere Co. of Kan. City*, 383 U.S. 1, 17–18, 30 (1966)).

A. The Claims of the '328 Patent Are *Prima Facie* Obvious over Each of the Primary References in View of the Knowledge of a Person of Ordinary Skill in the Art

The level of ordinary skill in the art is described above in Section VIII.

The scope and content of the prior art in this case is described above, in Section XI. The scope and content of the prior art also includes the disclosures of each of the Primary References.

In this case, there are no discernable differences between the claims and the prior art. 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. (*See, e.g.*, Section XI; Ex. 1002 (Mehta Dec.) at ¶ 79.) The

prior art also teaches that deferiprone should be formulated with other excipients, as required by claim 12. (*See, e.g.*, Ex. 1021 (Hider Patent) at claim 1 (requiring a formulation of deferiprone with "a physiologically acceptable diluent or carrier").) As admitted in the patent specification, 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. (Ex. 1002 (Mehta Dec.) at ¶ 79; Ex. 1001 ('328 Patent) at col. 9, ll. 35–37 ("a general view of the literature reveals that deferiprone is effective in removing iron from patients who are iron loaded").) Thus, the prior art teaches every limitation of at least claims 3, 4, 5, 10–17 and 19, and a person of ordinary skill in the art would have known as much. Because there are no discernible differences between the claims and the prior art, the prior art renders claims 3, 4, 5, 10–17, and 19 obvious.

The prior art as a whole also taught the treatment of iron-overload conditions of the heart, e.g., cardiac disease due to iron overload, as discussed in Section XI on anticipation. To the extent that Patent Owner argues that the prior art, which, according to the specification of the '328 Patent, discloses the use of deferiprone to treat and reduce cardiac disease due to iron overload, such use would have been obvious. 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. (Ex. 1002 (Mehta Dec.) at ¶¶ 82-83.)

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. (Ex. 1002 (Mehta Dec.) at ¶¶ 82-83.) 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. (Ex. 1002 (Mehta Dec.) at ¶ 83; *see also* Ex. 1024 (Olson 1989[25]) at 116.) Further, it was well known that cardiac disease was a common cause of death in thalassemia patients and heart conditions such as cardiac disease were caused by iron overload. (Ex. 1002 (Mehta Dec.) at ¶ 29; *see also* Ex. 1001 ('328 patent) at col. 13, ll. 41-50; Ex. 1004 (Office Action Response,

[25] Olson et al., *Endomyocardial Biopsy in Hemochromatosis: Clinicopathologic Correlates in Six Cases*, JACC, 13(1):116–20, 1989 ("Olson 1989," Ex. 1024.)

July 30, 2004) ("the primary cause of death in patients with thalassemia is due to iron-induced heart disease"); Ex. 1022 (Diav-Citrin) at 239 ("the leading cause of death in iron-loaded patients is cardiac iron loading.").) Therefore, a person of ordinary skill would have understood prior-art statements regarding the efficacy of deferiprone to mean that the drug was efficacious in treating iron-overload conditions of the heart. (Ex. 1002 (Mehta Dec.) at ¶ 83.)

Further, the prior art expressly teaches, and a person of skill in the art would have understood, that patients with established heart disease due to iron overload were successfully treated with deferiprone. (*Id*.) For example, Olivieri 1992 reports on the successful improvement of cardiac function following nine months of treatment with deferiprone in a patient with iron-related organ toxicity, including cardiac dysfunction.[26] (*See* Ex. 1005 (Olivieri 1992) at 2747 (describing the condition of the patient as "mild cardiac diastolic dysfunction with lack of

[26] Although the patient had thalassemia intermedia and was not blood-transfusion dependent, he had iron-induced cardiac disease, which is the same disease that is targeted by the treatment method in the claims. As Dr. Mehta explains, a POSA would have looked to the success in Olivieri 1992 as relevant to iron-overloaded patients who are transfusion dependent. (Ex. 1002 (Mehta Dec.) at ¶ 83.)

systolic increase with exercise."); *see also* Ex. 1030 (Matsui[27]) (disussing a decrease in cardiac iron in a patient with established cardiac disease); Ex. 1002 (Mehta Dec.) at ¶ 83.)

Moreover, given the certainty of death resulting from untreated cardiac disease due to iron overload, and given the existence of only two agents that were approved and had been shown to be effective at chelating iron from the bodies of iron-overloaded patients, doctors certainly would have been motivated to use deferiprone to treat iron-overloaded patients, regardless of the specific level of cardiac disease an individual patient may have had. (Ex. 1002 (Mehta Dec.) at ¶ 82.) And, given the track record of deferiprone, which proved that deferiprone successfully chelated iron from iron-overloaded patients, doctors would have had a reasonable expectation that the deferiprone would reduce the iron load in the bodies of these patients, including in the hearts of these patients, thereby treating iron-overload conditions of the heart. (*Id.* at 83.)

A finding of obviousness requires only a reasonable expectation of success, not a guarantee of success. *See Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364

[27] Matsui, *Effective Iron Chelation Using the Oral Iron Chelator 1,2,-dimethyl-3-hydroxypyrid-4-one (L1), in Homozygous b-Thalassemia Major (HBT) Patients*, Abstract P1-43, Clinical Pharmacology & Therapeutics, 53(2) (1993) ("Matsui," Ex. 1030.)

(Fed. Cir. 2007) ("only a reasonable expectation of success, not a guarantee, is needed"); *see also In re Droge*, 695 F.3d 1334, 1338 (Fed. Cir. 2012) ("Obviousness does not require absolute predictability of success . . . .") (citation and internal quotation marks omitted). Here, the prior art's teachings that deferiprone treats iron overload, and that treatment of iron overload treats and reduces the risk of cardiac disease caused by iron overload, similarly provide reasonable expectation of success that treating patients with deferiprone would treat and reduce iron-overload conditions of the heart.

Therefore, the challenged claims are obvious over each of the Primary References in view of the knowledge of a person of ordinary skill in the art.

To the extent that, contrary to Federal Circuit precedent, the intended-results language in claims 1, 2, 4–10, and 19 are construed to be limitations, these results are inherent in the claimed method and, therefore, do not render the claims nonobvious. (Ex. 1002 (Mehta Dec.) at ¶¶ 67, 77, 84.) Inherency may supply a claim limitation that is not explicitly disclosed in the prior art in an obviousness analysis, when the limitation is "necessarily . . . present, or the natural result of the combination of elements explicitly disclosed by the prior art." *Par Pharm., Inc. v. TWi Pharm., Inc.*, 773 F.3d 1186, 1196 (Fed. Cir. 2014). For example, in *Alcon Research, Ltd. v. Apotex Inc.*, the Federal Circuit held that a claim to a "method of treating allergic eye diseases" with the drug olopatadine was obvious, and

concluded, *inter alia*, that the claim term "stabilizing conjunctival mast cells" was an inherent result of prior art disclosing administration of olopatadine at therapeutic concentrations, because "mast cell stabilization [is] a property that is necessarily present at those concentrations." *Alcon Research, Ltd. v. Apotex Inc.*, 687 F.3d 1362, 1367, 1369 (Fed. Cir. 2012). Similarly, in *Santarus, Inc. v. Par Pharmaceuticals, Inc.*, the court concluded that a claimed "method of treating a gastric acid related disorder" with a proton pump inhibitor ("PPI") was obvious and found that a claim term "reciting specific blood serum concentrations of PPI" was inherent in the prior art. *Santarus, Inc. v. Par Pharmaceuticals, Inc*., 694 F.3d 1344, 1354 (Fed. Cir. 2012). "The initial blood serum concentration resulting from administering a PPI dosage is an inherent property of the formulation, and an obvious formulation cannot become nonobvious simply by administering it to a patient and claiming the resulting serum concentrations." *Id.* Here, the intended results in claims 1, 2, 4–10, and 19 simply describe the intended results of treatment of patients with deferiprone—e.g., stabilization or removal of iron in the heart. Because the prior art disclosed the manipulative steps of the claims identically, the recited results are inherent in the prior art disclosures.

To the extent that Patent Owner argues that in 2002 a person of ordinary skill in the art would not have been motivated to treat transfusion-dependent patients with deferiprone, the prior art as a whole belies that argument: it is

undisputable that many prior art references taught the success of deferiprone in treating patients who had iron overload (and iron-overload conditions of the heart), that deferiprone has been approved by many regulatory agencies internationally, and that it had been used continuously since 1995. (Ex. 1002 (Mehta Dec.) at ¶ 35.)

B. No Secondary Considerations Overcome the *Prima Facie* Obviousness of the Claims

Secondary considerations of non-obviousness, such as commercial success, long-felt but unsolved needs, failure of others, and unexpected results, if present, must also be considered. *Stratoflex, Inc. v. Aeroquip Corp.,* 713 F.2d 1530, 1538–39 (Fed. Cir. 1983). However, for secondary considerations to be probative of non-obviousness, "its proponent must establish a nexus between the evidence and the merits of the claimed invention." *Wyers v. Master Lock Co*., 616 F.3d 1231, 1246 (Fed. Cir. 2010) (quotation omitted). Where the offered secondary consideration "actually results from something other than what is both claimed and novel in the claim, there is no nexus to the merits of the claimed invention." *In re Huai-Hung Kao,* 639 F. 3d 1057, 1068 (Fed. Cir. 2011).

In this case, Petitioner is 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, because the claims are directed to the known method of treating iron overload conditions in transfusion-

dependent patients administering the old drug deferiprone. Because the claimed methods are no different from the prior art methods, there is no secondary consideration of nonobviousness with a nexus to the claimed methods. (*See also* Ex. 1002 (Mehta Dec.) at ¶ 85.)

XIII. CONCLUSION

For the reasons set forth above, Petitioner respectfully submits that it has established a reasonable likelihood of success with respect to the challenged claims and requests that this petition be granted and the challenged claims cancelled.

Respectfully submitted,

Dated: May 16, 2017

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CERTIFICATE OF WORD COUNT

The undersigned certifies that the attached Petition for *Inter Partes* Review of U.S. Patent No. 7,049,328 contains 11,397 words (as calculated by the word processing system used to prepare this Petition), excluding the parts of the Petition exempted by 37 C.F.R. §42.24(a)(1).

Dated: May 16, 2017 By: /Huiya Wu/

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§ 42.6(e) and 42.105, I certify that on this 16th day of May, 2017 I served a copy of this PETITION FOR INTER PARTES REVIEW and copies of all supporting materials and exhibits by Federal Express Next Business Day Delivery on the following address for Patent Owner.

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