

**IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE**

ENDO PHARMACEUTICALS INC.,

Plaintiff,

v.

PERRIGO UK FINCO LIMITED
PARTNERSHIP,

Defendant.

C.A. No. 1:19-cv-00437-MN

**ANSWER, SEPARATE DEFENSES, AND COUNTERCLAIMS OF DEFENDANT
PERRIGO UK FINCO LIMITED PARTNERSHIP TO PLAINTIFF’S COMPLAINT**

Defendant Perrigo UK FINCO Limited Partnership (“Perrigo”), by and through the undersigned attorneys, hereby answers the Complaint of Plaintiff Endo Pharmaceuticals Inc. (“Endo” or “Plaintiff”) as follows:

NATURE OF ACTION

COMPLAINT:

1. This is a civil action for infringement of U.S. Patent No. 7,229,636 (“the ‘636 patent”), U.S. Patent No. 7,404,489 (“the ‘489 patent”), U.S. Patent No. 7,879,349 (“the ‘349 patent”), U.S. Patent No. 8,003,353 (“the ‘353 patent”), U.S. Patent No. 8,940,714 (“the ‘714 patent”), and U.S. Patent No. 9,415,007 (“the ‘007 patent”) (collectively, the “Patents-in-Suit”) pursuant to the Patent Laws of the United States, 35 U.S.C. § 1, *et seq.*

ANSWER: This paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, Perrigo admits that Plaintiff’s Complaint is for alleged patent infringement of U.S. Patent No. 7,229,636 (“the ‘636 patent”), U.S. Patent No. 7,404,489 (“the ‘489 patent”), U.S. Patent No. 7,879,349 (“the ‘349 patent”), U.S. Patent No. 8,003,353 (“the ‘353 patent”), U.S. Patent No. 8,940,714 (“the ‘714 patent”), and U.S. Patent

No. 9,415,007 (“the ‘007 patent”), but denies that Plaintiff is entitled to any relief. Perrigo denies the remaining allegations contained in this paragraph.

PARTIES

COMPLAINT:

2. Endo is a corporation organized and existing under the laws of the State of Delaware, having a principal place of business at 1400 Atwater Drive, Malvern, Pennsylvania 19355.

ANSWER: On information and belief, admitted.

COMPLAINT:

3. On information and belief, Perrigo is a limited partnership organized and existing under the laws of the United Kingdom, having a principal place of business at Wrafton, Branton, Devon, EX33 2DL, United Kingdom.

ANSWER: Perrigo admits that Perrigo is a United Kingdom entity with a place of business at Wrafton, Branton, Devon, EX33 2DL, United Kingdom. Perrigo denies the remaining allegations contained in this paragraph.

JURISDICTION AND VENUE

COMPLAINT:

4. This Court has subject matter jurisdiction over this action under 28 U.S.C. §§ 1331, 1338(a), 2201, and 2202.

ANSWER: This paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, denied. Answering further, Perrigo does not contest subject matter jurisdiction over Plaintiff’s infringement claims with respect to the ‘636, ‘489, ‘349, ‘353, ‘714, and ‘007 patents against Perrigo under 35 U.S.C. § 271(e)(2)(A) for purposes of this action only.

COMPLAINT:

5. This Court has personal jurisdiction over Perrigo by virtue of actions Perrigo has taken for the purpose of engaging in injury-causing and wrongful marketing conduct in this District. *See Acorda Therapeutics, Inc. v. Mylan Pharms. Inc.*, 817 F.3d 755, 759-60 (Fed. Cir. 2016), *cert. denied*, 137 S. Ct. 625 (2017).

ANSWER: This paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, denied. Answering further, Perrigo does not contest personal jurisdiction solely for the limited purpose of this action only.

COMPLAINT:

6. On information and belief, Perrigo submitted to the United States Food and Drug Administration (“FDA”) an Abbreviated New Drug Application (“ANDA”) for a generic copy of Nascobal® nasal spray (“Perrigo ANDA”), and seeks FDA approval to market and sell a generic copy of Nascobal® nasal spray (“Perrigo ANDA Product”).

ANSWER: This paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, Perrigo admits that Perrigo submitted Abbreviated New Drug Application (“ANDA”) No. 212458 to the U.S. Food and Drug Administration (“FDA”), pursuant to 21 U.S.C. § 355(j); that Perrigo’s ANDA contains paragraph IV certifications to the ‘636 patent, the ‘489 patent, the ‘349 patent, the ‘353 patent, the ‘714 patent, and the ‘007 patent; and that Perrigo seeks approval from FDA to engage in the commercial manufacture, use, sale, or importation of Cyanocobalamin Nasal Spray, 500 mcg/spray, before the expiration of the ‘636, ‘489, ‘349, ‘353, ‘714, and ‘007 patents. Answering further, Perrigo admits that the reference listed drug (“RLD”) identified in Perrigo’s ANDA No. 212458 is Nascobal® (cyanocobalamin) Nasal Spray, 500 mcg/spray. Perrigo denies the remaining allegations contained in this paragraph.

COMPLAINT:

7. On information and belief, Perrigo through the submission of the Perrigo ANDA, intends to commercially manufacture, use, import, market, offer for sale, and sell the Perrigo

ANDA Product throughout the United States, including in Delaware and in this District, in the event FDA approves the Perrigo ANDA. On information and belief, Perrigo intends to derive benefit from the Perrigo ANDA.

ANSWER: This paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, Perrigo admits that Perrigo submitted ANDA No. 212458 to FDA, pursuant to 21 U.S.C. § 355(j); that Perrigo's ANDA contains paragraph IV certifications to the '636 patent, the '489 patent, the '349 patent, the '353 patent, the '714 patent, and the '007 patent; and that Perrigo seeks approval from FDA to engage in the commercial manufacture, use, sale, or importation of Cyanocobalamin Nasal Spray, 500 mcg/spray, before the expiration of the '636, '489, '349, '353, '714, and '007 patents. Answering further, Perrigo does not contest personal jurisdiction solely for the limited purpose of this action only. Perrigo denies the remaining allegations contained in this paragraph.

COMPLAINT:

8. On information and belief, Perrigo is in the business of developing pharmaceutical drug products that are distributed in the United States, including in Delaware and in this District.

ANSWER: This paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, Perrigo admits that it makes and sells pharmaceutical products, including quality generic medicines. Answering further, Perrigo does not contest personal jurisdiction solely for the limited purpose of this action only. Perrigo denies the remaining allegations contained in this paragraph.

COMPLAINT:

9. On information and belief, Perrigo, itself or through one of its business partners or affiliates, has agreements with pharmaceutical retailers, wholesalers, or distributors, providing for the distribution of its products throughout the United States, including in Delaware and in this District.

ANSWER: This paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, Perrigo admits that it makes and sells pharmaceutical products, including quality generic medicines. Answering further, Perrigo does not contest personal jurisdiction solely for the limited purpose of this action only. Perrigo denies the remaining allegations contained in this paragraph.

COMPLAINT:

10. On information and belief, Perrigo, itself or through one of its business partners or affiliates, distributes pharmaceutical drug products throughout the United States, including in Delaware and in this District.

ANSWER: This paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, Perrigo admits that it makes and sells pharmaceutical products, including quality generic medicines. Answering further, Perrigo does not contest personal jurisdiction solely for the limited purpose of this action only. Perrigo denies the remaining allegations contained in this paragraph.

COMPLAINT:

11. On information and belief, Perrigo products are sold in pharmacies throughout the United States, including in Delaware and in this District.

ANSWER: This paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, Perrigo does not contest personal jurisdiction solely for the limited purpose of this action only. Perrigo denies the remaining allegations contained in this paragraph.

COMPLAINT:

12. On information and belief, Perrigo derives substantial revenue from selling various pharmaceutical drug products and doing business throughout the United States, including in Delaware and in this District.

ANSWER: This paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, Perrigo admits that it makes and sells pharmaceutical products, including quality generic medicines. Answering further, Perrigo does not contest personal jurisdiction solely for the limited purpose of this action only. Perrigo denies the remaining allegations contained in this paragraph.

COMPLAINT:

13. Alternatively, this Court has jurisdiction over Perrigo under Federal Rule of Civil Procedure 4(k)(2)(A) because: (a) Endo's claims arise under federal law; (b) Perrigo is a foreign defendant not subject to general personal jurisdiction in the courts of any state; and (c) Perrigo has sufficient contacts with the United States as a whole, not least through its development of generic drugs for sale in the United States, such that this Court's exercise of jurisdiction over Perrigo satisfies due process.

ANSWER: This paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, denied. Answering further, Perrigo does not contest personal jurisdiction solely for the limited purpose of this action only.

COMPLAINT:

14. Venue is proper in this judicial district under 28 U.S.C. §§ 1391(c)(3) and/or 1400(b). On information and belief, Perrigo is a foreign entity that may be sued in any judicial district in the United States, in which it is subject to the court's personal jurisdiction. As set forth *supra*, Perrigo is subject to the Court's personal jurisdiction in this District.

ANSWER: This paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, denied. Answering further, Perrigo does not contest venue solely for the limited purpose of this action only.

THE PATENTS-IN-SUIT

COMPLAINT:

15. The '636 patent, titled "Cyanocobalamin Low Viscosity Aqueous Formulations for Intranasal Delivery," was duly and legally issued by the United States Patent and Trademark Office ("USPTO") on June 12, 2007. Endo owns and has exclusive rights to the '636 patent, including all rights to sue for infringement thereof.

ANSWER: This paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, Perrigo admits that, according to the online records of the U.S. Patent & Trademark Office (“USPTO”), the ‘636 patent is entitled “CYANOCOBALAMIN LOW VISCOSITY AQUEOUS FORMULATIONS FOR INTRANASAL DELIVERY,” and issued on June 12, 2007. Answering further, Perrigo admits that, according to the online records of the USPTO, Endo is the current assignee of the ‘636 patent. Perrigo denies any suggestion that the ‘636 patent was duly and legally issued, as well as any suggestion or implication that the ‘636 patent is valid or enforceable or that Perrigo infringes any claim of the ‘636 patent. Perrigo is without sufficient knowledge to admit or deny the remaining allegations of this paragraph, and therefore denies same.

COMPLAINT:

16. A true and correct copy of the ‘636 patent is attached hereto as Exhibit A.

ANSWER: This paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, Perrigo admits that what purports to be a copy of the ‘636 patent is attached to Plaintiff’s Complaint as Exhibit A.

COMPLAINT:

17. The ‘489 patent, titled “Cyanocobalamin Low Viscosity Aqueous Formulations for Intranasal Delivery,” was duly and legally issued by the USPTO on July 29, 2008. Endo owns and has exclusive rights to the ‘489 patent, including all rights to sue for infringement thereof.

ANSWER: This paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, Perrigo admits that, according to the online records of the USPTO, the ‘489 patent is entitled “CYANOCOBALAMIN LOW VISCOSITY AQUEOUS FORMULATIONS FOR INTRANASAL DELIVERY,” and issued on July 29,

2008. Answering further, Perrigo admits that, according to the online records of the USPTO, Endo is the current assignee of the ‘489 patent. Perrigo denies any suggestion that the ‘489 patent was duly and legally issued, as well as any suggestion or implication that the ‘489 patent is valid or enforceable or that Perrigo infringes any claim of the ‘489 patent. Perrigo is without sufficient knowledge to admit or deny the remaining allegations of this paragraph, and therefore denies same.

COMPLAINT:

18. A true and correct copy of the ‘489 patent is attached hereto as Exhibit B.

ANSWER: This paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, Perrigo admits that what purports to be a copy of the ‘489 patent is attached to Plaintiff’s Complaint as Exhibit B.

COMPLAINT:

19. The ‘349 patent, titled “Cyanocobalamin Low Viscosity Aqueous Formulations for Intranasal Delivery,” was duly and legally issued by the USPTO on February 1, 2011. Endo owns and has exclusive rights to the ‘349 patent, including all rights to sue for infringement thereof.

ANSWER: This paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, Perrigo admits that, according to the online records of the USPTO, the ‘349 patent is entitled “CYANOCOBALAMIN LOW VISCOSITY AQUEOUS FORMULATIONS FOR INTRANASAL DELIVERY,” and issued on February 1, 2011. Answering further, Perrigo admits that, according to the online records of the USPTO, Endo is the current assignee of the ‘349 patent. Perrigo denies any suggestion that the ‘349 patent was duly and legally issued, as well as any suggestion or implication that the ‘349 patent is valid or enforceable or that Perrigo infringes any claim of the ‘349 patent. Perrigo is without

sufficient knowledge to admit or deny the remaining allegations of this paragraph, and therefore denies same.

COMPLAINT:

20. A true and correct copy of the '349 patent is attached hereto as Exhibit C.

ANSWER: This paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, Perrigo admits that what purports to be a copy of the '349 patent is attached to Plaintiff's Complaint as Exhibit C.

COMPLAINT:

21. The '353 patent, titled "Cyanocobalamin Low Viscosity Aqueous Formulations for Intranasal Delivery," was duly and legally issued by the USPTO on August 23, 2011. Endo owns and has exclusive rights to the '353 patent, including all rights to sue for infringement thereof.

ANSWER: This paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, Perrigo admits that, according to the online records of the USPTO, the '353 patent is entitled "CYANOCOBALAMIN LOW VISCOSITY AQUEOUS FORMULATIONS FOR INTRANASAL DELIVERY," and issued on August 23, 2011. Answering further, Perrigo admits that, according to the online records of the USPTO, Endo is the current assignee of the '353 patent. Perrigo denies any suggestion that the '353 patent was duly and legally issued, as well as any suggestion or implication that the '353 patent is valid or enforceable or that Perrigo infringes any claim of the '353 patent. Perrigo is without sufficient knowledge to admit or deny the remaining allegations of this paragraph, and therefore denies same.

COMPLAINT:

22. A true and correct copy of the '353 patent is attached hereto as Exhibit D.

ANSWER: This paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, Perrigo admits that what purports to be a copy of the ‘353 patent is attached to Plaintiff’s Complaint as Exhibit D.

COMPLAINT:

23. The ‘714 patent, titled “Cyanocobalamin Low Viscosity Aqueous Formulations for Intranasal Delivery,” was duly and legally issued by the USPTO on January 27, 2015. Endo owns and has exclusive rights to the ‘714 patent, including all rights to sue for infringement thereof.

ANSWER: This paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, Perrigo admits that, according to the online records of the USPTO, the ‘714 patent is entitled “CYANOCOBALAMIN LOW VISCOSITY AQUEOUS FORMULATIONS FOR INTRANASAL DELIVERY,” and issued on January 27, 2015. Answering further, Perrigo admits that, according to the online records of the USPTO, Endo is the current assignee of the ‘714 patent. Perrigo denies any suggestion that the ‘714 patent was duly and legally issued, as well as any suggestion or implication that the ‘714 patent is valid or enforceable or that Perrigo infringes any claim of the ‘714 patent. Perrigo is without sufficient knowledge to admit or deny the remaining allegations of this paragraph, and therefore denies same.

COMPLAINT:

24. A true and correct copy of the ‘714 patent is attached hereto as Exhibit E.

ANSWER: This paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, Perrigo admits that what purports to be a copy of the ‘714 patent is attached to Plaintiff’s Complaint as Exhibit E.

COMPLAINT:

25. The ‘007 patent, titled “Cyanocobalamin Low Viscosity Aqueous Formulations for Intranasal Delivery,” was duly and legally issued by the USPTO on August 16, 2016. Endo owns and has exclusive rights to the ‘007 patent, including all rights to sue for infringement thereof.

ANSWER: This paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, Perrigo admits that, according to the online records of the USPTO, the ‘007 patent is entitled “CYANOCOBALAMIN LOW VISCOSITY AQUEOUS FORMULATIONS FOR INTRANASAL DELIVERY,” and issued on August 16, 2016. Answering further, Perrigo admits that, according to the online records of the USPTO, Endo is the current assignee of the ‘007 patent. Perrigo denies any suggestion that the ‘007 patent was duly and legally issued, as well as any suggestion or implication that the ‘007 patent is valid or enforceable or that Perrigo infringes any claim of the ‘007 patent. Perrigo is without sufficient knowledge to admit or deny the remaining allegations of this paragraph, and therefore denies same.

COMPLAINT:

26. A true and correct copy of the ‘007 patent is attached hereto as Exhibit F.

ANSWER: This paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, Perrigo admits that what purports to be a copy of the ‘007 patent is attached to Plaintiff’s Complaint as Exhibit F.

ENDO’S NASCOBAL® NASAL SPRAY PRODUCT

COMPLAINT:

27. Endo is the holder of approved New Drug Application (“NDA”) No. 021642 for Nascobal® brand cyanocobalamin, USP nasal spray 500 mcg/spray. Cyanocobalamin is a synthetic form of vitamin B₁₂ with equivalent vitamin B₁₂ activity. Nascobal® nasal spray is the only FDA-approved vitamin B₁₂ nasal spray.

ANSWER: This paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, Perrigo admits that, according to FDA's online records, "ENDO PHARMACEUTICALS INC" is the holder of NDA No. 021642 for Nascobal® (cyanocobalamin), Nasal Spray 500 mcg/spray. Perrigo further admits that, according to the approved label, available from the online records of FDA, "[c]yanocobalamin is a synthetic form of vitamin B₁₂." Perrigo is without sufficient knowledge to admit or deny the remaining allegations of this paragraph, and therefore denies same.

COMPLAINT:

28. Nascobal® nasal spray is a solution of cyanocobalamin, USP for administration as a spray to the nasal mucosa. Each unit dose device of Nascobal® nasal spray contains 0.125 mL of a 500 mcg/0.1 mL solution of cyanocobalamin with sodium citrate, citric acid, glycerin and benzalkonium chloride in purified water. The spray solution has a pH between 4.5 and 5.5. Each spray delivers an average of 500 mcg of cyanocobalamin.

ANSWER: This paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, Perrigo admits that, according to the approved label, available from the online records of FDA:

NASCOBAL (cyanocobalamin) nasal spray is a solution of cyanocobalamin, USP (vitamin B₁₂) for administration as a spray to the nasal mucosa. Each single-use device of NASCOBAL NASAL SPRAY contains 0.125 mL of a 500 mcg/0.1 mL solution of cyanocobalamin with, benzalkonium chloride in purified water, citric acid, glycerin and sodium citrate. The spray solution has a pH between 4.5 and 5.5. Each spray delivers an average of 500 mcg of cyanocobalamin per actuation.

Perrigo denies the remaining allegations in this paragraph.

COMPLAINT:

29. Nascobal® nasal spray is a prescription medicine used to treat vitamin B₁₂ deficiency. Nascobal® nasal spray is used for vitamin B₁₂ deficiency after bariatric (weight loss) surgery, because persons who have undergone bariatric surgery may not absorb enough vitamin B₁₂ from food. Nascobal® nasal spray may also be used for other causes of vitamin B₁₂ deficiency. Nascobal® is a fine-mist nasal spray that is absorbed into the bloodstream through the nasal mucosa, bypassing the stomach and digestive tract.

ANSWER: This paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, Perrigo admits that, according to the approved label, available from the online records of FDA:

-----INDICATIONS AND USAGE-----

NASCOBAL is a vitamin B₁₂ indicated for:

- Vitamin B12 maintenance therapy in adult patients with pernicious anemia who are in remission following intramuscular vitamin B12 therapy and who have no nervous system involvement (1)
- Treatment of adult patients with dietary, drug-induced, or malabsorption-related vitamin B12 deficiency not due to pernicious anemia (1)
- Prevention of vitamin B12 deficiency in adult patients with vitamin B12 requirements in excess of normal (1)

Answering further, Perrigo admits that, according to FDA's online records, the "marketing status" for Nascobal® is "prescription." Perrigo denies the remaining allegations contained in this paragraph.

COMPLAINT:

30. Nascobal® nasal spray is indicated for the maintenance of normal hematologic status in pernicious anemia patients who are in remission following intramuscular vitamin B₁₂ therapy and who have no nervous system involvement. Nascobal® nasal spray is also indicated as a supplement for other vitamin B₁₂ deficiencies, including: (i) dietary deficiency of vitamin B₁₂ occurring in strict vegetarians; (ii) malabsorption of vitamin B₁₂ resulting from structural or functional damage to the stomach or the ileum; (iii) inadequate secretion of intrinsic factor, resulting from lesions that destroy the gastric mucosa, and a number of conditions associated with a variable degree of gastric atrophy; (iv) competition for vitamin B₁₂ by intestinal parasites or bacteria; (v) inadequate utilization of vitamin B₁₂.

ANSWER: This paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, Perrigo admits that, according to the approved label, available from the online records of FDA:

-----**INDICATIONS AND USAGE**-----

NASCOBAL is a vitamin B₁₂ indicated for:

- Vitamin B12 maintenance therapy in adult patients with pernicious anemia who are in remission following intramuscular vitamin B12 therapy and who have no nervous system involvement (1)
- Treatment of adult patients with dietary, drug-induced, or malabsorption-related vitamin B12 deficiency not due to pernicious anemia (1)
- Prevention of vitamin B12 deficiency in adult patients with vitamin B12 requirements in excess of normal (1)

Perrigo denies the remaining allegations contained in this paragraph.

COMPLAINT:

31. Prior to the availability of Nascobal[®] nasal spray, therapeutic amounts of cyanocobalamin were administered by intramuscular or deep subcutaneous injection of cyanocobalamin. Patients had to return to the physician's office periodically to receive additional injections to maintain their levels of vitamin B₁₂. The invention of the Patents-in-Suit—as embodied in the commercial Nascobal[®] nasal spray product—provides for an effective and convenient self-administration option that greatly improves patient compliance. Pursuant to 21 U.S.C. § 355(b)(1) and attendant FDA regulations, the '636, '489, '349, '353, '714 and '007 patents are listed in the *Approved Drug Products with Therapeutic Equivalence Evaluations* ("Orange Book") with respect to Nascobal[®] nasal spray.

ANSWER: This paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, Perrigo admits that the '636, '489, '349, '353, '714, and '007 patents currently are listed in the FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* ("the Orange Book") in conjunction with NDA No. 021642 for Nascobal[®]. Perrigo denies any suggestion that the '636, '489, '349, '353, '714, and '007 patents were duly and legally issued, as well as any suggestion or implication that the '636, '489, '349, '353, '714, and '007 patents are valid or enforceable or that Perrigo infringes the claims of any of these patents. Perrigo further denies that Plaintiff has presented any evidence that would prove that the '636, '489, '349, '353, '714, and '007 patents cover Nascobal[®]. Perrigo denies the remaining allegations contained in this paragraph.

THE PERRIGO ANDA

COMPLAINT:

32. On information and belief, Perrigo submitted the Perrigo ANDA to FDA, under 21 U.S.C. § 355(j), seeking approval to engage in the commercial manufacture, use, sale, offer for sale, and/or importation of a generic copy of Nascobal[®] nasal spray, prior to the expiration of the Patents-in-Suit.

ANSWER: This paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, Perrigo admits that Perrigo submitted ANDA No. 212458 to FDA, pursuant to 21 U.S.C. § 355(j); that Perrigo's ANDA contains paragraph IV certifications to the '636 patent, the '489 patent, the '349 patent, the '353 patent, the '714 patent, and the '007 patent; and that Perrigo seeks approval from FDA to engage in the commercial manufacture, use, sale, or importation of Cyanocobalamin Nasal Spray, 500 mcg/spray, before the expiration of the '636, '489, '349, '353, '714, and '007 patents. Perrigo denies the remaining allegations contained in this paragraph.

COMPLAINT:

33. By letter dated January 24, 2019 (the "Notice Letter"), Perrigo asserted that it submitted the Perrigo ANDA to FDA seeking approval to engage in the commercial manufacture, use, sale, or importation of a generic copy of Nascobal[®] nasal spray prior to the expiration of the Patents-in-Suit.

ANSWER: This paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, Perrigo admits that by letter dated January 24, 2019 ("Perrigo's January 24, 2019 Notice Letter"), Perrigo gave written notice to, among others, Endo of the paragraph IV certifications to the '636, '489, '349, '353, '714, and '007 patents contained in Perrigo's ANDA No. 212458. Answering further, Perrigo admits that Perrigo's January 24, 2019 Notice Letter states, *inter alia*, that FDA has received ANDA No. 212458, which contains paragraph IV certifications to obtain approval to engage in the commercial

manufacture, use, sale, or importation of Cyanocobalamin Nasal Spray, 500 mcg/spray, before the expiration of the ‘636, ‘489, ‘349, ‘353, ‘714, and ‘007 patents. Perrigo denies the remaining allegations contained in this paragraph.

COMPLAINT:

34. The Notice Letter also asserted that the ANDA contains certifications by Perrigo pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV) (“Paragraph IV Certifications”) contending that the Patents-in-Suit are invalid, unenforceable, and/or will not be infringed by the commercial manufacture, use, sale, or importation of the Perrigo ANDA Product.

ANSWER: This paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, Perrigo admits that by Perrigo’s January 24, 2019 Notice Letter, Perrigo gave written notice to, among others, Endo of the paragraph IV certifications to the ‘636, ‘489, ‘349, ‘353, ‘714, and ‘007 patents contained in Perrigo’s ANDA No. 212458. Answering further, Perrigo admits that Perrigo’s January 24, 2019 Notice Letter states, *inter alia*, that FDA has received ANDA No. 212458, which contains paragraph IV certifications to obtain approval to engage in the commercial manufacture, use, sale, or importation of Cyanocobalamin Nasal Spray, 500 mcg/spray, before the expiration of the ‘636, ‘489, ‘349, ‘353, ‘714, and ‘007 patents. Perrigo denies the remaining allegations contained in this paragraph.

COMPLAINT:

35. On information and belief, Perrigo was aware of the Patents-in-Suit at the time it submitted the Paragraph IV Certifications to FDA.

ANSWER: This paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, Perrigo admits that Perrigo submitted ANDA No. 212458 to FDA, pursuant to 21 U.S.C. § 355(j); that Perrigo’s ANDA contains paragraph IV certifications to the ‘636 patent, the ‘489 patent, the ‘349 patent, the ‘353 patent, the ‘714 patent,

and the '007 patent; and that Perrigo seeks approval from FDA to engage in the commercial manufacture, use, sale, or importation of Cyanocobalamin Nasal Spray, 500 mcg/spray, before the expiration of the '636, '489, '349, '353, '714, and '007 patents. Perrigo denies the remaining allegations contained in this paragraph.

COMPLAINT:

36. Endo commenced this action within 45 days of receiving the Notice Letter pursuant to 21 U.S.C. § 355(j)(5)(B)(iii).

ANSWER: This paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, Perrigo admits that according to the online records of this judicial District, Plaintiff filed the instant action on March 1, 2019. Perrigo denies the remaining allegations contained in this paragraph.

COUNT ONE
'636 Patent

COMPLAINT:

37. Endo realleges and incorporates each of the preceding paragraphs as if fully set forth herein.

ANSWER: Perrigo restates and incorporates each of its responses to the preceding paragraphs as if fully set forth herein.

COMPLAINT:

38. Perrigo's submission of the Perrigo ANDA to FDA to engage in the commercial manufacture, use, sale, offer for sale, or importation of the Perrigo ANDA Product, prior to the expiration of the '636 patent, constitutes infringement of at least one claim, including at least claims 1, 24, 30, and/or 31 of the '636 patent, under 35 U.S.C. § 271(e)(2), literally and/or by the doctrine of equivalents.

ANSWER: Denied.

COMPLAINT:

39. On FDA approval of the Perrigo ANDA, Perrigo will infringe at least one claim, including at least claim 1 of the '636 patent, by manufacturing, using, offering to sell, or selling

the Perrigo ANDA Product in the United States and/or importing the Perrigo ANDA Product into the United States, and by actively inducing and/or contributing to infringement by others, in violation of 35 U.S.C. §§ 271(a), (b), and/or (c), literally and/or by the doctrine of equivalents.

ANSWER: Denied.

COMPLAINT:

40. On information and belief, the Perrigo ANDA Product contains the same active ingredient and in the same concentration as Nascobal® brand cyanocobalamin, USP nasal spray 500 mcg/spray.

ANSWER: This paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, Perrigo admits that Perrigo submitted ANDA No. 212458 to FDA, pursuant to 21 U.S.C. § 355(j), seeking approval to engage in the commercial manufacture, use, sale, or importation of Cyanocobalamin Nasal Spray, 500 mcg/spray. Perrigo denies the remaining allegations in this paragraph.

COMPLAINT:

41. On information and belief, the Perrigo ANDA Product infringes at least one claim, including at least claim 1 of the '636 patent, literally and/or by the doctrine of equivalents.

ANSWER: Denied.

COMPLAINT:

42. On information and belief, the Perrigo ANDA Product is a stable pharmaceutical aqueous solution comprising cyanocobalamin, water, a preservative selected from the group consisting of benzyl alcohol, parabens thimerosal, chlorobutanol, benzethonium chloride, and benzalkonium chloride, and combinations thereof, a buffer selected from the group consisting of citric acid, sodium citrate, monopotassium phosphate, disodium phosphate, potassium biphthalate, sodium hydroxide, sodium acetate, acetic acid, and combinations thereof, and a humectant selected from the group consisting of sorbitol, propylene glycol, and glycerin, and combinations thereof, wherein said solution of cyanocobalamin is suitable for intranasal administration, has a viscosity less than about 1000 cPs, and wherein said solution of cyanocobalamin has a bioavailability of cyanocobalamin when administered intranasally of at least about 7% relative to an intramuscular injection of cyanocobalamin with the proviso that the solution contains no mercury or mercury compounds, as claimed in at least one claim, including at least claim 1 of the '636 patent, literally and/or by the doctrine of equivalents.

ANSWER: This paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, denied.

COMPLAINT:

43. On FDA approval of the Perrigo ANDA, Perrigo will induce infringement of at least one claim, including at least claims 24, 30, and/or 31 of the '636 patent, by promoting, encouraging, and/or recommending that persons perform methods of administering cyanocobalamin by infusing the nose with the claimed aqueous solution of cyanocobalamin, or administering intranasally a sufficient amount of the claimed solution of cyanocobalamin, and/or by contributing to the performance of said method, in violation of 35 U.S.C. §§ 271(a), (b), and/or (c), literally and/or by the doctrine of equivalents.

ANSWER: Denied.

COMPLAINT:

44. As part of the Perrigo ANDA, Perrigo must show that “the labeling proposed for the new drug is the same as the labeling approved for the listed drug,” except for changes indicating that the drug is produced or distributed by different manufacturers. 21 U.S.C. § 355(j)(2)(A)(v).

ANSWER: This paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, Perrigo admits that 21 U.S.C. § 355(j)(2)(A)(v) contains the quoted language. Perrigo denies the remaining allegations contained in this paragraph.

COMPLAINT:

45. The label for Nascobal[®] nasal spray states that Nascobal[®] nasal spray is administered in the nostril.

ANSWER: This paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, Perrigo admits that, according to the approved label, available from the online records of FDA:

- The recommended initial dose is one spray (500 mcg) in one nostril once weekly. (2.2)

Perrigo denies the remaining allegations contained in this paragraph.

COMPLAINT:

46. On information and belief, the proposed label for the Perrigo ANDA Product is substantially identical to the approved label for Nascobal[®] nasal spray, and the Perrigo ANDA Product, if approved, will be marketed, sold, and/or distributed with labeling that is substantially identical to the labeling for Nascobal[®] nasal spray.

ANSWER: This paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, Perrigo admits that Perrigo's ANDA meets the requirements of, *inter alia*, 21 U.S.C. § 355(j)(2)(A)(v). Perrigo denies the remaining allegations contained in this paragraph.

COMPLAINT:

47. On information and belief, the proposed label for the Perrigo ANDA Product also states that the Perrigo ANDA Product is administered in the nostril. Therefore, the proposed label promotes or encourages persons to perform methods of administering cyanocobalamin by infusing the nose with the Perrigo ANDA Product, or administering intranasally a sufficient amount of the Perrigo ANDA Product.

ANSWER: This paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, Perrigo admits that Perrigo's ANDA meets the requirements of, *inter alia*, 21 U.S.C. § 355(j)(2)(A)(v). Perrigo denies the remaining allegations contained in this paragraph.

COMPLAINT:

48. On information and belief, Perrigo knowingly provides instruction in the proposed label for persons to administer the Perrigo ANDA Product intranasally or by infusing the nose, and the proposed label reflects a specific intent to encourage persons to directly infringe at least one claim, including at least claims 24, 30, and/or 31 of the '636 patent, literally and/or by the doctrine of equivalents.

ANSWER: Denied.

COMPLAINT:

49. Unless enjoined by the Court, on FDA approval of the Perrigo ANDA, Perrigo will infringe at least one claim, including at least claims 1, 24, 30, and/or 31 of the '636 patent,

literally and/or by the doctrine of equivalents, under 35 U.S.C. § 271(a) by making, using, offering to sell, selling, and/or importing the Perrigo ANDA Product into the United States.

ANSWER: Denied.

COMPLAINT:

50. Unless enjoined by the Court, on FDA approval of the Perrigo ANDA, Perrigo will infringe at least one claim, including at least claims 1, 24, 30, and/or 31 of the ‘636 patent, literally and/or by the doctrine of equivalents, under 35 U.S.C. § 271(b) by making, using, offering to sell, selling, and/or importing the Perrigo ANDA Product into the United States. On information and belief, Perrigo will knowingly encourage direct infringement of the ‘636 patent, and possess specific intent to encourage another’s direct infringement of the ‘636 patent.

ANSWER: Denied.

COMPLAINT:

51. Unless enjoined by the Court, on FDA approval of the Perrigo ANDA, Perrigo will infringe at least one claim, including at least claims 1, 24, 30, and/or 31 of the ‘636 patent, literally and/or by the doctrine of equivalents, under 35 U.S.C. § 271(c) by making, using, offering to sell, selling, and/or importing the Perrigo ANDA Product into the United States. On information and belief, the act of direct infringement of the ‘636 patent is attributed to a single entity. On information and belief, the Perrigo ANDA Product is a material part of the claimed invention, and is not suitable for substantial non-infringing uses.

ANSWER: Denied.

COMPLAINT:

52. Endo will be irreparably harmed if Perrigo is not enjoined from infringing, inducing, or contributing to infringement of the ‘636 patent. Endo does not have an adequate remedy at law.

ANSWER: Denied.

COMPLAINT:

53. This case is exceptional and Endo is entitled to an award of reasonable attorney fees under 35 U.S.C. § 285.

ANSWER: Denied.

COUNT TWO
'636 Patent

COMPLAINT:

54. Endo realleges and incorporates each of the preceding paragraphs as if fully set forth herein.

ANSWER: Perrigo restates and incorporates each of its responses to the preceding paragraphs as if fully set forth herein.

COMPLAINT:

55. These claims arise under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

ANSWER: This paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, Perrigo admits that Plaintiff's Complaint is for alleged patent infringement and for declaratory judgment of alleged patent infringement, but denies that Plaintiff is entitled to any relief. Answering further, Perrigo does not contest subject matter jurisdiction under 35 U.S.C. § 271(e)(2)(A) for purposes of this action only. Perrigo denies the remaining allegations contained in this paragraph.

COMPLAINT:

56. There is an actual case or controversy such that the Court may resolve Endo's request for declaratory relief consistent with Article III of the United States Constitution.

ANSWER: This paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, Perrigo admits that Plaintiff's Complaint is for alleged patent infringement and for declaratory judgment of alleged patent infringement, but denies that Plaintiff is entitled to any relief. Answering further, Perrigo does not contest subject matter jurisdiction under 35 U.S.C. § 271(e)(2)(A) for purposes of this action only. Perrigo denies the remaining allegations contained in this paragraph.

COMPLAINT:

57. On information and belief, unless enjoined by this Court, Perrigo plans and intends to engage in the manufacture, use, offer for sale, sale, marketing, distribution, and/or importation of the Perrigo ANDA Product immediately following approval of the Perrigo ANDA.

ANSWER: This paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, Perrigo admits that Perrigo submitted ANDA No. 212458 to FDA, pursuant to 21 U.S.C. § 355(j); that Perrigo's ANDA contains paragraph IV certifications to the '636 patent, the '489 patent, the '349 patent, the '353 patent, the '714 patent, and the '007 patent; and that Perrigo seeks approval from FDA to engage in the commercial manufacture, use, sale, or importation of Cyanocobalamin Nasal Spray, 500 mcg/spray, before the expiration of the '636, '489, '349, '353, '714, and '007 patents. Perrigo denies the remaining allegations contained in this paragraph.

COMPLAINT:

58. The commercial use of the Perrigo ANDA Product will directly infringe the '636 patent.

ANSWER: Denied.

COMPLAINT:

59. The commercial offer for sale and sale of the Perrigo ANDA Product, in conjunction with the labeling and instructions for use thereof, will constitute an act of inducement of infringement of the '636 patent.

ANSWER: Denied.

COMPLAINT:

60. On information and belief, Perrigo had knowledge of the '636 patent since at least the time Perrigo submitted the Paragraph IV Certifications to FDA.

ANSWER: This paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, Perrigo admits that Perrigo submitted ANDA No.

212458 to FDA, pursuant to 21 U.S.C. § 355(j); that Perrigo's ANDA contains paragraph IV certifications to the '636 patent, the '489 patent, the '349 patent, the '353 patent, the '714 patent, and the '007 patent; and that Perrigo seeks approval from FDA to engage in the commercial manufacture, use, sale, or importation of Cyanocobalamin Nasal Spray, 500 mcg/spray, before the expiration of the '636, '489, '349, '353, '714, and '007 patents. Perrigo denies the remaining allegations contained in this paragraph.

COMPLAINT:

61. Because the Perrigo ANDA Product is especially made or adapted for use in the claims of the '636 patent, and has no substantially non-infringing use, the commercial manufacture, offer for sale, sale and/or importation of the Perrigo ANDA Product will constitute an act of contributory infringement of the '636 patent.

ANSWER: Denied.

COMPLAINT:

62. Endo is entitled to a declaratory judgment that the commercial manufacture, use, offer to sell, or sale within the United States, and/or importation into the United States, of the Perrigo ANDA Product, or the inducement of and/or contribution to the commercial manufacture, use, offer for sale, or sale within the United States, and/or importation into the United States, of the Perrigo ANDA Product before expiration of the '636 patent by Perrigo or its agents, will constitute infringement, inducement of infringement, and/or contributory infringement of the '636 patent under 35 U.S.C. §§ 271(a), (b), and/or (c).

ANSWER: Denied.

COMPLAINT:

63. Endo will be irreparably harmed if Perrigo is not enjoined from infringing, inducing, or contributing to infringement of the '636 patent. Endo does not have an adequate remedy at law.

ANSWER: Denied.

COMPLAINT:

64. This case is exceptional and Endo is entitled to an award of reasonable attorney fees under 35 U.S.C. § 285.

ANSWER: Denied.

COUNT THREE
'489 Patent

COMPLAINT:

65. Endo realleges and incorporates each of the preceding paragraphs as if fully set forth herein.

ANSWER: Perrigo restates and incorporates each of its responses to the preceding paragraphs as if fully set forth herein.

COMPLAINT:

66. Perrigo's submission of the Perrigo ANDA to FDA to engage in the commercial manufacture, use, sale, offer for sale, or importation of the Perrigo ANDA Product, prior to the expiration of the '489 patent, constitutes infringement of at least one claim, including at least claim 1 of the '489 patent, under 35 U.S.C. § 271(e)(2), literally and/or by the doctrine of equivalents.

ANSWER: Denied.

COMPLAINT:

67. On FDA approval of the Perrigo ANDA, Perrigo will infringe at least one claim, including at least claim 1 of the '489 patent, by manufacturing, using, offering to sell, or selling the Perrigo ANDA Product in the United States and/or importing the Perrigo ANDA Product into the United States, and by actively inducing and/or contributing to infringement by others, in violation of 35 U.S.C. §§ 271(a), (b), and/or (c), literally and/or by the doctrine of equivalents.

ANSWER: Denied.

COMPLAINT:

68. On information and belief, the Perrigo ANDA Product contains the same active ingredient and in the same concentration as Nascobal® brand cyanocobalamin, USP nasal spray 500 mcg/spray.

ANSWER: This paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, Perrigo admits that Perrigo submitted ANDA No. 212458 to FDA, pursuant to 21 U.S.C. § 355(j), seeking approval to engage in the commercial

manufacture, use, sale, or importation of Cyanocobalamin Nasal Spray, 500 mcg/spray. Perrigo denies the remaining allegations in this paragraph.

COMPLAINT:

69. On information and belief, the Perrigo ANDA Product infringes at least one claim, including at least claim 1 of the '489 patent, literally and/or by the doctrine of equivalents.

ANSWER: Denied.

COMPLAINT:

70. On information and belief, the Perrigo ANDA Product is a kit for nasal drug delivery comprising an aqueous solution of cyanocobalamin and excipients in a container, and a droplet-generating actuator attached to said container and fluidly connected to the cyanocobalamin solution in the container; wherein said actuator produces a spray of the cyanocobalamin solution through a tip of the actuator when said actuator is engaged, wherein said spray of cyanocobalamin solution has a spray pattern ellipticity ratio of from about 1.0 to about 1.4 when measured at a height of 3.0 cm from the actuator tip, as claimed in at least one claim, including at least claim 1 of the '489 patent.

ANSWER: This paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, denied.

COMPLAINT:

71. Unless enjoined by the Court, on FDA approval of the Perrigo ANDA, Perrigo will infringe at least one claim, including at least claim 1 of the '489 patent, literally and/or by the doctrine of equivalents, under 35 U.S.C. § 271(a) by making, using, offering to sell, selling, and/or importing the Perrigo ANDA Product into the United States.

ANSWER: Denied.

COMPLAINT:

72. Unless enjoined by the Court, on FDA approval of the Perrigo ANDA, Perrigo will infringe at least one claim, including at least claim 1 of the '489 patent, literally and/or by the doctrine of equivalents, under 35 U.S.C. § 271(b) by making, using, offering to sell, selling, and/or importing the Perrigo ANDA Product into the United States. On information and belief, Perrigo will knowingly encourage direct infringement of the '489 patent, and possess specific intent to encourage another's direct infringement of the '489 patent.

ANSWER: Denied.

COMPLAINT:

73. Unless enjoined by the Court, on FDA approval of the Perrigo ANDA, Perrigo will infringe at least one claim, including at least claim 1 of the '489 patent, literally and/or by the doctrine of equivalents, under 35 U.S.C. § 271(c) by making, using, offering to sell, selling, and/or importing the Perrigo ANDA Product into the United States. On information and belief, the act of direct infringement of the '489 patent is attributed to a single entity. On information and belief, the Perrigo ANDA Product is a material part of the claimed invention, and is not suitable for substantial non-infringing uses.

ANSWER: Denied.

COMPLAINT:

74. Endo will be irreparably harmed if Perrigo is not enjoined from infringing, inducing, or contributing to infringement of the '489 patent. Endo does not have an adequate remedy at law.

ANSWER: Denied.

COMPLAINT:

75. This case is exceptional and Endo is entitled to an award of reasonable attorney fees under 35 U.S.C. § 285.

ANSWER: Denied.

COUNT FOUR
'489 Patent

COMPLAINT:

76. Endo realleges and incorporates each of the preceding paragraphs as if fully set forth herein.

ANSWER: Perrigo restates and incorporates each of its responses to the preceding paragraphs as if fully set forth herein.

COMPLAINT:

77. These claims arise under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

ANSWER: This paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, Perrigo admits that Plaintiff's Complaint is for alleged patent infringement and for declaratory judgment of alleged patent infringement, but denies that Plaintiff is entitled to any relief. Answering further, Perrigo does not contest subject matter jurisdiction under 35 U.S.C. § 271(e)(2)(A) for purposes of this action only. Perrigo denies the remaining allegations contained in this paragraph.

COMPLAINT:

78. There is an actual case or controversy such that the Court may resolve Endo's request for declaratory relief consistent with Article III of the United States Constitution.

ANSWER: This paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, Perrigo admits that Plaintiff's Complaint is for alleged patent infringement and for declaratory judgment of alleged patent infringement, but denies that Plaintiff is entitled to any relief. Answering further, Perrigo does not contest subject matter jurisdiction under 35 U.S.C. § 271(e)(2)(A) for purposes of this action only. Perrigo denies the remaining allegations contained in this paragraph.

COMPLAINT:

79. On information and belief, unless enjoined by this Court, Perrigo plans and intends to engage in the manufacture, use, offer for sale, sale, marketing, distribution, and/or importation of the Perrigo ANDA Product immediately following approval of the Perrigo ANDA.

ANSWER: This paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, Perrigo admits that Perrigo submitted ANDA No. 212458 to FDA, pursuant to 21 U.S.C. § 355(j); that Perrigo's ANDA contains paragraph IV certifications to the '636 patent, the '489 patent, the '349 patent, the '353 patent, the '714 patent, and the '007 patent; and that Perrigo seeks approval from FDA to engage in the commercial

manufacture, use, sale, or importation of Cyanocobalamin Nasal Spray, 500 mcg/spray, before the expiration of the ‘636, ‘489, ‘349, ‘353, ‘714, and ‘007 patents. Perrigo denies the remaining allegations contained in this paragraph.

COMPLAINT:

80. The commercial use of the Perrigo ANDA Product will directly infringe the ‘489 patent.

ANSWER: Denied.

COMPLAINT:

81. The commercial offer for sale and sale of the Perrigo ANDA Product, in conjunction with the labeling and instructions for use thereof, will constitute an act of inducement of infringement of the ‘489 patent.

ANSWER: Denied.

COMPLAINT:

82. On information and belief, Perrigo had knowledge of the ‘489 patent since at least the time Perrigo submitted the Paragraph IV Certifications to FDA.

ANSWER: This paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, Perrigo admits that Perrigo submitted ANDA No. 212458 to FDA, pursuant to 21 U.S.C. § 355(j); that Perrigo’s ANDA contains paragraph IV certifications to the ‘636 patent, the ‘489 patent, the ‘349 patent, the ‘353 patent, the ‘714 patent, and the ‘007 patent; and that Perrigo seeks approval from FDA to engage in the commercial manufacture, use, sale, or importation of Cyanocobalamin Nasal Spray, 500 mcg/spray, before the expiration of the ‘636, ‘489, ‘349, ‘353, ‘714, and ‘007 patents. Perrigo denies the remaining allegations contained in this paragraph.

COMPLAINT:

83. Because the Perrigo ANDA Product is especially made or adapted for use in the claims of the ‘489 patent, and has no substantially non-infringing use, the commercial

manufacture, offer for sale, sale and/or importation of the Perrigo ANDA Product will constitute an act of contributory infringement of the '489 patent.

ANSWER: Denied.

COMPLAINT:

84. Endo is entitled to a declaratory judgment that the commercial manufacture, use, offer to sell, or sale within the United States, and/or importation into the United States, of the Perrigo ANDA Product, or the inducement of and/or contribution to the commercial manufacture, use, offer for sale, or sale within the United States, and/or importation into the United States, of the Perrigo ANDA Product before expiration of the '489 patent by Perrigo or its agents, will constitute infringement, inducement of infringement, and/or contributory infringement of the '489 patent under 35 U.S.C. §§ 271(a), (b), and/or (c).

ANSWER: Denied.

COMPLAINT:

85. Endo will be irreparably harmed if Perrigo is not enjoined from infringing, inducing, or contributing to infringement of the '489 patent. Endo does not have an adequate remedy at law.

ANSWER: Denied.

COMPLAINT:

86. This case is exceptional and Endo is entitled to an award of reasonable attorney fees under 35 U.S.C. § 285.

ANSWER: Denied.

COUNT FIVE
'349 Patent

COMPLAINT:

87. Endo realleges and incorporates each of the preceding paragraphs as if fully set forth herein.

ANSWER: Perrigo restates and incorporates each of its responses to the preceding paragraphs as if fully set forth herein.

COMPLAINT:

88. Perrigo's submission of the Perrigo ANDA to FDA to engage in the commercial manufacture, use, sale, offer for sale, or importation of the Perrigo ANDA Product, prior to the expiration of the '349 patent, constitutes infringement of at least one claim, including at least claims 1, 9, and/or 17 of the '349 patent, under 35 U.S.C. § 271(e)(2), literally and/or by the doctrine of equivalents.

ANSWER: Denied.

COMPLAINT:

89. On FDA approval of the Perrigo ANDA, Perrigo will infringe at least one claim, including at least claim 1 of the '349 patent, by manufacturing, using, offering to sell, or selling the Perrigo ANDA Product in the United States and/or importing the Perrigo ANDA Product into the United States, and by actively inducing and/or contributing to infringement by others, in violation of 35 U.S.C. §§ 271(a), (b), and/or (c), literally and/or by the doctrine of equivalents.

ANSWER: Denied.

COMPLAINT:

90. On information and belief, the Perrigo ANDA Product contains the same active ingredient and in the same concentration as Nascobal[®] brand cyanocobalamin, USP nasal spray 500 mcg/spray.

ANSWER: This paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, Perrigo admits that Perrigo submitted ANDA No. 212458 to FDA, pursuant to 21 U.S.C. § 355(j), seeking approval to engage in the commercial manufacture, use, sale, or importation of Cyanocobalamin Nasal Spray, 500 mcg/spray. Perrigo denies the remaining allegations in this paragraph.

COMPLAINT:

91. On information and belief, the Perrigo ANDA Product infringes at least one claim, including at least claim 1 of the '349 patent, literally and/or by the doctrine of equivalents.

ANSWER: Denied.

COMPLAINT:

92. On information and belief, the Perrigo ANDA Product is a stable pharmaceutical aqueous solution comprising cyanocobalamin and water, a preservative selected from the group consisting of benzyl alcohol, parabens, chlorobutanol, benzethonium chloride, and benzalkonium chloride, and combinations thereof, and a buffer selected from the group consisting of citric acid, sodium citrate, monopotassium phosphate, disodium phosphate, potassium biphthalate, sodium hydroxide, sodium acetate, acetic acid, and combinations thereof, wherein said solution of cyanocobalamin is suitable for intranasal administration, and has a viscosity less than about 1000 cPs, and wherein said solution of cyanocobalamin has a bioavailability of cyanocobalamin when administered intranasally of at least about 7% relative to an intramuscular injection of cyanocobalamin, with the proviso that the solution contains no mercury or mercury compounds, as claimed in at least one claim, including at least claim 1 of the '349 patent, literally and/or by the doctrine of equivalents.

ANSWER: This paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, denied.

COMPLAINT:

93. On FDA approval of the Perrigo ANDA, Perrigo will induce infringement of at least one claim, including at least claims 9 and/or 17 of the '349 patent, by promoting, encouraging, and/or recommending that persons perform methods of administering cyanocobalamin by infusing the nose with the claimed aqueous solution of cyanocobalamin, or administering intranasally the claimed aqueous solution of cyanocobalamin, and/or by contributing to the performance of said method, in violation of 35 U.S.C. §§ 271(a), (b), and/or (c), literally and/or by the doctrine of equivalents.

ANSWER: Denied.

COMPLAINT:

94. As part of the Perrigo ANDA, Perrigo must show that "the labeling proposed for the new drug is the same as the labeling approved for the listed drug," except for changes indicating that the drug is produced or distributed by different manufacturers. 21 U.S.C. § 355(j)(2)(A)(v).

ANSWER: This paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, Perrigo admits that 21 U.S.C. § 355(j)(2)(A)(v) contains the quoted language. Perrigo denies the remaining allegations contained in this paragraph.

COMPLAINT:

95. The label for Nascobal[®] nasal spray states that Nascobal[®] nasal spray is administered in the nostril.

ANSWER: This paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, Perrigo admits that, according to the approved label, available from the online records of FDA:

- The recommended initial dose is one spray (500 mcg) in one nostril once weekly. (2.2)

Perrigo denies the remaining allegations contained in this paragraph.

COMPLAINT:

96. On information and belief, the proposed label for the Perrigo ANDA Product is substantially identical to the approved label for Nascobal[®] nasal spray, and the Perrigo ANDA Product, if approved, will be marketed, sold, and/or distributed with labeling that is substantially identical to the labeling for Nascobal[®] nasal spray.

ANSWER: This paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, Perrigo admits that Perrigo's ANDA meets the requirements of, *inter alia*, 21 U.S.C. § 355(j)(2)(A)(v). Perrigo denies the remaining allegations contained in this paragraph.

COMPLAINT:

97. On information and belief, the proposed label for the Perrigo ANDA Product also states that the Perrigo ANDA Product is administered in the nostril. Therefore, the proposed label promotes or encourages persons to perform methods of administering cyanocobalamin by infusing the nose with the Perrigo ANDA Product, or administering intranasally a sufficient amount of the Perrigo ANDA Product.

ANSWER: This paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, Perrigo admits that Perrigo's ANDA meets the requirements of, *inter alia*, 21 U.S.C. § 355(j)(2)(A)(v). Perrigo denies the remaining allegations contained in this paragraph.

COMPLAINT:

98. On information and belief, Perrigo knowingly provides instruction in the proposed label for persons to administer the Perrigo ANDA Product intranasally or by infusing the nose, and the proposed label reflects a specific intent to encourage persons to directly infringe at least one claim, including at least claim 9 and/or 17 of the '349 patent, literally and/or by the doctrine of equivalents.

ANSWER: Denied.

COMPLAINT:

99. Unless enjoined by the Court, on FDA approval of the Perrigo ANDA, Perrigo will infringe at least one claim, including at least claims 1, 9, and/or 17 of the '349 patent, literally and/or by the doctrine of equivalents, under 35 U.S.C. § 271(a) by making, using, offering to sell, selling, and/or importing the Perrigo ANDA Product into the United States.

ANSWER: Denied.

COMPLAINT:

100. Unless enjoined by the Court, on FDA approval of the Perrigo ANDA, Perrigo will infringe at least one claim, including at least claims 1, 9, and/or 17 of the '349 patent, literally and/or by the doctrine of equivalents, under 35 U.S.C. § 271(b) by making, using, offering to sell, selling, and/or importing the Perrigo ANDA Product into the United States. On information and belief, Perrigo will knowingly encourage direct infringement of the '349 patent, and possesses specific intent to encourage another's direct infringement of the '349 patent.

ANSWER: Denied.

COMPLAINT:

101. Unless enjoined by the Court, on FDA approval of the Perrigo ANDA, Perrigo will infringe at least one claim, including at least claims 1, 9, and/or 17 of the '349 patent, literally and/or by the doctrine of equivalents, under 35 U.S.C. § 271(c) by making, using, offering to sell, selling, and/or importing the Perrigo ANDA Product into the United States. On information and belief, the act of direct infringement of the '349 patent is attributed to a single entity. On information and belief, the Perrigo ANDA Product is a material part of the claimed invention, and is not suitable for substantial non-infringing uses.

ANSWER: Denied.

COMPLAINT:

102. Endo will be irreparably harmed if Perrigo is not enjoined from infringing, inducing, or contributing to infringement of the '349 patent. Endo does not have an adequate remedy at law.

ANSWER: Denied.

COMPLAINT:

103. This case is exceptional and Endo is entitled to an award of reasonable attorney fees under 35 U.S.C. § 285.

ANSWER: Denied.

COUNT SIX
'349 Patent

COMPLAINT:

104. Endo realleges and incorporates each of the preceding paragraphs as if fully set forth herein.

ANSWER: Perrigo restates and incorporates each of its responses to the preceding paragraphs as if fully set forth herein.

COMPLAINT:

105. These claims arise under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

ANSWER: This paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, Perrigo admits that Plaintiff's Complaint is for alleged patent infringement and for declaratory judgment of alleged patent infringement, but denies that Plaintiff is entitled to any relief. Answering further, Perrigo does not contest subject matter jurisdiction under 35 U.S.C. § 271(e)(2)(A) for purposes of this action only. Perrigo denies the remaining allegations contained in this paragraph.

COMPLAINT:

106. There is an actual case or controversy such that the Court may resolve Endo's request for declaratory relief consistent with Article III of the United States Constitution.

ANSWER: This paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, Perrigo admits that Plaintiff's Complaint is for alleged patent infringement and for declaratory judgment of alleged patent infringement, but denies that Plaintiff is entitled to any relief. Answering further, Perrigo does not contest subject matter jurisdiction under 35 U.S.C. § 271(e)(2)(A) for purposes of this action only. Perrigo denies the remaining allegations contained in this paragraph.

COMPLAINT:

107. On information and belief, unless enjoined by this Court, Perrigo plans and intends to engage in the manufacture, use, offer for sale, sale, marketing, distribution, and/or importation of the Perrigo ANDA Product immediately following approval of the Perrigo ANDA.

ANSWER: This paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, Perrigo admits that Perrigo submitted ANDA No. 212458 to FDA, pursuant to 21 U.S.C. § 355(j); that Perrigo's ANDA contains paragraph IV certifications to the '636 patent, the '489 patent, the '349 patent, the '353 patent, the '714 patent, and the '007 patent; and that Perrigo seeks approval from FDA to engage in the commercial manufacture, use, sale, or importation of Cyanocobalamin Nasal Spray, 500 mcg/spray, before the expiration of the '636, '489, '349, '353, '714, and '007 patents. Perrigo denies the remaining allegations contained in this paragraph.

COMPLAINT:

108. The commercial use of the Perrigo ANDA Product will directly infringe the '349 patent.

ANSWER: Denied.

COMPLAINT:

109. The commercial offer for sale and sale of the Perrigo ANDA Product, in conjunction with the labeling and instructions for use thereof, will constitute an act of inducement of infringement of the '349 patent.

ANSWER: Denied.

COMPLAINT:

110. On information and belief, Perrigo had knowledge of the '349 patent since at least the time Perrigo submitted the Paragraph IV Certifications to FDA.

ANSWER: This paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, Perrigo admits that Perrigo submitted ANDA No. 212458 to FDA, pursuant to 21 U.S.C. § 355(j); that Perrigo's ANDA contains paragraph IV certifications to the '636 patent, the '489 patent, the '349 patent, the '353 patent, the '714 patent, and the '007 patent; and that Perrigo seeks approval from FDA to engage in the commercial manufacture, use, sale, or importation of Cyanocobalamin Nasal Spray, 500 mcg/spray, before the expiration of the '636, '489, '349, '353, '714, and '007 patents. Perrigo denies the remaining allegations contained in this paragraph.

COMPLAINT:

111. Because the Perrigo ANDA Product is especially made or adapted for use in the claims of the '349 patent, and has no substantially non-infringing use, the commercial manufacture, offer for sale, sale and/or importation of the Perrigo ANDA Product will constitute an act of contributory infringement of the '349 patent.

ANSWER: Denied.

COMPLAINT:

112. Endo is entitled to a declaratory judgment that the commercial manufacture, use, offer to sell, or sale within the United States, and/or importation into the United States, of the Perrigo ANDA Product, or the inducement of and/or contribution to the commercial manufacture, use, offer for sale, or sale within the United States, and/or importation into the United States, of the Perrigo ANDA Product before expiration of the '349 patent by Perrigo or

its agents, will constitute infringement, inducement of infringement, and/or contributory infringement of the '349 patent under 35 U.S.C. §§ 271(a), (b), and/or (c).

ANSWER: Denied.

COMPLAINT:

113. Endo will be irreparably harmed if Perrigo is not enjoined from infringing, inducing, or contributing to infringement of the '349 patent. Endo does not have an adequate remedy at law.

ANSWER: Denied.

COMPLAINT:

114. This case is exceptional and Endo is entitled to an award of reasonable attorney fees under 35 U.S.C. § 285.

ANSWER: Denied.

COUNT SEVEN
'353 Patent

COMPLAINT:

115. Endo realleges and incorporates each of the preceding paragraphs as if fully set forth herein.

ANSWER: Perrigo restates and incorporates each of its responses to the preceding paragraphs as if fully set forth herein.

COMPLAINT:

116. Perrigo's submission of the Perrigo ANDA to FDA to engage in the commercial manufacture, use, sale, offer for sale, or importation of the Perrigo ANDA Product, prior to the expiration of the '353 patent, constitutes infringement of at least one claim, including at least claim 1 of the '353 patent, under 35 U.S.C. § 271(e)(2), literally and/or by the doctrine of equivalents.

ANSWER: Denied.

COMPLAINT:

117. On FDA approval of the Perrigo ANDA, Perrigo will induce infringement of at least one claim, including at least claim 1 of the '353 patent, by promoting, encouraging, and/or

recommending that persons administer the claimed cyanocobalamin solution into a nose of an individual through an actuator tip as a spray, wherein the spray has a spray pattern ellipticity ratio of from about 1.0 to about 1.4 when measured at a height of 3.0 cm from the actuator tip, and/or by contributing to the performance of said method, in violation of 35 U.S.C. §§ 271(a), (b), and/or (c), literally and/or by the doctrine of equivalents.

ANSWER: Denied.

COMPLAINT:

118. As part of the Perrigo ANDA, Perrigo must show that “the labeling proposed for the new drug is the same as the labeling approved for the listed drug,” except for changes indicating that the drug is produced or distributed by different manufacturers. 21 U.S.C. § 355(j)(2)(A)(v).

ANSWER: This paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, Perrigo admits that 21 U.S.C. § 355(j)(2)(A)(v) contains the quoted language. Perrigo denies the remaining allegations contained in this paragraph.

COMPLAINT:

119. The label for Nascobal[®] nasal spray states that Nascobal[®] nasal spray is administered in the nostril.

ANSWER: This paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, Perrigo admits that, according to the approved label, available from the online records of FDA:

- The recommended initial dose is one spray (500 mcg) in one nostril once weekly. (2.2)

Perrigo denies the remaining allegations contained in this paragraph.

COMPLAINT:

120. On information and belief, the proposed label for the Perrigo ANDA Product is substantially identical to the approved label for Nascobal[®] nasal spray, and the Perrigo ANDA Product, if approved, will be marketed, sold, and/or distributed with labeling that is substantially identical to the labeling for Nascobal[®] nasal spray.

ANSWER: This paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, Perrigo admits that Perrigo's ANDA meets the requirements of, *inter alia*, 21 U.S.C. § 355(j)(2)(A)(v). Perrigo denies the remaining allegations contained in this paragraph.

COMPLAINT:

121. On information and belief, the proposed label for the Perrigo ANDA Product also states that the Perrigo ANDA Product is administered in the nostril. Therefore, the proposed label promotes or encourages persons to administer the Perrigo ANDA Product into a nose of an individual.

ANSWER: This paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, Perrigo admits that Perrigo's ANDA meets the requirements of, *inter alia*, 21 U.S.C. § 355(j)(2)(A)(v). Perrigo denies the remaining allegations contained in this paragraph.

COMPLAINT:

122. On information and belief, Perrigo knowingly provides instruction in the proposed label for persons to administer the Perrigo ANDA Product into a nose of an individual, and the proposed label reflects a specific intent to encourage persons to directly infringe at least one claim, including at least claim 1 of the '353 patent, literally and/or by the doctrine of equivalents.

ANSWER: Denied.

COMPLAINT:

123. On information and belief, the administration of the Perrigo ANDA Product into a nose of an individual infringes at least one claim, including at least claim 1 of the '353 patent, literally and/or by the doctrine of equivalents.

ANSWER: Denied.

COMPLAINT:

124. On information and belief, the Perrigo ANDA Product is an aqueous solution of cyanocobalamin comprising cyanocobalamin at a concentration of about 0.5% of total weight of solution, citric acid at a concentration of about 0.12%, sodium citrate at a concentration of about

0.32%, glycerin at a concentration of about 2.23%, benzalkonium chloride at concentration of about 0.02% and water, wherein said solution of cyanocobalamin is suitable for intranasal administration and has a viscosity less than about 1000 cPs, with the proviso that the solution of cyanocobalamin contains no mercury or mercury-containing compounds, as claimed in at least one claim, including at least claim 1 of the '353 patent, literally and/or by the doctrine of equivalents.

ANSWER: This paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, denied.

COMPLAINT:

125. On information and belief, the Perrigo ANDA Product is administered into a nose of an individual through an actuator tip as a spray, wherein the spray has a spray pattern ellipticity ratio of from about 1.0 to about 1.4 when measured at a height of 3.0 cm from the actuator tip, as claimed in at least one claim, including at least claim 1 of the '353 patent, literally and/or by the doctrine of equivalents.

ANSWER: This paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, denied.

COMPLAINT:

126. Endo will be irreparably harmed if Perrigo is not enjoined from infringing, inducing, or contributing to infringement of the '353 patent. Endo does not have an adequate remedy at law.

ANSWER: Denied.

COMPLAINT:

127. This case is exceptional and Endo is entitled to an award of reasonable attorney fees under 35 U.S.C. § 285.

ANSWER: Denied.

COUNT EIGHT
'353 Patent

COMPLAINT:

128. Endo realleges and incorporates each of the preceding paragraphs as if fully set forth herein.

ANSWER: Perrigo restates and incorporates each of its responses to the preceding paragraphs as if fully set forth herein.

COMPLAINT:

129. These claims arise under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

ANSWER: This paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, Perrigo admits that Plaintiff's Complaint is for alleged patent infringement and for declaratory judgment of alleged patent infringement, but denies that Plaintiff is entitled to any relief. Answering further, Perrigo does not contest subject matter jurisdiction under 35 U.S.C. § 271(e)(2)(A) for purposes of this action only. Perrigo denies the remaining allegations contained in this paragraph.

COMPLAINT:

130. There is an actual case or controversy such that the Court may resolve Endo's request for declaratory relief consistent with Article III of the United States Constitution.

ANSWER: This paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, Perrigo admits that Plaintiff's Complaint is for alleged patent infringement and for declaratory judgment of alleged patent infringement, but denies that Plaintiff is entitled to any relief. Answering further, Perrigo does not contest subject matter jurisdiction under 35 U.S.C. § 271(e)(2)(A) for purposes of this action only. Perrigo denies the remaining allegations contained in this paragraph.

COMPLAINT:

131. On information and belief, unless enjoined by this Court, Perrigo plans and intends to engage in the manufacture, use, offer for sale, sale, marketing, distribution, and/or importation of the Perrigo ANDA Product immediately following approval of the Perrigo ANDA.

ANSWER: This paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, Perrigo admits that Perrigo submitted ANDA No. 212458 to FDA, pursuant to 21 U.S.C. § 355(j); that Perrigo's ANDA contains paragraph IV certifications to the '636 patent, the '489 patent, the '349 patent, the '353 patent, the '714 patent, and the '007 patent; and that Perrigo seeks approval from FDA to engage in the commercial manufacture, use, sale, or importation of Cyanocobalamin Nasal Spray, 500 mcg/spray, before the expiration of the '636, '489, '349, '353, '714, and '007 patents. Perrigo denies the remaining allegations contained in this paragraph.

COMPLAINT:

132. The commercial use of the Perrigo ANDA Product will directly infringe the '353 patent.

ANSWER: Denied.

COMPLAINT:

133. The commercial offer for sale and sale of the Perrigo ANDA Product, in conjunction with the labeling and instructions for use thereof, will constitute an act of inducement of infringement of the '353 patent.

ANSWER: Denied.

COMPLAINT:

134. On information and belief, Perrigo had knowledge of the '353 patent since at least the time Perrigo submitted the Paragraph IV Certifications to FDA.

ANSWER: This paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, Perrigo admits that Perrigo submitted ANDA No. 212458 to FDA, pursuant to 21 U.S.C. § 355(j); that Perrigo's ANDA contains paragraph IV certifications to the '636 patent, the '489 patent, the '349 patent, the '353 patent, the '714 patent, and the '007 patent; and that Perrigo seeks approval from FDA to engage in the commercial

manufacture, use, sale, or importation of Cyanocobalamin Nasal Spray, 500 mcg/spray, before the expiration of the '636, '489, '349, '353, '714, and '007 patents. Perrigo denies the remaining allegations contained in this paragraph.

COMPLAINT:

135. Because the Perrigo ANDA Product is especially made or adapted for use in the claims of the '353 patent, and has no substantially non-infringing use, the commercial manufacture, offer for sale, sale and/or importation of the Perrigo ANDA Product will constitute an act of contributory infringement of the '353 patent.

ANSWER: Denied.

COMPLAINT:

136. Endo is entitled to a declaratory judgment that the commercial manufacture, use, offer to sell, or sale within the United States, and/or importation into the United States, of the Perrigo ANDA Product, or the inducement of and/or contribution to the commercial manufacture, use, offer for sale, or sale within the United States, and/or importation into the United States, of the Perrigo ANDA Product before expiration of the '353 patent by Perrigo or its agents, will constitute infringement, inducement of infringement, and/or contributory infringement of the '353 patent under 35 U.S.C. §§ 271(a), (b), and/or (c).

ANSWER: Denied.

COMPLAINT:

137. Endo will be irreparably harmed if Perrigo is not enjoined from infringing, inducing, or contributing to infringement of the '353 patent. Endo does not have an adequate remedy at law.

ANSWER: Denied.

COMPLAINT:

138. This case is exceptional and Endo is entitled to an award of reasonable attorney fees under 35 U.S.C. § 285.

ANSWER: Denied.

COUNT NINE
'714 Patent

COMPLAINT:

139. Endo realleges and incorporates each of the preceding paragraphs as if fully set forth herein.

ANSWER: Perrigo restates and incorporates each of its responses to the preceding paragraphs as if fully set forth herein.

COMPLAINT:

140. Perrigo's submission of the Perrigo ANDA to FDA to engage in the commercial manufacture, use, sale, offer for sale, or importation of the Perrigo ANDA Product, prior to the expiration of the '714 patent, constitutes infringement of at least one claim, including at least claims 1 and/or 10 of the '714 patent, under 35 U.S.C. § 271(e)(2), literally and/or by the doctrine of equivalents.

ANSWER: Denied.

COMPLAINT:

141. On FDA approval of the Perrigo ANDA, Perrigo will infringe at least one claim, including at least claims 1 and/or 10 of the '714 patent, by manufacturing, using, offering to sell, or selling the Perrigo ANDA Product in the United States and/or importing the Perrigo ANDA Product into the United States, and by actively inducing and/or contributing to infringement by others, in violation of 35 U.S.C. §§ 271(a), (b), and/or (c), literally and/or by the doctrine of equivalents.

ANSWER: Denied.

COMPLAINT:

142. As part of the Perrigo ANDA, Perrigo must show that "the labeling proposed for the new drug is the same as the labeling approved for the listed drug," except for changes indicating that the drug is produced or distributed by different manufacturers. 21 U.S.C. § 355(j)(2)(A)(v).

ANSWER: This paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, Perrigo admits that 21 U.S.C. § 355(j)(2)(A)(v)

contains the quoted language. Perrigo denies the remaining allegations contained in this paragraph.

COMPLAINT:

143. The label for Nascobal[®] nasal spray states that Nascobal[®] nasal spray is administered in the nostril to a subject in need thereof.

ANSWER: This paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, Perrigo admits that, according to the approved label, available from the online records of FDA:

- The recommended initial dose is one spray (500 mcg) in one nostril once weekly. (2.2)

Perrigo denies the remaining allegations contained in this paragraph.

COMPLAINT:

144. On information and belief, the proposed label for the Perrigo ANDA Product is substantially identical to the approved label for Nascobal[®] nasal spray, and the Perrigo ANDA Product, if approved, will be marketed, sold, and/or distributed with labeling that is substantially identical to the labeling for Nascobal[®] nasal spray.

ANSWER: This paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, Perrigo admits that Perrigo's ANDA meets the requirements of, *inter alia*, 21 U.S.C. § 355(j)(2)(A)(v). Perrigo denies the remaining allegations contained in this paragraph.

COMPLAINT:

145. On information and belief, the proposed label for the Perrigo ANDA Product also states that the Perrigo ANDA Product is administered in the nostril to a subject in need thereof. Therefore, the proposed label promotes or encourages persons to administer the Perrigo ANDA Product by infusing the nose of a subject in need thereof.

ANSWER: This paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, Perrigo admits that Perrigo's ANDA meets the

requirements of, *inter alia*, 21 U.S.C. § 355(j)(2)(A)(v). Perrigo denies the remaining allegations contained in this paragraph.

COMPLAINT:

146. On information and belief, Perrigo knowingly provides instruction in the proposed label for persons to administer the Perrigo ANDA Product by infusing the nose of a subject in need thereof, and the proposed label reflects a specific intent to encourage persons to directly infringe at least one claim, including at least claims 1 and/or 10 of the '714 patent, literally and/or by the doctrine of equivalents.

ANSWER: Denied.

COMPLAINT:

147. On information and belief, the administration of the Perrigo ANDA Product by infusing the nose of a subject in need thereof infringes at least one claim, including at least claims 1 and/or 10 of the '714 patent, literally and/or by the doctrine of equivalents.

ANSWER: Denied.

COMPLAINT:

148. On information and belief, the Perrigo ANDA Product comprises a pharmaceutically effective amount of cyanocobalamin at a concentration of about 0.5% of total weight of solution, wherein the solution has a viscosity of less than 1000 cPs, and wherein the solution has a bioavailability of about 7% or more relative to the bioavailability of an intramuscular injection containing cyanocobalamin at a concentration of 0.1% of the total weight based on a same volume as the solution, as claimed in at least one claim, including at least claim 1 of the '714 patent, literally and/or by the doctrine of equivalents.

ANSWER: This paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, denied.

COMPLAINT:

149. On information and belief, the Perrigo ANDA Product comprises a pharmaceutically effective amount of cyanocobalamin at a concentration of about 0.5% of total weight of solution, citric acid, sodium citrate, benzalkonium chloride, and glycerin, wherein the solution has a viscosity of less than 1000 cPs, and wherein the solution has a bioavailability of about 7% or more relative to the bioavailability of an intramuscular injection containing cyanocobalamin at a concentration of 0.1% of the total weight based on a same volume as the solution, as claimed in at least one claim, including at least claim 10 of the '714 patent, literally and/or by the doctrine of equivalents.

ANSWER: This paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, denied.

COMPLAINT:

150. Endo will be irreparably harmed if Perrigo is not enjoined from infringing, inducing, or contributing to infringement of the '714 patent. Endo does not have an adequate remedy at law.

ANSWER: Denied.

COMPLAINT:

151. This case is exceptional and Endo is entitled to an award of reasonable attorney fees under 35 U.S.C. § 285.

ANSWER: Denied.

COUNT TEN
'714 Patent

COMPLAINT:

152. Endo realleges and incorporates each of the preceding paragraphs as if fully set forth herein.

ANSWER: Perrigo restates and incorporates each of its responses to the preceding paragraphs as if fully set forth herein.

COMPLAINT:

153. These claims arise under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

ANSWER: This paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, Perrigo admits that Plaintiff's Complaint is for alleged patent infringement and for declaratory judgment of alleged patent infringement, but denies that Plaintiff is entitled to any relief. Answering further, Perrigo does not contest subject

matter jurisdiction under 35 U.S.C. § 271(e)(2)(A) for purposes of this action only. Perrigo denies the remaining allegations contained in this paragraph.

COMPLAINT:

154. There is an actual case or controversy such that the Court may resolve Endo's request for declaratory relief consistent with Article III of the United States Constitution.

ANSWER: This paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, Perrigo admits that Plaintiff's Complaint is for alleged patent infringement and for declaratory judgment of alleged patent infringement, but denies that Plaintiff is entitled to any relief. Answering further, Perrigo does not contest subject matter jurisdiction under 35 U.S.C. § 271(e)(2)(A) for purposes of this action only. Perrigo denies the remaining allegations contained in this paragraph.

COMPLAINT:

155. On information and belief, unless enjoined by this Court, Perrigo plans and intends to engage in the manufacture, use, offer for sale, sale, marketing, distribution, and/or importation of the Perrigo ANDA Product immediately following approval of the Perrigo ANDA.

ANSWER: This paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, Perrigo admits that Perrigo submitted ANDA No. 212458 to FDA, pursuant to 21 U.S.C. § 355(j); that Perrigo's ANDA contains paragraph IV certifications to the '636 patent, the '489 patent, the '349 patent, the '353 patent, the '714 patent, and the '007 patent; and that Perrigo seeks approval from FDA to engage in the commercial manufacture, use, sale, or importation of Cyanocobalamin Nasal Spray, 500 mcg/spray, before the expiration of the '636, '489, '349, '353, '714, and '007 patents. Perrigo denies the remaining allegations contained in this paragraph.

COMPLAINT:

156. The commercial use of the Perrigo ANDA Product will directly infringe the ‘714 patent.

ANSWER: Denied.

COMPLAINT:

157. The commercial offer for sale and sale of the Perrigo ANDA Product, in conjunction with the labeling and instructions for use thereof, will constitute an act of inducement of infringement of the ‘714 patent.

ANSWER: Denied.

COMPLAINT:

158. On information and belief, Perrigo had knowledge of the ‘714 patent since at least the time Perrigo submitted the Paragraph IV Certifications to FDA.

ANSWER: This paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, Perrigo admits that Perrigo submitted ANDA No. 212458 to FDA, pursuant to 21 U.S.C. § 355(j); that Perrigo’s ANDA contains paragraph IV certifications to the ‘636 patent, the ‘489 patent, the ‘349 patent, the ‘353 patent, the ‘714 patent, and the ‘007 patent; and that Perrigo seeks approval from FDA to engage in the commercial manufacture, use, sale, or importation of Cyanocobalamin Nasal Spray, 500 mcg/spray, before the expiration of the ‘636, ‘489, ‘349, ‘353, ‘714, and ‘007 patents. Perrigo denies the remaining allegations contained in this paragraph.

COMPLAINT:

159. Because the Perrigo ANDA Product is especially made or adapted for use in the claims of the ‘714 patent, and has no substantially non-infringing use, the commercial manufacture, offer for sale, sale and/or importation of the Perrigo ANDA Product will constitute an act of contributory infringement of the ‘714 patent.

ANSWER: Denied.

COMPLAINT:

160. Endo is entitled to a declaratory judgment that the commercial manufacture, use, offer to sell, or sale within the United States, and/or importation into the United States, of the Perrigo ANDA Product, or the inducement of and/or contribution to the commercial manufacture, use, offer for sale, or sale within the United States, and/or importation into the United States, of the Perrigo ANDA Product before expiration of the '714 patent by Perrigo or its agents, will constitute infringement, inducement of infringement, and/or contributory infringement of the '714 patent under 35 U.S.C. §§ 271(a), (b), and/or (c).

ANSWER: Denied.

COMPLAINT:

161. Endo will be irreparably harmed if Perrigo is not enjoined from infringing, inducing, or contributing to infringement of the '714 patent. Endo does not have an adequate remedy at law.

ANSWER: Denied.

COMPLAINT:

162. This case is exceptional and Endo is entitled to an award of reasonable attorney fees under 35 U.S.C. § 285.

ANSWER: Denied.

COUNT ELEVEN

'007 Patent

COMPLAINT:

163. Endo realleges and incorporates each of the preceding paragraphs as if fully set forth herein.

ANSWER: Perrigo restates and incorporates each of its responses to the preceding paragraphs as if fully set forth herein.

COMPLAINT:

164. Perrigo's submission of the Perrigo ANDA to FDA to engage in the commercial manufacture, use, sale, offer for sale, or importation of the Perrigo ANDA Product, prior to the expiration of the '007 patent, constitutes infringement of at least one claim, including at least claims 1 and/or 13 of the '007 patent, under 35 U.S.C. § 271(e)(2), literally and/or by the doctrine of equivalents.

ANSWER: Denied.

COMPLAINT:

165. On FDA approval of the Perrigo ANDA, Perrigo will infringe at least one claim, including at least claims 1 and/or 13 of the '007 patent, by manufacturing, using, offering to sell, or selling the Perrigo ANDA Product in the United States and/or importing the Perrigo ANDA Product into the United States, and by actively inducing and/or contributing to infringement by others, in violation of 35 U.S.C. §§ 271(a), (b), and/or (c), literally and/or by the doctrine of equivalents.

ANSWER: Denied.

COMPLAINT:

166. As part of the Perrigo ANDA, Perrigo must show that “the labeling proposed for the new drug is the same as the labeling approved for the listed drug,” except for changes indicating that the drug is produced or distributed by different manufacturers. 21 U.S.C. § 355(j)(2)(A)(v).

ANSWER: This paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, Perrigo admits that 21 U.S.C. § 355(j)(2)(A)(v) contains the quoted language. Perrigo denies the remaining allegations contained in this paragraph.

COMPLAINT:

167. The label for Nascobal® nasal spray indicates that Nascobal® nasal spray may be administered to a subject having vitamin B12 deficiency associated with gastric surgery.

ANSWER: This paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, Perrigo admits that, according to the approved label, available from the online records of FDA:

-----INDICATIONS AND USAGE-----

NASCOBAL is a vitamin B₁₂ indicated for:

- Vitamin B12 maintenance therapy in adult patients with pernicious anemia who are in remission following intramuscular vitamin B12 therapy and who have no nervous system involvement (1)
- Treatment of adult patients with dietary, drug-induced, or malabsorption-related vitamin B12 deficiency not due to pernicious anemia (1)
- Prevention of vitamin B12 deficiency in adult patients with vitamin B12 requirements in excess of normal (1)

Limitations of Use:

- Should not be used for the vitamin B12 absorption test (Schilling test). (1)
- In patients with correctible or temporary causes of vitamin B12 deficiency the benefit of continued long-term use following correction of vitamin B₁₂ deficiency and underlying disease has not been established. (1)
- In patients with active symptoms of nasal congestion, allergic rhinitis or upper respiratory infection effectiveness has not been established. (1)

Perrigo denies the remaining allegations contained in this paragraph.

COMPLAINT:

168. On information and belief, the proposed label for the Perrigo ANDA Product is substantially identical to the approved label for Nascobal[®] nasal spray, and the Perrigo ANDA Product, if approved, will be marketed, sold, and/or distributed with labeling that is substantially identical to the labeling for Nascobal[®] nasal spray.

ANSWER: This paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, Perrigo admits that Perrigo's ANDA meets the requirements of, *inter alia*, 21 U.S.C. § 355(j)(2)(A)(v). Perrigo denies the remaining allegations contained in this paragraph.

COMPLAINT:

169. On information and belief, the proposed label for the Perrigo ANDA Product also indicates that the Perrigo ANDA Product may be administered to a subject having vitamin B12 deficiency associated with gastric surgery. Therefore, the proposed label promotes or encourages persons to administer the Perrigo ANDA Product to a subject having vitamin B12 deficiency associated with gastric surgery.

ANSWER: This paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, Perrigo admits that Perrigo's ANDA meets the

requirements of, *inter alia*, 21 U.S.C. § 355(j)(2)(A)(v). Perrigo denies the remaining allegations contained in this paragraph.

COMPLAINT:

170. On information and belief, Perrigo knowingly provides instruction in the proposed label to administer the Perrigo ANDA Product to a subject having vitamin B12 deficiency associated with gastric surgery, and the proposed label reflects a specific intent to encourage persons to directly infringe at least one claim, including at least claims 1 and/or 13 of the '007 patent, literally and/or by the doctrine of equivalents.

ANSWER: Denied.

COMPLAINT:

171. On information and belief, the administration of the Perrigo ANDA Product to a subject having vitamin B12 deficiency associated with gastric surgery infringes at least one claim, including at least claims 1 and/or 13 of the '007 patent, literally and/or by the doctrine of equivalents.

ANSWER: Denied.

COMPLAINT:

172. On information and belief, the Perrigo ANDA Product comprises cyanocobalamin; water; a buffer selected from the group consisting of citric acid, sodium citrate, monopotassium phosphate, disodium phosphate, potassium biphthalate, sodium hydroxide, sodium acetate, acetic acid, and combinations thereof; optionally, a humectant selected from the group consisting of sorbitol, propylene glycol, and glycerin, and combinations thereof; and optionally, a preservative selected from the group consisting of benzyl alcohol, parabens thimerosal, chlorobutanol, benzethonium chloride, and benzalkonium chloride, and combinations thereof; wherein the aqueous solution of cyanocobalamin is suitable for intranasal administration, has a viscosity of less than about 1000 cPs, and a bioavailability of cyanocobalamin when administered intranasally of at least about 7% relative to an intramuscular injection of cyanocobalamin, as claimed in at least one claim, including at least claims 1 and/or 13 of the '007 patent, literally and/or by the doctrine of equivalents.

ANSWER: This paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, denied.

COMPLAINT:

173. On information and belief, the Perrigo ANDA Product comprises an aqueous solution of cyanocobalamin in a container; and an actuator coupled to the container, the actuator

comprising a tip for producing a spray of the aqueous solution of cyanocobalamin when the actuator is engaged, as claimed in at least one claim, including at least claim 13 of the '007 patent, literally and/or by the doctrine of equivalents.

ANSWER: This paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, denied.

COMPLAINT:

174. Endo will be irreparably harmed if Perrigo is not enjoined from infringing, inducing, or contributing to infringement of the '007 patent. Endo does not have an adequate remedy at law.

ANSWER: Denied.

COMPLAINT:

175. This case is exceptional and Endo is entitled to an award of reasonable attorney fees under 35 U.S.C. § 285.

ANSWER: Denied.

COUNT TWELVE
'007 Patent

COMPLAINT:

176. Endo realleges and incorporates each of the preceding paragraphs as if fully set forth herein.

ANSWER: Perrigo restates and incorporates each of its responses to the preceding paragraphs as if fully set forth herein.

COMPLAINT:

177. These claims arise under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

ANSWER: This paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, Perrigo admits that Plaintiff's Complaint is for alleged patent infringement and for declaratory judgment of alleged patent infringement, but denies that Plaintiff is entitled to any relief. Answering further, Perrigo does not contest subject

matter jurisdiction under 35 U.S.C. § 271(e)(2)(A) for purposes of this action only. Perrigo denies the remaining allegations contained in this paragraph.

COMPLAINT:

178. There is an actual case or controversy such that the Court may resolve Endo's request for declaratory relief consistent with Article III of the United States Constitution.

ANSWER: This paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, Perrigo admits that Plaintiff's Complaint is for alleged patent infringement and for declaratory judgment of alleged patent infringement, but denies that Plaintiff is entitled to any relief. Answering further, Perrigo does not contest subject matter jurisdiction under 35 U.S.C. § 271(e)(2)(A) for purposes of this action only. Perrigo denies the remaining allegations contained in this paragraph.

COMPLAINT:

179. On information and belief, unless enjoined by this Court, Perrigo plans and intends to engage in the manufacture, use, offer for sale, sale, marketing, distribution, and/or importation of the Perrigo ANDA Product immediately following approval of the Perrigo ANDA.

ANSWER: This paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, Perrigo admits that Perrigo submitted ANDA No. 212458 to FDA, pursuant to 21 U.S.C. § 355(j); that Perrigo's ANDA contains paragraph IV certifications to the '636 patent, the '489 patent, the '349 patent, the '353 patent, the '714 patent, and the '007 patent; and that Perrigo seeks approval from FDA to engage in the commercial manufacture, use, sale, or importation of Cyanocobalamin Nasal Spray, 500 mcg/spray, before the expiration of the '636, '489, '349, '353, '714, and '007 patents. Perrigo denies the remaining allegations contained in this paragraph.

COMPLAINT:

180. The commercial use of the Perrigo ANDA Product will directly infringe the ‘007 patent.

ANSWER: Denied.

COMPLAINT:

181. The commercial offer for sale and sale of the Perrigo ANDA Product, in conjunction with the labeling and instructions for use thereof, will constitute an act of inducement of infringement of the ‘007 patent.

ANSWER: Denied.

COMPLAINT:

182. On information and belief, Perrigo had knowledge of the ‘007 patent since at least the time Perrigo submitted the Paragraph IV Certifications to FDA.

ANSWER: This paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, Perrigo admits that Perrigo submitted ANDA No. 212458 to FDA, pursuant to 21 U.S.C. § 355(j); that Perrigo’s ANDA contains paragraph IV certifications to the ‘636 patent, the ‘489 patent, the ‘349 patent, the ‘353 patent, the ‘714 patent, and the ‘007 patent; and that Perrigo seeks approval from FDA to engage in the commercial manufacture, use, sale, or importation of Cyanocobalamin Nasal Spray, 500 mcg/spray, before the expiration of the ‘636, ‘489, ‘349, ‘353, ‘714, and ‘007 patents. Perrigo denies the remaining allegations contained in this paragraph.

COMPLAINT:

183. Because the Perrigo ANDA Product is especially made or adapted for use in the claims of the ‘007 patent, and has no substantially non-infringing use, the commercial manufacture, offer for sale, sale and/or importation of the Perrigo ANDA Product will constitute an act of contributory infringement of the ‘007 patent.

ANSWER: Denied.

COMPLAINT:

184. Endo is entitled to a declaratory judgment that the commercial manufacture, use, offer to sell, or sale within the United States, and/or importation into the United States, of the Perrigo ANDA Product, or the inducement of and/or contribution to the commercial manufacture, use, offer for sale, or sale within the United States, and/or importation into the United States, of the Perrigo ANDA Product before expiration of the '007 patent by Perrigo or its agents, will constitute infringement, inducement of infringement, and/or contributory infringement of the '007 patent under 35 U.S.C. §§ 271(a), (b), and/or (c).

ANSWER: Denied.

COMPLAINT:

185. Endo will be irreparably harmed if Perrigo is not enjoined from infringing, inducing, or contributing to infringement of the '007 patent. Endo does not have an adequate remedy at law.

ANSWER: Denied.

COMPLAINT:

186. This case is exceptional and Endo is entitled to an award of reasonable attorney fees under 35 U.S.C. § 285.

ANSWER: Denied.

* * *

RESPONSE TO PRAYER FOR RELIEF

Perrigo denies that Plaintiff is entitled to any relief as set forth in Paragraphs (A)-(Z) of the Complaint, or to any relief whatsoever, and further requests that Plaintiff's Complaint be dismissed with prejudice and that Perrigo be awarded its attorney fees and costs incurred in defending this suit under 35 U.S.C. § 285.

SEPARATE DEFENSES

Without prejudice to the denials set forth in its Answer, without admitting allegations of the Complaint not otherwise admitted, and without undertaking any of the burdens imposed by law on Plaintiff, Perrigo asserts the following defenses to the Complaint:

First Defense

The claims of the ‘636 patent are invalid for failure to satisfy one or more conditions for patentability set forth in 35 U.S.C. § 101 *et seq.*

Second Defense

The claims of the ‘489 patent are invalid for failure to satisfy one or more conditions for patentability set forth in 35 U.S.C. § 101 *et seq.*

Third Defense

The claims of the ‘349 patent are invalid for failure to satisfy one or more conditions for patentability set forth in 35 U.S.C. § 101 *et seq.*

Fourth Defense

The claims of the ‘353 patent are invalid for failure to satisfy one or more conditions for patentability set forth in 35 U.S.C. § 101 *et seq.*

Fifth Defense

The claims of the ‘714 patent are invalid for failure to satisfy one or more conditions for patentability set forth in 35 U.S.C. § 101 *et seq.*

Sixth Defense

The claims of the ‘007 patent are invalid for failure to satisfy one or more conditions for patentability set forth in 35 U.S.C. § 101 *et seq.*

Seventh Defense

The manufacture, use, sale, offer for sale, or importation of Cyanocobalamin Nasal Spray, 500 mcg/spray, that is the subject of Perrigo’s ANDA, has not infringed, does not infringe, and would not, if marketed, sold or used, infringe any valid and enforceable claim of the ‘636 patent.

Eighth Defense

The manufacture, use, sale, offer for sale, or importation of Cyanocobalamin Nasal Spray, 500 mcg/spray, that is the subject of Perrigo's ANDA, has not infringed, does not infringe, and would not, if marketed, sold or used, infringe any valid and enforceable claim of the '489 patent.

Ninth Defense

The manufacture, use, sale, offer for sale, or importation of Cyanocobalamin Nasal Spray, 500 mcg/spray, that is the subject of Perrigo's ANDA, has not infringed, does not infringe, and would not, if marketed, sold or used, infringe any valid and enforceable claim of the '349 patent.

Tenth Defense

The manufacture, use, sale, offer for sale, or importation of Cyanocobalamin Nasal Spray, 500 mcg/spray, that is the subject of Perrigo's ANDA, has not infringed, does not infringe, and would not, if marketed, sold or used, infringe any valid and enforceable claim of the '353 patent.

Eleventh Defense

The manufacture, use, sale, offer for sale, or importation of Cyanocobalamin Nasal Spray, 500 mcg/spray, that is the subject of Perrigo's ANDA, has not infringed, does not infringe, and would not, if marketed, sold or used, infringe any valid and enforceable claim of the '714 patent.

Twelfth Defense

The manufacture, use, sale, offer for sale, or importation of Cyanocobalamin Nasal Spray, 500 mcg/spray, that is the subject of Perrigo's ANDA, has not infringed, does not

infringe, and would not, if marketed, sold or used, infringe any valid and enforceable claim of the '007 patent.

Thirteenth Defense

The Complaint fails to state a claim upon which relief can be granted.

Fourteenth Defense

The '636, '489, '349, '353, '714, and '007 patents (collectively, the "Patents-in-Suit") are unenforceable due to inequitable conduct as further described with particularity below.

1. Anthony P. Sileno is listed as a co-inventor of each of the '636, '489, '349, '353, '714, and '007 patents. During the relevant time period, Mr. Sileno was employed by Natestch Pharmaceutical Company Inc. ("Natestch") as Senior Director of Clinical Affairs and Toxicology.

2. Peter J. Knudsen was an attorney for Natestch representing the patent applicants, including Mr. Sileno, with respect to prosecution of the '636 patent and '489 patent before the U.S. Patent and Trademark Office ("USPTO"). The assignee listed on the face of the '636 patent is Natestch.

3. Messrs. Sileno and Knudsen each owed a duty of candor, duty of good faith, and duty of disclosure to the USPTO.

4. During prosecution of the '636 patent, Mr. Knudsen submitted to the USPTO a draft declaration by Mr. Sileno to overcome a rejection by the patent examiner that the pending claims, which recited a comparison of the relative bioavailability of the claimed intranasal solution of cyanocobalamin to an intramuscular injection of cyanocobalamin, were invalid under 35 U.S.C. § 112 for lack of enablement.

5. Upon information and belief, Mr. Sileno knowingly misrepresented in his declaration to the USPTO a clinical trial comparing the bioavailability of the active ingredient cyanocobalamin following administration of an intranasal solution and intramuscular injection of cyanocobalamin, and the U.S. Food and Drug Administration's ("FDA") review of the results of that clinical trial, with intent to deceive.

6. Alternatively, upon information and belief, if Mr. Knudsen submitted Mr. Sileno's unsigned declaration without prior review and approval for filing by Mr. Sileno, Mr. Knudsen knowingly made material misrepresentations in his response to the USPTO, with intent to deceive.

7. Mr. Sileno's declaration presenting the results of that clinical trial and Mr. Knudsen's arguments to the USPTO relying upon Mr. Sileno's declaration were material to overcoming the patent examiner's rejection for lack of enablement and resulted in the issuance of the '636 patent. But for the submission of Mr. Sileno's declaration and/or Mr. Knudsen's arguments relying upon Mr. Sileno's declaration, the '636 patent would not have issued.

8. In addition, upon information and belief, Messrs. Sileno and Knudsen knowingly withheld from the USPTO the FDA-approved label for Nascobal® (cyanocobalamin) nasal spray and the correspondence between Natestch and the FDA relating to review of the application for Nascobal® (cyanocobalamin) nasal spray, with the intent to deceive. These withheld documents address the claimed comparison of the bioavailability of the active ingredient cyanocobalamin following administration by intranasal spray and intramuscular injection. These withheld documents refute the applicants' assertions during prosecution of the '636 patent of the bioavailability of the claimed intranasal solution of cyanocobalamin relative to an intramuscular injection of cyanocobalamin.

9. But for the withholding of the FDA-approved label for Nascobal® (cyanocobalamin) nasal spray and the correspondence between Natestch and the FDA relating to review of the application for Nascobal® (cyanocobalamin) nasal spray, the ‘636 patent would not have issued.

10. The material misrepresentations and omission of material information during the prosecution of the ‘636 patent had an immediate and necessary relation to the issuance of the ‘489 patent, ‘349 patent, ‘353 patent, ‘714 patent, and ‘007 patent.

A. Background On Nascobal® (Cyanocobalamin) Nasal Spray.

11. In November 1996, Natestch received FDA approval of New Drug Application (“NDA”) No. 19-722 for Nascobal® (cyanocobalamin) nasal gel.

12. In December 2003, Natestch filed New Drug Application No. 21-642 seeking FDA approval for Nascobal® (cyanocobalamin) nasal spray.

13. Natestch filed NDA No. 21-642 pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act, as a new dosage form (a nasal spray) for the marketed Nascobal® (cyanocobalamin) nasal gel.

14. To support FDA approval for Nascobal® (cyanocobalamin) nasal spray, Natestch conducted a “three way crossover bioequivalence study comparing the nasal spray to the approved nasal gel (NDA 19-722) and an intramuscular dosage form of cyanocobalamin in normal, healthy subjects.” (New Drug Application No. 21-642, 12/26/2003 Cover Letter, at 2.)

15. Natestch presented the results of the bioequivalence study to the FDA in its NDA No. 21-642. In summarizing the bioequivalence study, Natestch explained that one of the objectives was “to compare the pharmacokinetic profile of a single intranasally-administered spray, single intranasally-administered gel (Nascobal®), and single intramuscular-administered vitamin B12 in a fasted state in normal healthy male and female subjects.” (New Drug

Application No. 21-642, 12/26/2003 Human Pharmacokinetic and Bioavailability Summary, at

1.) Another objective was “to evaluate the bioequivalence of the vitamin B12 nasal gel versus the nasal spray in a fasted state in normal healthy male and female subjects.” (*Id.*).

16. Based on Natestech’s evaluation of the bioequivalence study, Natestech reported to the FDA that the relative bioavailability following administration of a 500 µg cyanocobalamin intranasal spray versus administration of a 100 µg cyanocobalamin intramuscular injection was 0.61 (or 61%) without adjustment for the dosage administered:

Compared to the IN gel formulation, the relative bioavailability for the IN spray formulation was 1.04. Relative bioavailability for Treatment A (spray) versus Treatment C (IM) was 0.61, and 0.63 when comparing Treatment B (gel) versus Treatment C (IM).

(*Id.* at 2.)

17. Based on Natestech’s evaluation of the bioequivalence study, Natestech reported that the intranasal spray was bioequivalent to the intranasal gel:

Bioequivalence between the Vitamin B12 spray formulation and the Vitamin B12 gel formulation was established using 90% confidence intervals for log_e-transformed dose-normalized values of AUC_{0-t} and C_{max}.

(*Id.*).

18. On October 1, 2004, the FDA’s Office of Clinical Pharmacology and Biopharmaceutics completed its review of the bioequivalence study submitted with Natestech’s NDA No. 21-642. The Office of Clinical Pharmacology and Biopharmaceutics summarized its recommendation as follows:

The Office of Clinical Pharmacology and Biopharmaceutics, Division of Pharmaceutical Evaluation II (OCPB/DPE-2) reviewed NDA 21-642 and finds the results unacceptable due to lack of demonstration of bioequivalence between the nasal spray and nasal gel formulations using baseline corrected analysis. The nasal spray had 10% less AUC than the nasal gel using baseline corrected

analysis. Since there are no clinical trials conducted, the clinical significance of the reduced exposure obtained with the nasal spray is not known. Before it is approved, it is recommended to change the formulation of the nasal spray and conduct a bioequivalence trial with baseline corrected analysis.

(Food and Drug Administration, Center for Drug Evaluation and Research, Application Number 21-642, Clinical and Pharmacology and Biopharmaceutics Review(s), at 2.)

19. The FDA's Office of Clinical Pharmacology and Biopharmaceutics found that "pre-dose plasma cyanocobalamin levels contribute significantly to the AUC." (*Id.* at 7.) Accordingly, the Office conducted a baseline corrected analysis of the data from the study. (*Id.*)

20. Based on the FDA's baseline corrected analysis of the data, the FDA concluded that the nasal spray had a bioavailability relative to the intramuscular injection of 0.061 (or 6.1%):

The relative bioavailability (baseline corrected) of the two intranasal formulations as compared to the intramuscular injection was found to be 0.061 (Spray) and 0.071 (Gel).

(*Id.* at 10.)

21. Based on the FDA's baseline corrected analysis of the bioequivalence study, the FDA concluded that the nasal spray and nasal gel were not bioequivalent:

The 90% confidence interval for baseline corrected AUC and C_{max} was outside the 80-125% range, the intranasal spray had 10% less AUC as compared to the intranasal gel.

(*Id.*).

22. On October 28, 2004, the FDA sent an action letter to Natestch stating that the FDA had completed its review of NDA 21-642. (10/28/2004 Ltr. from FDA re NDA 21-642, at 1.) The FDA informed Natestch that the issue of bioavailability must be addressed:

After correcting for baseline values, the intranasal spray was 10% less bioavailable than the intranasal gel. This product is also less bioavailable than the intramuscular formulation. Since this

product cannot be considered bioequivalent to the reference listed product, clinical use of this product or any cyanocobalamin formulation will require close monitoring of vitamin B₁₂ levels. Patients not achieving adequate vitamin B₁₂ levels will require increased dosing with subsequent blood monitoring.

(*Id.*). Among other things, the FDA recommended that Natestch “[r]evis[e] your package insert (PI) to include a discussion of the difference in pharmacokinetics of the two intranasal products and advice that patients treated with the nasal spray should have vitamin B₁₂ levels closely monitored with dose amount and/or frequency adjusted to achieve adequate levels.” (*Id.*).

23. On November 8, 2004, in response to the FDA’s October 28, 2004 action letter, Natestch requested a telephone conference to clarify the analysis of the bioequivalence study by the FDA’s Clinical Pharmacology and Biopharmaceutics reviewer. (11/8/2004 Ltr. from Natestch re NDA 21-642, at 1.)

24. On November 19, 2004, the FDA held a telephone conference to clarify deficiencies in the clinical and biopharmaceutical review of NDA No. 21-642. (Memorandum of 11/19/2004 T-Con Meeting Minutes, Application Number 21-642, at 1.) Dr. Gordon Brandt, Executive Vice President of Medical Affairs, and Anthony Sileno, Senior Director of Toxicology and Clinical Trials, attended the teleconference as representatives of Natestch. (*Id.*).

25. The November 19, 2004 teleconference meeting minutes reflect that the FDA and Natestch discussed the FDA’s re-analysis of the bioequivalence data submitted by Natestch:

Sponsor: What is the basis for the statement that the spray is 10% less bioavailable than the gel? If this is based on an FDA conducted re-analysis of the bioequivalence data, what is the FDA-determined relative bioavailability of gel vs IM, spray vs IM, and gel vs spray? In the ITT analysis submitted with NDA, the spray had an AUC of 104% relative to the gel with 95% CI of 97.7 – 111.2% (NDA Volume 1.11, page 43). A total of three analyses were submitted with the NDA, and none of them came to the conclusion that the spray was 10% less bioavailable than the gel.

FDA: Baseline corrected analysis was done during the review process. The baseline value was obtained by taking the average of three pre-dose vitamin B12 concentrations in plasma. The relative bioavailability of gel vs. IM, spray vs. IM, and spray vs. gel was found to be 7.1%, 6.1%, and 90.4% respectively. The log transformed 90% confidence intervals for AUC(0-t) and Cmax were 71.71-114.19 and 71.6-118.66 respectively. The spray had 10% less bioavailability as compared to the gel; bioequivalency was not established.

(*Id.* at 2.)

26. On December 1, 2004, Natestech submitted an amendment to NDA No. 21-642 to address the FDA's analysis of the bioequivalence data submitted by Natestech. (NDA No. 21-642, 12/1/2004 Amendment 14, at 3.) In response to the clinical pharmacology and biopharmaceutics reviewer's comments regarding the bioequivalence data, Natestech responded that "[w]e agree with the reviewer's comments, and have made a number of changes to the package insert in response." (*Id.*) For example, with respect to the discussion on the difference in pharmacokinetics, Natestech responded as follows:

The comparative pharmacokinetic data previously included in the package insert has been revised per the reviewer's calculations to compare both gel and spray nasal administrations to intramuscular injection. Additionally, a statement has been added in two places emphasizing that

- nasal formulation have lower absorption than intramuscular formulations, and that
- weekly dosing is therefore required for the nasal products.

(*Id.* at 3-4.)

27. In its December 1, 2004 amendment, Natestech deleted the following passage from the "Pharmacokinetics" section of the proposed label for Nascobal® (cyanocobalamin) nasal spray:

In a pharmacokinetic study comparing B₁₂ nasal spray and B₁₂ nasal gel in 25 healthy male and female subjects, bioequivalence between the B₁₂ spray and gel formulation was established using the 90% confidence intervals for the log_e-transformed pharmacokinetic parameters and fell within the range of 80%-125%.

Compared to the B₁₂ nasal gel, the relative bioavailability for the B₁₂ nasal spray was 1.04. Relative bioavailability for B₁₂ nasal gel and spray versus 100 mcg intramuscular injection was 0.63 and 0.61, respectively.

(*Id.* at 5.) In its place, Natestch added the following statement to its proposed label for Nascobal® (cyanocobalamin) nasal spray:

In a subsequent pharmacokinetic study in 25 healthy subjects, the relative bioavailability for B₁₂ nasal gel and spray versus 100 mcg intramuscular injection was 7% and 6%, respectively.

(*Id.*).

28. On January 20, 2005, Natestch submitted an amendment to NDA No. 21-642 with a revision to its proposed label for Nascobal® (cyanocobalamin) nasal spray. (NDA No. 21-642, 1/20/2005 Amendment 15, at 1.) In its amended proposed label, Natestch deleted the following passages:

In a bioavailability study in 24 pernicious anemia patients comparing B₁₂ nasal gel to intramuscular B₁₂, peak concentrations of B₁₂ after intranasal administration were reached in 1-2 hours. The average peak concentration of B₁₂ after intranasal administration was 1,414 ± 1,003 pg/mL. The bioavailability of the nasal gel relative to an intramuscular injection was found to be 8.9% (90% confidence intervals 7.1-11.2%).

...

In a subsequent pharmacokinetic study in 25 healthy subjects, the relative bioavailability for B₁₂ nasal gel and spray versus 100 mcg intramuscular injection was 7% and 6%, respectively.

(*Id.* at 2.) In their place, Natestch added the following paragraph to its proposed label for Nascobal® (cyanocobalamin) nasal spray:

A three way crossover study in 25 fasting healthy subjects was conducted to compare the bioavailability of the B₁₂ nasal spray to the B₁₂ nasal gel and to evaluate the relative bioavailability of the nasal formulations as compared to the intramuscular injection. The peak concentrations after administration of intranasal spray were reached in 1.25 +/- 1.9 hours. The average peak concentration of B₁₂ obtained after baseline correction following administration of intranasal spray was 757.96 +/- 532.17 pg/mL. The bioavailability of the nasal spray relative to the intramuscular injection was found to be 6.1%. The bioavailability of the B₁₂ nasal spray was found to be 10% less than the B₁₂ nasal gel. The 90% confidence intervals for the log_e-transformed AUC_(0-t) and C_{max} was 71.71% - 114.19% and 71.6% - 118.66% respectively.

(*Id.*).

29. On January 31, 2005, Nascotech received FDA approval of NDA No. 21-642 for Nascobal® (cyanocobalamin) nasal spray.

30. The originally approved label for Nascobal® (cyanocobalamin) nasal spray states that “[t]he bioavailability of the nasal spray relative to the intramuscular injection was found to be 6.1%.” (Nascobal® (cyanocobalamin) nasal spray Prescribing Information at 1.)

B. Patents-In-Suit.

31. U.S. Patent Application No. 10/787,385 (“the ‘385 application”) was filed on February 26, 2004, and issued as the ‘636 patent on June 12, 2007.

32. U.S. Patent Application No. 10/814,399 (“the ‘399 application”) was filed on March 31, 2004, and issued as the ‘489 patent on July 29, 2008.

33. U.S. Patent Application No. 12/079,875 (“the ‘875 application”) was filed on March 27, 2008, and issued as the ‘349 patent on February 1, 2011.

34. U.S. Patent Application No. 12/142,240 (“the ‘240 application”) was filed on June 19, 2008, and issued as the ‘353 patent on August 23, 2011.

35. U.S. Patent Application No. 13/189,061 (“the ‘061 application”) was filed on July 22, 2011, and issued as the ‘714 patent on January 27, 2015.

36. U.S. Patent Application No. 14/485,228 (“the ‘228 application”) was filed on September 12, 2014, and issued as the ‘007 patent on August 16, 2016.

37. Each of the ‘636 patent, ‘489 patent, ‘349 patent, ‘353 patent, ‘714 patent, and ‘007 patent derive from and are related to the ‘385 application.

38. The named inventors for all of the Patents-in-Suit are Steven C. Quay, Peter C. Aprile, Zenaida O. Go, and Anthony P. Sileno.

C. Prosecution History Of U.S. Patent Application No. 10/787,385.

39. On February 26, 2004, Mr. Sileno and the other co-inventors filed the ‘385 application with the USPTO.

40. The ‘385 application was originally filed with 31 claims. Claims 1, 23, 24, 30, and 31 of the ‘385 application, as originally filed, recited as follows:

1. A stable pharmaceutical aqueous solution of cyanocobalamin comprised of cyanocobalamin and water wherein said solution of cyanocobalamin is suitable for intranasal administration, has a viscosity less than about 1000 cPs, and wherein said solution of cyanocobalamin has a bioavailability of cyanocobalamin when administered intranasally of at least about 7% relative to an intramuscular injection of cyanocobalamin with the proviso that the solution contains no mercury or mercury compounds.

23. A stable pharmaceutical aqueous solution of cyanocobalamin comprised of cyanocobalamin at a concentration of about 0.5% of total weight of solution, citric acid at a concentration of about 0.12%, sodium citrate at a concentration of about 0.32% glycerin at a concentration of about 2.23%, benzalkonium chloride at concentration of about 0.02% and water wherein said solution of cyanocobalamin is suitable for intranasal administration, has a viscosity less than about 1000 cPs, and wherein said solution of cyanocobalamin has a bioavailability of cyanocobalamin when administered intranasally of at least about 7% relative to an intramuscular injection of cyanocobalamin with the proviso that mercury and mercury containing compounds are not present.

24. A method for administering cyanocobalamin comprised of infusing the nose with an aqueous solution of cyanocobalamin, wherein the solution of cyanocobalamin has a viscosity of less than 1000 cPs, and wherein said solution of cyanocobalamin has a bioavailability of cyanocobalamin of about 7% relative to an intramuscular injection of cyanocobalamin, with the proviso that mercury and mercury containing compounds are not present in the solution.

30. A method for administering cyanocobalamin comprised of infusing the nose with an aqueous solution of cyanocobalamin wherein said aqueous solution of cyanocobalamin is comprised of cyanocobalamin at a concentration of about 0.5% of total weight of solution, citric acid at a concentration of about 0.12%, sodium citrate at a concentration of about 0.32%, glycerin at a concentration of about 2.23%, benzalkonium chloride at concentration of about 0.02% and water wherein said solution of cyanocobalamin is suitable for intranasal administration, has a viscosity less than about 1000 cPs, and wherein said solution of cyanocobalamin has a bioavailability of cyanocobalamin when administered intranasally of at least about 7% relative to an intramuscular injection of cyanocobalamin, with the proviso that the solution of cyanocobalamin contains no mercury or mercury-containing compounds.

31. A method for elevating the vitamin B 12 levels in the cerebral spinal fluid (CSF) comprising administering intranasally a sufficient amount of a solution of cyanocobalamin so that the average ratio of vitamin B12 in the CSF to that in the blood serum ($B12\text{ CSF}/B12\text{ Serum} \times 100$) is increased to at least about 1.1, wherein said aqueous solution of cyanocobalamin is comprised of cyanocobalamin at a concentration of about 0.5% of total weight of solution, citric acid at a concentration of about 0.12%, sodium citrate at a concentration of about 0.32%, glycerin at a concentration of about 2.23%, benzalkonium chloride at concentration of about 0.02% and water wherein said solution of cyanocobalamin is suitable for intranasal administration, has a viscosity less than about 1000 cPs, and wherein said solution of cyanocobalamin has a bioavailability of cyanocobalamin when administered intranasally of at least about 7% relative to an intramuscular injection of cyanocobalamin, with the proviso that the cyanocobalamin solution contains no mercury or mercury-containing compounds.

(‘636 Patent Prosecution History (“PH”), 2/26/2004 Claims, at 23-26.)

41. On April 27, 2005, the patent examiner issued an Office Action with a non-final rejection. The patent examiner rejected pending claims 1, 23, 24, 30, and 31 under 35 U.S.C. § 112 as failing to comply with the enablement requirement, because the specification does not provide “all of the data necessary to calculate the bioavailability claimed relative to that of an intramuscular injection.” The patent examiner stated as follows:

Claims 1, 23, 24, 30 and 31 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contains [*sic*] subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The aforementioned claims are directed to a solution that, when administered intranasally, have a bioavailability of at least 7% relative to an intramuscular injection. An adequate representation regarding the bioavailability claimed would be one that provides all of the data necessary to calculate the bioavailability claimed relative to that of an intramuscular injection.

(‘636 Patent PH, 4/27/2005 Office Action at 7.)

42. On September 22, 2005, the applicants filed their Amendment and Response to the April 27, 2005 Office Action. The applicants acknowledged that “[t]he central factual basis for this rejection asserted by the Office is that the disclosure allegedly lacks ‘sufficient AUC data’ to support Applicants’ claims to a solution of cyanocobalamin providing ‘a bioavailability of cyanocobalamin, when administered nasally, of at least about 7% relative to an intramuscular injection of cyanocobalamin.’” (‘636 Patent PH, 9/22/2005 Amendment and Response at 6.)

43. In the September 22, 2005 Amendment and Response, the applicants “concede[d] the Office’s point that explicit AUC data are not provided for bioavailability of cyanocobalamin delivered via intramuscular injection.” (*Id.*).

44. In the September 22, 2005 Amendment and Response, the applicants stated that “the subject data are directly derivable from comparative data provided in the application, which fully support the subject, ‘at least 7%’ relative bioavailability functional limitation recited in Applicants’ claims.” (*Id.*). The applicants explained as follows:

Despite that these data do not expressly provide comparative AUC values for IM [intramuscular] bioavailability of cyanocobalamin from Applicants’ studies, these values are readily and accurately derivable from the data that are presented. In particular, the comparative bioavailability study results presented above demonstrate that the ‘relative bioavailability’ ratio of the spray versus IM, and gel versus IM, is 0.6105, and 0.6284, respectively. These values represent ratios of the natural log of geometric means of the AUC based on nominal doses (see, e.g., page 17). These data were dose normalized according to conventional practice to the appropriate dose multiple based on a dose of 500 µg given intranasal and 100 µg given by IM (see, e.g., page 12).

The skilled artisan will readily comprehend these data and fully appreciate that the dose normalized data yield a ratio of bioavailability between Applicants’ IN [intranasal] cyanocobalamin solution and IM-administration that reasonably corresponds to the claimed value of “at least about 7%”. This determination requires nothing more than a standard mathematical operation to derive the dose normalized relative AUC values for the IN spray and IM injection. In the example provided on page 17, this standard operation/result is $0.6105 \times 100 \mu\text{g}/500\mu\text{g} \times 100 = 12\%$; or a ratio of the AUC between the IN spray and IM injection of 0.12. In addition to these clearly founded values, the actual arithmetic AUC are provided on page 17 of the specification for the spray and gel as 92000 and 97000 pg*hr/mL, respectively. These data likewise fully evince the corresponding AUC for the IM injected study comparator, according to Applicants’ disclosure. For example, the arithmetic mean of the AUC for IM is calculated as 147155 pg*hr/mL (as readily derived by reverse mathematical operation from the ratios given-for example for the spray $92000/147155 = 0.62$ ratio). When dose normalized according to the disclosure, these data correspond directly to an exemplary relative bioavailability value within Applicants’ described range of at least 7% and preferably 9, 10, 11 or 12 % for the Spray versus IM.

(*Id.* at 7-8.)

45. On July 31, 2006, the patent examiner issued an Office Action with a final rejection. The patent examiner maintained the rejection of claims 1, 23, 24, 30, and 31 under 35 U.S.C. § 112, first paragraph, for failing to comply with the enablement requirement.

46. In the July 31, 2006 Office Action, the patent examiner explained that the specification does not provide the necessary data to calculate the claimed bioavailability of the intranasal spray relative to that intramuscular injection:

The claims are directed to a solution that, when administered intranasally, have a bioavailability of at least 7% relative to an intramuscular injection. An adequate representation regarding the bioavailability claimed would be one that provides all of the data necessary to calculate the bioavailability claimed relative to that of an intramuscular injection.

Additionally, there are several methods of assessing bioavailability in humans and other animals. The selection of methods depends on the nature of the drug product and makes use of such parameters as time of peak plasma concentration, peak plasma concentration and area under the plasma-time curve (AUC). However, Applicant does not provide any AUC data for bioavailability of cyanocobalamin delivered via intramuscular injection.

Further, Applicant discloses several examples in the specification to demonstrate the relative bioavailability relating to the compositions and methods claims. However, in order to demonstrate relative bioavailability, Applicant must provide four variables for the bioavailability equation. Applicant's disclosure fails to demonstrate relative bioavailability in its examples and does not disclose any AUC data for either route of administration. Thus, as a result of this finding and the lack of adequate representations in the specification, Applicant has not enabled this aspect of the claimed composition or methods for using the same. The skilled artisan in this field would not accept the representations set forth in the instant disclosure as sufficient to enable cyanocobalamin compositions and methods of using the composition based on the bioavailability of about 7% relative to and intramuscular injection of cyanocobalamin.

Moreover, pharmacokinetic profiles are predictable and are routinely demonstrated when an applicant claims that a

formulation has a specific relative bioavailability. Thus, it would be expected that the applicant could demonstrate that the formulations and methods claimed have a bioavailability of cyanocobalamin, when administered nasally, of at least 7% relative to an intramuscular injection of cyanocobalamin, and in demonstrating this, Applicant would provide the data necessary to calculate the relative bioavailability.

Thus, in order to accomplish the showing that the bioavailability of cyanocobalamin, when administered nasally, is at least 7% relative to an intramuscular injection of cyanocobalamin, the Applicant would have to show the AUC and those administered for both the intranasal and intramuscular routes to calculate the bioavailability. Therefore, the rejection of the claims under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and as set forth herein.

(‘636 Patent PH, 7/31/2006 Office Action at 2-4 (emphasis added).)

47. An interview between the patent examiner and the applicants was scheduled for October 4, 2006.

48. On October 3, 2006, in advance of the interview, Mr. Knudsen submitted to the patent examiner a draft response to the July 31, 2006 Office Action and a draft declaration by Mr. Sileno.

49. Mr. Sileno’s declaration identified that he is “presently employed by Natestech Pharmaceutical Inc. . . . as Senior Director of Clinical Affairs and Toxicology.” (‘636 Patent PH, 10/3/2006 Sileno Declaration, ¶ 1.)

50. Mr. Sileno states that “I have designed and implemented pre-clinical studies at Natestech to assess pharmacokinetics and pharmacodynamics for formulations, methods and devices for intranasal drug delivery—including the formulations, methods and devices for intranasal drug delivery of cyanocobalamin described in the above- referenced United States Patent Application Serial No. 10/787,385 entitled CYANOCOBALAMIN LOW VISCOSITY

AQUEOUS FORMULATIONS FOR INTRANASAL DELIVERY, filed on February 26, 2004.”
(*Id.*).

51. Mr. Sileno’s declaration identifies himself as a named inventor of the ‘385 application and affirms that he has “carefully reviewed and analyzed the complete file history of the ‘385 application”:

2. I am a named inventor in the ‘385 application, and I have carefully reviewed and analyzed the complete file history of the ‘385 application. In particular, I have reviewed and fully understand the ‘385 specification and all claims presented in this application, including the currently pending claims 1-31 (as set forth in the Current Listing of Claims presented in the Response to Office Action filed contemporaneously herewith). I have also reviewed all substantive Office Actions in the ‘385 application, including the most recent Office Action mailed July 31, 2006 (Paper No./Mail Date 20060722), to which my remarks herein, below are directed.

(*Id.* ¶ 2.)

52. Mr. Sileno’s declaration states, in response to the patent examiner’s rejection for lack of enablement, that “I consider that a person of ordinary skill in the art would view the instant disclosure as fully enabling for the subject matter of the current pending claims. In particular, a person of ordinary skill in the art, would consider that the instant specification provides clear evidence that the claimed cyanocobalamin compositions achieve ‘a bioavailability of cyanocobalamin when administered nasally of at least about 7% relative to an intramuscular injection of cyanocobalamin.’” (*Id.* ¶ 5.)

53. Mr. Sileno’s declaration states that “the specification provides explicit methodology and results, in the form of detailed comparative bioavailability studies and data presented in the Examples, which demonstrate the relative bioavailability characteristics of the claimed solutions. The data from these examples clearly and comprehensively support this

relative bioavailability characteristic in a manner that would be readily understood and practiced by persons of ordinary skill in the art.” (*Id.* ¶ 8.) As an example, Mr. Sileno’s declaration quotes the following section of the specification under the heading “Pharmacokinetic Results”:

The relative bioavailability for the two IN formulations was 0.9715. Bioavailability when comparing treatment A (Spray) versus treatment C (IM) was 0.6105, and 0.6284 when comparing Treatment B (gel) versus Treatment C (IM).

* * *

The pharmacokinetic profiles of the spray formulation and the gel formulation are similar for C_{max} (1480 pg/mL, 1670 pg/mL, respectively) and AUC_{0-t} (9200 pg*hr/mL, 9700 pg*hr/mL, respectively). Additionally, the median difference for T_{max} between the spray and gel IN formulation was less than 15 minutes (-0.24). The C_{max} value for the IM formulation was significantly higher than the C_{max} values for the two IN formulations ($p < 0.0001$).

Relative Bioavailability was assessed by examining the ratio of the nasal B12 spray group mean to the reference group mean with regard to AUC. The ratio is derived by dividing the AUC IN by the AUC IM, therefore, the IM AUC is used in the equation to calculate the relative bioavailability, even if it’s not present in the application. The ratio of the AUC is an appropriate way to represent bioavailability, for example 12% bioavailability is just a 0.12 ratio of the AUC and multiplied by 100 is 12%.

(*Id.* ¶ 9 (quoting page 17 of the specification).)

54. Mr. Sileno’s declaration acknowledged that “these data do not expressly provide comparative AUC values for IM bioavailability of cyanocobalamin from the described studies.” (*Id.* ¶ 10.) However, Mr. Sileno’s declaration asserted that “these values are readily and accurately derivable from the data that are presented.” (*Id.*).

55. Mr. Sileno’s declaration stated that “[p]ersons of ordinary skill in the art would readily discern this aspect of the description, and no experimentation beyond the results provided in the disclosure would be necessary to determine the subject, relative AUC values.” (*Id.*) Mr.

Sileno's declaration asserted that comparative bioavailability between the administration of an intranasal solution and intramuscular injection may be derived as follows from the data presented in the specification:

11. The comparative bioavailability study results cited from the specification above, demonstrate that the "relative bioavailability" ratio of the spray versus IM, and gel versus IM, is 0.6105, and 0.6284, respectively. As the disclosure clearly indicates, these ratios were obtained by dividing the AUC of the spray, or gel, by the AUC of IM-administered cyanocobalamin. Therefore, the AUC for the IM is readily discerned based on the ratios 0.6105 and 0.6284—a simple mathematical calculation from the AUC of spray and gel and the AUC for the IM is obtained as 15000 pg*hr/mL. As the specification also clearly indicates, these data were dosed normalized according to conventional practice (to the appropriate dose multiple based on a dose of 500 µg given intranasal and 100 µg given by IM; see, e.g., pages 12-16).

12. The skilled artisan would have readily understood these data and fully appreciated that the dose normalized data fully evinced a ratio of bioavailability between the IN cyanocobalamin solutions of the invention and IM-administered cyanocobalamin—which ratio as exemplified in the disclosure is shown to correspond reasonably to the claimed value of "at least about 7%." This determination requires nothing more than a standard mathematical operation to derive the dose normalized relative AUC values for the IN spray and IM injection. In the example provided on page 17, this standard operation/result is $0.6105 \times 100 \mu\text{g}/500 \mu\text{g} \times 100 = 12\%$; or a ratio of the AUC between the IN spray and IM injection of 0.12. In addition to these clearly founded values, the actual arithmetic AUC are provided on page 17 of the specification for the spray and gel as 92000 and 97000 pg*hr/mL, respectively. These data, cross referenced to the corresponding data for IM administration, likewise fully evince the corresponding AUC for the IM injected study comparator.

13. As such, the arithmetic mean of the AUC for IM is readily calculated as 15000 pg*hr/mL (derived quite simply by reverse mathematical operation from the ratios given—for example for the spray $92000/\text{AUC IM} = 0.61$ ratio). When dose normalized according to the disclosure, these data correspond directly to an exemplary relative bioavailability value within the described ranges set forth in the specification (e.g., as described at page 8, lines 32-35—"wherein the solution of cyanocobalamin has a bioavailability of at least 7%, more preferably at least about 8, 9,

10, 11, 12% or more of the bioavailability of an intramuscular injection of cyanocobalamin.”).

(*Id.* ¶¶ 11-13.)

56. Mr. Sileno’s declaration states that “[t]he comprehensiveness and accuracy of the instant disclosure regarding relative bioavailability of the claimed intranasal cyanocobalamin solutions (compared to IM delivery), is further evinced by a Phase I Pharmacokinetic Study completed on behalf of Natestech in September, 2002 (see Appendix B, attached hereto).” (*Id.* ¶ 15.) Appendix B was not attached to Mr. Sileno’s declaration that was submitted to the USPTO.

57. Mr. Sileno’s declaration asserts that “[t]he FDA reviewed and accepted these relative bioavailability data and findings” in approval of Natestech’s Nascobal® (cyanocobalamin) nasal spray product:

The resulting Phase I Pharmacokinetic Study Report was submitted and favorably reviewed by the U.S. Food and Drug Administration (FDA). The FDA specifically reviewed and considered relative bioavailability data and findings between intranasal and intramuscular delivery formulations and methods, as a key aspect of this Report. The FDA reviewed and accepted these relative bioavailability data and findings, and ultimately approved Natestech’s New Drug Application (NDA) for an intranasal cyanocobalamin solution (currently marketed as Nascobal®, a widely prescribed treatment for Vitamin B₁₂ deficiency). The relative bioavailability characteristics of the approved Nascobal® product compared to IM cyanocobalamin formulations and methods, are fully supported by the ‘385 specification, and accurately recited in the currently pending claims.

(*Id.*). Mr. Sileno’s declaration does not cite or attach any document reflecting that the FDA had accepted the relative bioavailability data and findings presented by Mr. Sileno.

58. Mr. Sileno's declaration attested that he "designed, directed, monitored, and reviewed the Phase I Pharmacokinetic Study and Report (Appendix B), and thereafter participated in its submission and review by the FDA." (*Id.* ¶ 16.)

59. Mr. Sileno's declaration asserts that "[t]here are no substantive/technical deficiencies in the relative bioavailability methods and results described in the '385, compared to the corresponding bioavailability methods and results presented in the Phase I Pharmacokinetic Study Report. Although some material from the Phase I Pharmacokinetic Study Report was not incorporated into the '385 specification, such material was omitted for purposes of economy, and is in no way essential for describing or implementing the invention set forth in the pending claims." (*Id.* ¶ 18.)

60. Mr. Sileno's declaration concludes that "the data and conclusions provided in the '385 specification are for all purposes *equivalent* to the data and conclusions provided in the Phase I Pharmacokinetic Study Report—which the FDA expressly relied upon to conclude that Nascobal® achieves high, therapeutically effective, relative bioavailability compared to IM cyanocobalamin formulations and methods, consistent with the relative bioavailability terms presented in the instant disclosure and recited in the pending claims." (*Id.* ¶ 19 (emphasis in original).)

61. Mr. Sileno's declaration was unsigned when it was submitted to the USPTO by Mr. Knudsen on October 3, 2006.

62. Contemporaneously with the submission of Mr. Sileno's declaration, on October 3, 2006, Mr. Knudsen submitted a Response to the patent examiner's July 31, 2006 Office Action. The October 3, 2006 Response was signed by Mr. Knudsen, with a certification that the response is being filed electronically with the USPTO.

63. At the time of the October 3, 2006 Response, Mr. Knudsen was Intellectual Property Counsel for Natestch and was an attorney for the applicants with respect to prosecution of the ‘385 application.

64. In the October 3, 2006 Response, Mr. Knudsen, on behalf of the applicants, asserted that “[d]espite that explicit AUC values may not be expressed in Applicant’s disclosure for IM- treated subjects, the specification nonetheless fully describes and enables these results. In particular, the data provided in the working examples of Applicant’s disclosure encompass all essential data necessary to demonstrate relative AUC values.” (‘636 Patent PH, 10/3/2006 Response at 9.)

65. In the October 3, 2006 Response, Mr. Knudsen, on behalf of the applicants, stated that “[t]o assist the Office in further considering the enablement issues in this case, Applicant submits herewith the Declaration of co-inventor, Anthony Sileno, M.S.” (*Id.* at 10.) In support of the response to the patent examiner’s rejection, Mr. Knudsen cites and/or quotes to paragraphs 7- 20 of Mr. Sileno’s declaration. (*Id.* at 10-12.)

66. In the October 3, 2006 Response, Mr. Knudsen, on behalf of applicants, relied upon Mr. Sileno’s declaration to assert that the specification provides “all essential data necessary to determine relative AUC values”:

The findings and conclusions presented in Mr. Sileno’s Declaration strongly support Applicant’s position—that their disclosure provides all essential data necessary to determine relative AUC values, for both IN- and IM- administered cyanocobalamin, and that the disclosure fully demonstrates that Applicant’s formulations and methods achieve “bioavailability of at least 7% of the bioavailability of an intramuscular (IM) injection of cyanocobalamin.”

(*Id.* at 14.)

67. In the October 3, 2006 Response, Mr. Knudsen, on behalf of applicants, further emphasized that the “similar focus and positive outcome of the FDA’s review of Nascobal®” demonstrated that specification enabled the claimed bioavailability limitations:

In addition to the foregoing facts and authority, Mr. Sileno provides additional evidence relating to enablement, by reference to a Phase I Pharmacokinetic Study that he designed, directed, monitored, and reviewed for an IN cyanocobalamin formulation according to the pending claims (Sileno Declaration at ¶¶ 16-20; Phase I Pharmacokinetic Study Report, Appendix B). Mr. Sileno also participated in submission and review of these Study results before the FDA.

As noted in ¶ 16 of Mr. Sileno’s Declaration, the FDA specifically reviewed and considered relative bioavailability data and findings between intranasal and intramuscular cyanocobalamin formulations and methods, “as a key aspect of this Report.”

The FDA accepted these relative bioavailability data and findings, and ultimately approved Natestech’s New Drug Application (NDA) for an intranasal cyanocobalamin solution (currently marketed as Nascobal®, a widely prescribed treatment for Vitamin B₁₂ deficiency). The relative bioavailability characteristics of the approved Nascobal® product compared to IM cyanocobalamin formulations and methods, are fully supported by the ‘385 specification, and accurately recited in the currently pending claims (id., underscore added)

Considering the similar focus and positive outcome of the FDA’s review of Nascobal® to the instant enablement issues, it is most significant that the relative bioavailability methods and results described in the ‘385 specification “were taken directly from the Phase I Pharmacokinetic Study” (Sileno Declaration, at ¶ 18; comparing pages 12-18 of specification, to pages 27-42 of the Phase I Pharmacokinetic Study Report, Appendix B).

(*Id.* (annotations in original).)

68. In the October 3, 2006 Response, Mr. Knudsen, on behalf of applicants, concluded that “[i]n view of the evidence and authority presented above, Applicant respectfully

submits that its disclosure fully supports the pending claims. In this regard, the disclosure is ‘reasonably correlated’ with the scope of the claims, such that skilled artisans would have been able to practice the invention commensurate with the claims, without ‘undue experimentation.’ Accordingly, the rejection of claims 3, 14, 20, 31, and 37 under 35 U.S.C. § 112 is respectfully submitted to be overcome.” (*Id.* at 15.)

69. On October 4, 2006, the patent examiner held an interview with Mr. Knudsen. The October 4, 2006 Interview Summary reflects that an agreement with respect to the claims had been reached. The interview is described as follows:

Applicant will submit an amendment to narrow independent claims, which will include adding a buffer *Markush* group and a preservative *Markush* group. If Applicant determines that client does not want to make the changes suggested, Examiner will withdraw the finality of last Office Action and issue a new Office Action based on U.S.C. 112, first paragraph scope of enablement.

(‘636 Patent PH, 10/4/2006 Interview Summary at 1.)

70. On November 29, 2006, Mr. Knudsen, on behalf of applicants, filed a Response to the July 31, 2006 Office Action. Mr. Knudsen explained that the patent examiner had withdrawn the original enablement rejection based on the October 4, 2006 interview:

The current Office Action presents a rejection of claims 1, 23, 24, 30, and 31 under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement. This rejection was specifically addressed in an Examiner Interview on October 4, 2006, between Applicant’s representative, Peter Knudsen, and Examiner Paul Ward and Supervisory Primary Examiner Thurman Page (see, Interview Summary Paper No. 20061004).

During the course of this Interview, Examiner indicated that the original enablement rejection (relating to determining bioavailability) presented in the current Office Action would be withdrawn, and that a new group for rejection was being considered relating to scope/enablement. In the context of discussing this new ground for rejection, Examiner indicated that the claims would be allowable over such scope rejection if

amended to include “a buffer Markush group and a preservative Markush group” (see, Interview Summary).

Applicant has amended the claims herein in accordance with Examiner’s suggestions to include an exemplary buffer Markush group and an exemplary preservative Markush group, in accordance with the teachings of the specification as detailed above. Applicant thereby respectfully submits that all groups for rejection under 35 U.S.C. § 112, first paragraph, have been overcome.

(‘636 Patent PH, 11/29/2006 Response at 8.)

71. On December 13, 2006, the USPTO issued a Notice of Allowance of the ‘385 application, which issued as the ‘636 patent on June 12, 2007. (‘636 Patent PH, 12/13/2006 Notice of Allowance at 1; ‘636 Patent PH, 6/12/2007 Issue Notification at 1.)

72. The ‘636 patent issued with 31 claims. Each of the claims of the ‘636 patent recites, *inter alia*, a solution of cyanocobalamin for intranasal administration that has bioavailability of cyanocobalamin of [at least] about 7% relative to an intramuscular injection of cyanocobalamin.

D. Inventor Anthony Sileno Made Material Misrepresentations And Intentionally Withheld Material Information With An Intent To Deceive.

1. Mr. Sileno’s Material Misrepresentations To The USPTO.

73. Mr. Sileno’s declaration to the USPTO included several misrepresentations of the clinical trial comparing the bioavailability of the active ingredient cyanocobalamin following administration of an intranasal solution and intramuscular injection of cyanocobalamin.

a. The Relative Bioavailability Of The Intranasal Cyanocobalamin Solution To The Intramuscular Cyanocobalamin Injection Is Not 12%.

74. Mr. Sileno declared that, based on the data presented in the specification, a skilled artisan could determine that the bioavailability of the intranasal cyanocobalamin solution relative to the intramuscular cyanocobalamin injection is 12% (*i.e.*, “a ratio of the AUC between the IN

spray and IM injection of 0.12”). (‘636 Patent PH, 10/3/2006 Sileno Declaration, ¶ 12.) Based on this calculation, Mr. Sileno declared that “the data provided in the specification directly evince that the formulations and methods claimed yield a bioavailability of cyanocobalamin, when administered nasally, of at least 7% relative to an intramuscular injection of cyanocobalamin.” (*Id.* ¶ 14.)

75. Mr. Sileno’s calculation of relative bioavailability is misleadingly false.

76. Mr. Sileno’s calculation did not baseline-correct for the pre-existing levels of cyanocobalamin in the blood plasma.

77. The specification states that the “[b]ioavailability of the intranasal spray relative to an intramuscular injection of cyanocobalamin’ means the percent amount of a dose of the intranasal taken up by the systemic vascular system in comparison to the same amount of cyanocobalamin injected.” (‘636 Patent at col. 3, ll. 56-61.) This comparison of the bioavailability of the intranasal spray relative to an intramuscular injection of cyanocobalamin requires the measurement of bioavailability to be baseline-corrected (*i.e.*, to exclude the pre-existing levels of cyanocobalamin in the blood plasma) to determine the amount of cyanocobalamin that is “taken up by the systemic vascular system” from administration of the nasal spray or intramuscular injection.

78. When the bioavailabilities of cyanocobalamin following administration of an intranasal solution and intramuscular injection of cyanocobalamin are corrected for baseline levels of cyanocobalamin, as analyzed by the FDA and agreed upon by Natestch in seeking approval of its NDA No. 21-642, the bioavailability of the intranasal cyanocobalamin solution relative to the intramuscular cyanocobalamin injection is only 6.1%, a fact which Mr. Sileno knew from his participation in meetings with FDA.

b. The FDA Reviewed And Rejected The Relative Bioavailability Data And Findings That Were Presented To The USPTO By Mr. Sileno.

79. Mr. Sileno declared that “[t]he comprehensiveness and accuracy of the instant disclosure regarding relative bioavailability of the claimed intranasal cyanocobalamin solutions (compared to IM delivery), is further evinced by a Phase I Pharmacokinetic Study completed on behalf of Natestech in September, 2002 (see Appendix B, attached hereto). The resulting Phase I Pharmacokinetic Study Report was submitted and favorably reviewed by the U.S. Food and Drug Administration (FDA). FDA specifically reviewed and considered relative bioavailability data and findings between intranasal and intramuscular delivery formulations and methods, as a key aspect of this Report.” (‘636 Patent PH, 10/3/2006 Sileno Declaration, ¶ 15.) Mr. Sileno declared that “[t]he FDA reviewed and accepted these relative bioavailability data and findings, and ultimately approved Natestech’s New Drug Application (NDA) for an intranasal cyanocobalamin solution (currently marketed as Nascobal®, a widely prescribed treatment for Vitamin B₁₂ deficiency).” (*Id.*).

80. Mr. Sileno’s assertion that, following FDA review, FDA “accepted these relative bioavailability data and findings” is misleadingly false.

81. FDA did not accept that the bioavailability of the intranasal cyanocobalamin solution relative to the intramuscular cyanocobalamin injection was 12%.

82. When FDA reviewed the Phase I Pharmacokinetic Study, the FDA initially disagreed with Natestech’s conclusion that the “[r]elative bioavailability for Treatment A (spray) versus Treatment C (IM) was 0.61, and 0.63 when comparing Treatment B (gel) versus Treatment C (IM).” (Phase I Pharmacokinetic Study Synopsis at 7; Food and Drug Administration, Center for Drug Evaluation and Research, Application Number 21-642, Clinical and Pharmacology and Biopharmaceutics Review(s), at 2.) Further, at FDA’s request, Natestech

deleted from its proposed label for Nascobal® (cyanocobalamin) nasal spray the statement that the “[r]elative bioavailability for B₁₂ nasal gel and spray versus 100 mcg intramuscular injection was 0.63 and 0.61, respectively.” (NDA No. 21-642, 12/1/2004 Amendment 14, at 5.) Mr. Sileno’s calculation that the bioavailability of the intranasal cyanocobalamin solution relative to the intramuscular cyanocobalamin injection is 12% relies on results of the bioequivalence study that were expressly rejected by the FDA.

83. Instead, when FDA reviewed the Phase I Pharmacokinetic Study, FDA concluded that the “pre-dose plasma cyanocobalamin levels contribute significantly to the AUC.” (Food and Drug Administration, Center for Drug Evaluation and Research, Application Number 21-642, Clinical and Pharmacology and Biopharmaceutics Review(s), at 7.) Accordingly, FDA conducted a baseline corrected analysis of the data from the study. FDA found that, in its baseline corrected analysis, “[t]he two intranasal formulations had a relative bioavailability of 0.061 (spray) and 0.071 (gel) to the intramuscular injection formulation used as a reference.” (*Id.*). Further, FDA’s approved label for Nascobal® (cyanocobalamin) nasal spray states that “[t]he bioavailability of the nasal spray relative to the intramuscular injection was found to be 6.1%.” (Nascobal® (cyanocobalamin) nasal spray Prescribing Information at 1.)

c. The Specification Does Not Provide Sufficient Data To Calculate The Relative Bioavailability.

84. Mr. Sileno declared that “[t]he relative bioavailability methods and results described in the ‘385 specification, referenced above, were taken directly from the Phase I Pharmacokinetic Study.” (‘636 Patent PH, 10/3/2006 Sileno Declaration, ¶ 17.) Mr. Sileno declared that “[t]here are no substantive/technical deficiencies in the relative bioavailability methods and results described in the ‘385, compared to the corresponding bioavailability methods and results presented in the Phase I Pharmacokinetic Study Report.” (*Id.* ¶ 18.) Mr.

Sileno declared that “the data and conclusions provided in the ‘385 specification are for all purposes *equivalent* to the data and conclusions provided in the Phase I Pharmacokinetic Study Report—which the FDA expressly relied upon to conclude that Nascobal® achieves high, therapeutically effective, relative bioavailability compared to IM cyanocobalamin formulations and methods, consistent with the relative bioavailability terms presented in the instant disclosure and recited in the pending claims.” (*Id.* ¶ 19 (emphasis in original).)

85. Mr. Sileno’s assertion that “the data and conclusions provided in the ‘385 specification are for all purposes *equivalent* to the data and conclusions provided in the Phase I Pharmacokinetic Study Report—which the FDA expressly relied upon to conclude that Nascobal® achieves high, therapeutically effective, relative bioavailability compared to IM cyanocobalamin formulations and methods, consistent with the relative bioavailability terms presented in the instant disclosure and recited in the pending claims” is misleadingly false.

86. The data and conclusions provided in the specification do not present data sufficient to conduct FDA’s baseline corrected analysis of the bioavailability of the intranasal cyanocobalamin solution relative to the intramuscular cyanocobalamin injection.

87. When FDA reviewed the Phase I Pharmacokinetic Study, the FDA concluded that the “pre-dose plasma cyanocobalamin levels contribute significantly to the AUC.” (Food and Drug Administration, Center for Drug Evaluation and Research, Application Number 21-642, Clinical and Pharmacology and Biopharmaceutics Review(s), at 7.) FDA baseline corrected the data “by taking the average of the individual baseline levels (3 points in the study) and subtracting it from the observed values at each time point for each treatment.” (*Id.*).

88. The specification does not provide sufficient data to calculate the pre-dose plasma cyanocobalamin levels for each of the treatment groups.

89. The specification does not provide sufficient data to calculate the baseline-corrected AUC following administration of the claimed intranasal cyanocobalamin solution or the intramuscular cyanocobalamin injection.

90. The specification does not provide sufficient data to calculate the baseline-corrected bioavailability of the intranasal cyanocobalamin solution relative to the intramuscular cyanocobalamin injection.

91. FDA relied upon data from the Phase I Pharmacokinetic Study that were not presented in the patent specification to calculate the pre-dose plasma cyanocobalamin levels for each of the treatment groups, the baseline-corrected AUC following administration of the claimed intranasal cyanocobalamin solution or the intramuscular cyanocobalamin injection, and the baseline-corrected bioavailability of the intranasal cyanocobalamin solution relative to the intramuscular cyanocobalamin injection.

92. Each of the misrepresentations of the relative bioavailability contained in Mr. Sileno's declaration, alone and collectively, were material to issuance of the '385 application.

93. The patent examiner relied upon Mr. Sileno's declaration to understand how a person of ordinary skill in the art would have reviewed the clinical data in the specification, how the FDA reviewed the clinical data, and how the specification supports the scope of the claims.

94. The patent examiner withdrew its enablement rejection based on the opinions by Mr. Sileno regarding support for the relative bioavailability limitations in the specification.

95. But for Mr. Sileno's declaration, the '385 application would not have been granted as the '636 patent.

2. Mr. Sileno's Material Omissions To The USPTO.

96. Mr. Sileno failed to disclose material information to the USPTO reflecting the FDA's calculation of the intranasal cyanocobalamin solution relative to the intramuscular cyanocobalamin injection, and Natestech's adoption of that calculation.

a. Nascobal® (Cyanocobalamin) Nasal Spray Prescribing Information.

97. The Nascobal® (cyanocobalamin) nasal spray prescribing information was not submitted to the USPTO during prosecution of the '385 application or during the prosecution of any of the Patents-in-Suit.

98. The Nascobal® (cyanocobalamin) nasal spray prescribing information reflects that "[t]he bioavailability of the nasal spray relative to the intramuscular injection was found to be 6.1%." (Nascobal® (cyanocobalamin) nasal spray Prescribing Information at 1.)

99. The Nascobal® (cyanocobalamin) nasal spray prescribing information was publicly available during the prosecution of the '385 application, including prior to the submission of Mr. Sileno's October 3, 2006 Declaration.

100. The Nascobal® (cyanocobalamin) nasal spray prescribing information was material to the prosecution of the '385 application in light of the arguments made by Mr. Knudsen and the declaration by Mr. Sileno responding to the patent examiner's rejection.

101. Prior to the submission of Mr. Sileno's declaration, the patent examiner issued a final rejection for lack of enablement, because the specification did not support a showing that "the bioavailability of cyanocobalamin, when administered nasally, is at least 7% relative to an intramuscular injection of cyanocobalamin." ('636 Patent PH, 7/31/2006 Office Action at 4.) The statement in the Nascobal® (cyanocobalamin) nasal spray prescribing information that "[t]he bioavailability of the nasal spray relative to the intramuscular injection was found to be

6.1%” shows that the claimed intranasal cyanocobalamin solution does not achieve a bioavailability of at least 7% relative to an intramuscular injection of cyanocobalamin.

102. After the submission of Mr. Sileno’s declaration, the statement in the Nascobal® (cyanocobalamin) nasal spray prescribing information that “[t]he bioavailability of the nasal spray relative to the intramuscular injection was found to be 6.1%” refutes Mr. Sileno’s calculation of the bioavailability of the intranasal cyanocobalamin solution relative to the intramuscular cyanocobalamin injection. But at no point during prosecution of the ‘636 patent or any of the other Patents-in-Suit did Mr. Sileno submit the Nascobal® (cyanocobalamin) nasal spray prescribing information to the USPTO.

103. The Nascobal® (cyanocobalamin) nasal spray prescribing information would not have been cumulative to the information that had been submitted to the USPTO. The USPTO was not informed that the FDA had determined, and Nasteck had agreed, that “[t]he bioavailability of the nasal spray relative to the intramuscular injection was found to be 6.1%.”

104. But for the fact that the Nascobal® (cyanocobalamin) nasal spray prescribing information had not been submitted for review by the USPTO, the ‘385 application would not have been granted as the ‘636 patent.

b. Correspondence Between FDA And Nasteck In Review Of NDA No. 21-642 Regarding Calculation Of Relative Bioavailability.

105. The correspondence between FDA and Nasteck in the review of NDA No. 21-642 regarding the appropriate measure of the bioavailability of an intranasal cyanocobalamin solution relative to an intramuscular cyanocobalamin injection were not submitted to the USPTO during prosecution of the ‘385 application or during the prosecution of any of the Patents-in-Suit. For example, the October 1, 2004 Review by FDA’s Office of Clinical Pharmacology and Biopharmaceutics of NDA No. 21-642 was not submitted to the USPTO during prosecution of

the '385 application or during the prosecution of any of the Patents-in-Suit. As another example, the November 19, 2004 Teleconference Meeting Minutes between FDA and Natestch was not submitted to the USPTO during prosecution of the '385 application or during the prosecution of any of the Patents-in-Suit.

106. The correspondence between FDA and Natestch in the review of NDA No. 21-642 reflect FDA's conclusion that, based on the data from the Phase I Pharmacokinetic Study submitted by Natestch, the bioavailability of an intranasal cyanocobalamin solution relative to an intramuscular cyanocobalamin injection was 6.1%.

107. Upon information and belief, certain correspondence between FDA and Natestch in the review of NDA No. 21-642, including the October 1, 2004 Review by FDA's Office of Clinical Pharmacology and Biopharmaceutics of NDA No. 21-642 and the November 19, 2004 Teleconference Meeting Minutes between the FDA and Natestch were publicly available during the prosecution of the '385 application, including prior to the submission of Mr. Sileno's October 3, 2006 Declaration.

108. The correspondence between FDA and Natestch in the review of NDA No. 21-642 were material to the prosecution of the '385 application in light of the arguments made by Mr. Knudsen and the declaration by Mr. Sileno responding to the patent examiner's rejection.

109. Prior to the submission of Mr. Sileno's declaration, the patent examiner issued a final rejection for lack of enablement, because the specification did not support a showing that "the bioavailability of cyanocobalamin, when administered nasally, is at least 7% relative to an intramuscular injection of cyanocobalamin." ('636 Patent PH, 7/31/2006 Office Action at 4.) The correspondence from FDA reflecting that, based on the data from the Phase I Pharmacokinetic Study submitted by Natestch, the bioavailability of an intranasal

cyanocobalamin solution relative to an intramuscular cyanocobalamin injection was 6.1% shows that the claimed intranasal cyanocobalamin solution does not achieve a bioavailability of at least 7% relative to an intramuscular injection of cyanocobalamin.

110. After the submission of Mr. Sileno's declaration, the correspondence from FDA reflecting that, based on the data from the Phase I Pharmacokinetic Study submitted by Natestch, the bioavailability of an intranasal cyanocobalamin solution relative to an intramuscular cyanocobalamin injection was 6.1% refute Mr. Sileno's calculation of the bioavailability of the intranasal cyanocobalamin solution relative to the intramuscular cyanocobalamin injection. But at no point during prosecution of the '636 patent or any of the other Patents-in-Suit did Mr. Sileno submit any of the correspondence between FDA and Natestch in the review of NDA No. 21-642 regarding the appropriate measure of the bioavailability of an intranasal cyanocobalamin solution relative to an intramuscular cyanocobalamin injection.

111. The correspondence between FDA and Natestch in the review of NDA No. 21-642 regarding the appropriate measure of the bioavailability of an intranasal cyanocobalamin solution relative to an intramuscular cyanocobalamin injection would not have been cumulative to the information that had been submitted to the USPTO. The USPTO was not informed that FDA had determined, and Natestch had agreed, that the bioavailability of an intranasal cyanocobalamin solution relative to an intramuscular cyanocobalamin injection was 6.1%.

112. But for the fact that the correspondence between FDA and Natestch in the review of NDA No. 21-642 regarding the appropriate measure of the bioavailability of an intranasal cyanocobalamin solution relative to an intramuscular cyanocobalamin injection had not been submitted to the USPTO for review, the '385 application would not have been granted as the '636 patent.

3. Mr. Sileno Knowingly Made Material Misrepresentations To The USPTO And Withheld Material Information From The USPTO With An Intent To Deceive.

113. Upon information and belief, Mr. Sileno had knowledge of the results of the Phase I Pharmacokinetic Study and FDA's calculation of the bioavailability of the intranasal cyanocobalamin solution relative to the intramuscular cyanocobalamin injection based on that study.

114. In his October 3, 2006 Declaration, Mr. Sileno declared that he was the "Senior Director of Clinical Affairs and Toxicology" at Natestech. ('636 Patent PH, 10/3/2006 Sileno Declaration, ¶ 1.) Mr. Sileno declared that "[w]ithin my professional knowledge and duties described above, I designed, directed, monitored, and reviewed the Phase I Pharmacokinetic Study and Report (Appendix B), and *thereafter participated in its submission and review by the FDA.*" ('636 Patent PH, 10/3/2006 Sileno Declaration, ¶ 16.)

115. Upon information and belief, prior to the submission of his declaration, Mr. Sileno was aware of the correspondence and discussions between FDA and Natestech in the review of NDA No. 21-642 regarding the appropriate measure of the bioavailability of an intranasal cyanocobalamin solution relative to an intramuscular cyanocobalamin injection. For example, Mr. Sileno participated in the November 19, 2004 telephone conference with FDA to discuss the FDA's clinical and biopharmaceutical review of the Phase I Pharmacokinetic Study. (Memorandum of 11/19/2004 T-Con Meeting Minutes, Application Number 21-642, at 1.) At the meeting, FDA discussed the need to baseline correct the bioequivalence data. (*Id.* at 2-3.) FDA also presented its calculation that the bioavailability of the intranasal cyanocobalamin solution relative to the intramuscular cyanocobalamin injection was 6.1%. (*Id.*)

116. Upon information and belief, prior to the submission of his declaration, Mr. Sileno was aware of FDA approval of Nascobal® (cyanocobalamin) nasal spray and the FDA-

approved label's statement that "[t]he bioavailability of the nasal spray relative to the intramuscular injection was found to be 6.1%." (Nascobal® (cyanocobalamin) nasal spray Prescribing Information at 1.)

117. Upon information and belief, at the time of his declaration, Mr. Sileno had knowledge of the importance of the calculation of relative bioavailability to the prosecution of the '385 application.

118. In his October 3, 2006 Declaration, Mr. Sileno declared to the USPTO that he was a named inventor of the '385 application and affirmed that he has "carefully reviewed and analyzed the complete file history of the '385 application":

2. I am a named inventor in the '385 application, and I have carefully reviewed and analyzed the complete file history of the '385 application. In particular, I have reviewed and fully understand the '385 specification and all claims presented in this application, including the currently pending claims 1-31 (as set forth in the Current Listing of Claims presented in the Response to Office Action filed contemporaneously herewith). I have also reviewed all substantive Office Actions in the '385 application, including the most recent Office Action mailed July 31, 2006 (Paper No./Mail Date 20060722), to which my remarks herein, below are directed.

('636 Patent PH, 10/3/2006 Sileno Declaration, ¶ 2.)

119. Upon information and belief, despite understanding the importance of the calculation of relative bioavailability to the prosecution of the '385 application, at the time of his declaration, Mr. Sileno made several misrepresentations relating to the clinical trial comparing the bioavailability of the active ingredient cyanocobalamin following administration of an intranasal solution and intramuscular injection of cyanocobalamin, and FDA's review of the clinical trial.

120. Upon information and belief, Mr. Sileno misrepresented to the USPTO that the bioavailability of the intranasal cyanocobalamin solution relative to the intramuscular

cyanocobalamin injection was 12%, despite knowing that FDA had determined, as agreed by Natestch, that the relative bioavailability is only 6.1%.

121. Upon information and belief, Mr. Sileno misrepresented to the USPTO that FDA had “accepted these relative bioavailability data and findings” in approving the new drug application for Nascobal® (cyanocobalamin) nasal spray, despite knowing that the clinical data from which he calculated the relative bioavailability (*e.g.*, the relative bioavailability of 500 µg cyanocobalamin nasal spray to 100 µg cyanocobalamin intramuscular injection was 0.61) had been rejected by FDA and deleted from the draft label for Nascobal® (cyanocobalamin) nasal spray.

122. Upon information and belief, Mr. Sileno misrepresented to the USPTO that “the data and conclusions provided in the ‘385 specification are for all purposes *equivalent* to the data and conclusions provided in the Phase I Pharmacokinetic Study Report—which the FDA expressly relied upon to conclude that Nascobal® achieves high, therapeutically effective, relative bioavailability compared to IM cyanocobalamin formulations,” despite knowing that the data and conclusions provided in the specification do not present sufficient data to conduct FDA’s baseline corrected analysis of the relative bioavailability.

123. Upon information and belief, Mr. Sileno knowingly withheld disclosure of the Nascobal® (cyanocobalamin) nasal spray prescribing information, despite knowing that the prescribing information reported the bioavailability of the intranasal cyanocobalamin solution relative to the intramuscular cyanocobalamin injection and knowing that this information was material to the prosecution of the ‘385 application.

124. Upon information and belief, Mr. Sileno knowingly withheld the correspondence between FDA and Natestch in the review of NDA No. 21-642 regarding the appropriate measure

of the bioavailability of an intranasal cyanocobalamin solution relative to an intramuscular cyanocobalamin injection, despite knowing that this information was material to the prosecution of the ‘385 application.

125. For at least the reasons above, the single most reasonable inference able to be drawn from the evidence is that Mr. Sileno intended to deceive the USPTO by misrepresenting the bioavailability of the claimed intranasal cyanocobalamin solution relative to the prior art intramuscular cyanocobalamin injection, in order to obtain allowance of the ‘385 application.

126. For at least the reasons above, the single most reasonable inference able to be drawn from the evidence is that Mr. Sileno intended to deceive the USPTO by withholding the FDA approved label for Nascobal® (cyanocobalamin) nasal spray and correspondence between FDA and Natestch in the review of NDA No. 21-642 in order to obtain allowance of the ‘385 application.

127. Accordingly, at least for the reasons discussed above, the ‘636 patent which issued from the ‘385 application is unenforceable for inequitable conduct.

E. Alternatively, Prosecuting Attorney Peter Knudsen Made Material Misrepresentations And Intentionally Withheld Material Information With An Intent To Deceive.

1. If Mr. Knudsen Submitted Mr. Sileno’s Unsigned Declaration Without Prior Review And Approval For Filing By Mr. Sileno, Mr. Knudsen Made Material Misrepresentations To The USPTO.

128. On October 3, 2006, Mr. Knudsen submitted to the USPTO a draft declaration from Mr. Sileno that was unsigned. To the extent that Mr. Knudsen submitted Mr. Sileno’s declaration without prior review and approval for filing by Mr. Sileno, Mr. Knudsen made material misrepresentations to the USPTO with intent to deceive.

129. In the October 3, 2006 Response submitted during the prosecution of the ‘385 application, Mr. Knudsen, on behalf of applicants, stated that “[t]o assist the Office in further

considering the enablement issues in this case, Applicant submits herewith the Declaration of co-inventor, Anthony Sileno, M.S.” (‘636 Patent PH, 10/3/2006 Response at 10.) In this response, Mr. Knudsen repeatedly cited and quoted Mr. Sileno’s declaration to overcome the USPTO’s rejection for lack of enablement.

130. To the extent that Mr. Knudsen submitted Mr. Sileno’s declaration without prior review and approval for filing by Mr. Sileno, the submission of Mr. Sileno’s declaration was a material misrepresentation to the USPTO. By submitting Mr. Sileno’s declaration, Mr. Knudsen was representing to the USPTO that Mr. Sileno, a named co-inventor of the ‘385 application and a proclaimed person of ordinary skill in the art, had reviewed and agreed with the facts and opinions contained in the declaration.

131. To the extent that Mr. Knudsen submitted Mr. Sileno’s declaration without prior review and approval for filing by Mr. Sileno, this misrepresentation was material to the issuance of the ‘385 application. Mr. Sileno’s declaration included several assertions regarding the clinical trial comparing the bioavailability of the active ingredient cyanocobalamin following administration of an intranasal solution and intramuscular injection of cyanocobalamin. Upon information and belief, had Mr. Sileno reviewed his declaration, he would have known that the draft declaration included several material misrepresentations. Based on Mr. Knudsen’s representation that Mr. Sileno had reviewed and approved the declaration, the patent examiner relied upon Mr. Sileno’s declaration to understand how a person of ordinary skill in the art would have reviewed the clinical data in the specification, how FDA reviewed the clinical data, and how the specification supports the scope of the claims. The patent examiner withdrew its enablement rejection based on the arguments by Mr. Knudsen that relied upon the opinions by Mr. Sileno regarding support for the relative bioavailability limitations in the specification. But

for Mr. Sileno's declaration and Mr. Knudsen's arguments based on that declaration, the '385 application would not have been granted as the '636 patent.

2. Mr. Knudsen's Material Omissions To The USPTO.

132. Mr. Knudsen failed to disclose material information to the USPTO reflecting FDA's calculation of the intranasal cyanocobalamin solution relative to the intramuscular cyanocobalamin injection, and Natestch's adoption of that calculation.

133. As discussed above, the Nascobal® (cyanocobalamin) nasal spray prescribing information was not submitted to the USPTO during prosecution of the '385 application or during prosecution of any of the Patents-in-Suit. This was material to the prosecution of the '385 application in light of the arguments made by Mr. Knudsen and the declaration by Mr. Sileno responding to the patent examiner's rejection. This would not have been cumulative to the information that had been submitted to the USPTO. But for the fact that the Nascobal® (cyanocobalamin) nasal spray prescribing information had not been submitted for review by the USPTO, the '385 application would not have been granted as the '636 patent.

134. As discussed above, the correspondence between FDA and Natestch in the review of NDA No. 21-642 regarding the appropriate measure of the bioavailability of an intranasal cyanocobalamin solution relative to an intramuscular cyanocobalamin injection were not submitted to the USPTO during prosecution of the '385 application or during prosecution of any of the Patents-in-Suit. These correspondences were material to the prosecution of the '385 application in light of the arguments made by Mr. Knudsen and the declaration by Mr. Sileno responding to the patent examiner's rejection. This would not have been cumulative to the information that had been submitted to the USPTO. But for the fact that the correspondence between FDA and Natestch in the review of NDA No. 21-642 regarding the appropriate measure of the bioavailability of an intranasal cyanocobalamin solution relative to an intramuscular

cyanocobalamin injection had not been submitted to the USPTO for review, the ‘385 application would not have been granted as the ‘636 patent.

3. Mr. Knudsen Knowingly Made Material Misrepresentations To The USPTO And Withheld Material Information From The USPTO With An Intent To Deceive.

135. Upon information and belief, to the extent that Mr. Knudsen submitted Mr. Sileno’s declaration without prior review and approval for filing by Mr. Sileno, Mr. Knudsen knowingly misrepresented the nature of Mr. Sileno’s declaration.

136. Upon information and belief, Mr. Knudsen knew that, upon submission of Mr. Sileno’s declaration, the patent examiner would infer that Mr. Sileno had previously reviewed and approved for filing his declaration.

137. For at least the reasons above, to the extent that Mr. Knudsen submitted Mr. Sileno’s declaration without prior review and approval for filing by Mr. Sileno, the single most reasonable inference able to be drawn from the evidence is that Mr. Sileno intended to deceive the USPTO by misrepresenting the nature of Mr. Sileno’s declaration, in order to obtain allowance of the ‘385 application.

138. Upon information and belief, Mr. Knudsen had knowledge of the results of the Phase I Pharmacokinetic Study and the FDA’s calculation of the bioavailability of the intranasal cyanocobalamin solution relative to the intramuscular cyanocobalamin injection based on that study.

139. In his October 3, 2006 Response, Mr. Knudsen identified himself as Intellectual Property Counsel at Natestech.

140. In his October 3, 2006 Response, Mr. Knudsen explains that “the FDA specifically reviewed and considered relative bioavailability data and findings between intranasal and intramuscular cyanocobalamin formulations and methods.” (‘636 Patent PH, 10/3/2006

Response at 14.) Mr. Knudsen further asserted that “[c]onsidering the similar focus and positive outcome of the FDA’s review of Nascobal® to the instant enablement issues, it is most significant that the relative bioavailability methods and results described in the ‘385 specification ‘were taken directly taken [*sic*] from the Phase I Pharmacokinetic Study.’” (*Id.*).

141. Upon information and belief, prior to the submission of his October 3, 2006 Response, Mr. Knudsen was aware of FDA approval of Nascobal® (cyanocobalamin) nasal spray and the FDA-approved label’s statement that “[t]he bioavailability of the nasal spray relative to the intramuscular injection was found to be 6.1%.” (Nascobal® (cyanocobalamin) nasal spray Prescribing Information at 1.)

142. Upon information and belief, prior to the submission of his October 3, 2006 Response, Mr. Knudsen was aware of the correspondence and discussions between the FDA and Nasteck in the review of NDA No. 21-642 regarding the appropriate measure of the bioavailability of an intranasal cyanocobalamin solution relative to an intramuscular cyanocobalamin injection.

143. Upon information and belief, as the prosecuting attorney, Mr. Knudsen had knowledge of the importance of the calculation of relative bioavailability to the prosecution of the ‘385 application.

144. Upon information and belief, Mr. Knudsen knowingly withheld disclosure of the Nascobal® (cyanocobalamin) nasal spray prescribing information, despite knowing that the prescribing information reported the bioavailability of the intranasal cyanocobalamin solution relative to the intramuscular cyanocobalamin injection and knowing that this information was material to the prosecution of the ‘385 application.

145. Upon information and belief, Mr. Knudsen knowingly withheld the correspondence between the FDA and Natestch in the review of NDA No. 21-642 regarding the appropriate measure of the bioavailability of an intranasal cyanocobalamin solution relative to an intramuscular cyanocobalamin injection, despite knowing that this information was material to the prosecution of the '385 application.

146. For at least the reasons above, the single most reasonable inference able to be drawn from the evidence is that Mr. Knudsen intended to deceive the USPTO by withholding the FDA approved label for Nascobal and correspondence between the FDA and Natestch in the review of NDA No. 21-642 in order to obtain allowance of the '385 application.

147. Accordingly, at least for the reasons discussed above, the '636 patent which issued from the '385 application is unenforceable for inequitable conduct.

F. The Material Misrepresentations And Omissions During Prosecution Of The '636 Patent Taint Each Of The Patents-in-Suit.

148. The acts of inequitable conduct described herein taint all of the patent applications within this patent family, including under the doctrine of infectious unenforceability. Because all of the patent applications that led to each of the Patents-in-Suit derive from and are related to the '385 application, each of the Patents-in-Suit is unenforceable as a result of inequitable conduct.

1. U.S. Patent No. 7,404,489.

149. The '489 patent issued from the '399 application, which was filed as a continuation-in-part of the '385 application. Paul Ward, who was patent examiner for the '385 application, also examined the '489 patent.

150. On April 21, 2005, during the prosecution of the '399 application, the patent examiner issued an Office Action that included a non-final rejection. The patent examiner

rejected the pending claims as obvious over the prior art, including Wenig (U.S. Patent No. 4,724,231), Grychowski (U.S. Patent No. 6,745,760), Slot *et al.*, Garcia-Arieta *et al.*, and Harris *et al.* (‘489 Patent PH, 4/21/2005 Office Action at 2-8.) The patent examiner also rejected claims 3, 14, 20, 31, and 37 as failing to comply with the enablement requirement with respect to the claimed bioavailability of the intranasal cyanocobalamin solution relative to an intramuscular cyanocobalamin injection. (*Id.* at 8-14.)

151. On September 22, 2005, the applicants filed an Amendment and Response to the April 21, 2005 Office Action. (‘489 Patent PH, 9/22/2005 Amendment and Response.) In response to the obviousness rejection, the applicants argued, *inter alia*, that “the art of record fails to evince practical motivation coupled with a reasonable expectation for developing the instant formulations and methods specifically characterized as providing a bioavailability ‘when administered intranasally of at least about 7% relative to an intramuscular injection of cyanocobalamin.’” (*Id.* at 23.)

152. In the September 22, 2005 Amendment and Response, in response to the enablement rejection, the applicants repeated the same arguments as raised in the September 22, 2005 Amendment and Response filed with the ‘385 application. (*Id.* at 9-12.) For example, the applicants argued that “[t]he skilled artisan will readily comprehend these data and fully appreciate that the dose normalized data yield a ratio of bioavailability between Applicants’ IN cyanocobalamin solution and IM-administration that reasonably corresponds to the claimed value of ‘at least about 7%.’” (*Id.* at 11.) The applicants repeated that, based on a standard mathematical operation of the data presented in the specification, the bioavailability of an intranasal cyanocobalamin solution relative to an intramuscular cyanocobalamin injection is 12%. (*Id.*)

153. On July 11, 2006, the patent examiner issued an Office Action with a final rejection. (‘489 Patent PH, 7/11/2006 Amendment and Response.) The patent examiner accepted that the applicants had overcome the obviousness rejection. (*Id.* at 2.) Thus, the applicant’s argument that “the art of record fails to evince practical motivation coupled with a reasonable expectation for developing the instant formulations and methods specifically characterized as providing a bioavailability ‘when administered intranasally of at least about 7% relative to an intramuscular injection of cyanocobalamin’” was material to overcoming the patent examiner’s obviousness rejection. The patent examiner further maintained his enablement rejection. (*Id.* at 2-4.)

154. On June 11, 2007, the applicants filed an Amendment and Response to the July 11, 2006 Final Office Action. (‘489 Patent PH, 6/11/2007 Amendment and Response.) The applicants overcame the final enablement rejection by amending the claims to delete the relative bioavailability limitation. (*Id.* at 9.)

155. On May 8, 2008, the patent examiner issued a Notice of Allowance of the ’399 application.

156. The material misrepresentations and omission of material information during the prosecution of the ‘636 patent had an immediate and necessary relation to the issuance of the ‘489 patent. The applicants overcame the obviousness rejection by arguing that “the art of record fails to evince practical motivation coupled with a reasonable expectation for developing the instant formulations and methods specifically characterized as providing a bioavailability ‘when administered intranasally of at least about 7% relative to an intramuscular injection of cyanocobalamin.’” Since the applicants misrepresented the bioavailability of the claimed intranasal cyanocobalamin solution relative to an intramuscular injection of cyanocobalamin and

omitted material information that would have corrected this misrepresentation, the inequitable conduct during prosecution of the '636 patent taints the prosecution of the '489 patent.

157. Accordingly, at least for the reasons discussed above, the '489 patent is unenforceable for inequitable conduct.

2. U.S. Patent No. 7,879,349.

158. The '349 patent issued from the '875 application, which is a continuation of the '399 application, which is a continuation-in-part of the '385 application. Paul Ward, who was patent examiner for the '385 application, also examined the '349 patent.

159. The material misrepresentations and omission of material information during the prosecution of the '636 patent had an immediate and necessary relation to the issuance of the '349 patent. The '349 patent issued with 17 claims. Each of the claims of the '349 patent recites, *inter alia*, a solution of cyanocobalamin for intranasal administration that has bioavailability of cyanocobalamin of at least about 7% relative to an intramuscular injection of cyanocobalamin. Since the applicants misrepresented the bioavailability of the claimed intranasal cyanocobalamin solution relative to an intramuscular injection of cyanocobalamin and omitted material information that would have corrected this misrepresentation, the inequitable conduct during prosecution of the '636 patent taints the prosecution of the '349 patent.

160. Accordingly, at least for the reasons discussed above, the '349 patent is unenforceable for inequitable conduct.

3. U.S. Patent No. 8,003,353.

161. The '353 patent issued from the '240 application, which is a division of the '399 application, which is a continuation-in-part of the '385 application. Paul Ward, who was patent examiner for the '385 application, also examined the '353 patent.

162. On November 26, 2010, the patent examiner issued an Office Action with a non-final rejection. (‘353 Patent PH, 11/26/2010 Office Action.) The patent examiner rejected all of the pending claims for obviousness-type double patenting over claim 30 of the ‘636 patent. (*Id.* at 3.) The patent examiner found that “the subject matter claimed in the instant application is fully disclosed in the [‘636] patent and is covered by the patent since the patent and the application are claiming common subject matter.” (*Id.*). The patent examiner did not issue any other rejections based on obviousness or enablement.

163. On February 23, 2011, the applicants filed a terminal disclaimer to overcome the patent examiner’s rejection on the ground of obviousness-type double patenting over claim 30 of the ‘636 patent. (‘353 Patent PH, 2/23/2011 Response at 2.)

164. On May 4, 2011, the patent examiner issued a Notice of Allowance.

165. The material misrepresentations and omission of material information during the prosecution of the ‘636 patent had an immediate and necessary relation to the issuance of the ‘353 patent. The patent examiner found that the ‘353 patent claimed “common subject matter” as the ‘636 patent, which required a terminal disclaimer to overcome the obviousness-type double patenting rejection. Upon information and belief, since the applicants had overcome the obviousness and enablement rejections in the earlier applications to which the ‘353 patent derived, the patent examiner did not renew any obviousness or enablement rejections. Since the applicants misrepresented the bioavailability of the claimed intranasal cyanocobalamin solution relative to an intramuscular injection of cyanocobalamin and omitted material information that would have corrected this misrepresentation to obtain issuance of the ‘636 patent, the inequitable conduct during prosecution of the ‘636 patent taints the prosecution of the ‘353 patent.

166. Accordingly, at least for the reasons discussed above, the ‘353 patent is unenforceable for inequitable conduct.

4. U.S. Patent No. 8,940,714.

167. The ‘714 patent issued from the ‘061 application, which is a continuation of the ‘240 application, which is a division of the ‘399 application, which is a continuation-in-part of the ‘385 application.

168. The material misrepresentations and omission of material information during the prosecution of the ‘636 patent had an immediate and necessary relation to the issuance of the ‘714 patent. The ‘714 patent issued with 11 claims. Each of the claims of the ‘714 patent recites, *inter alia*, a solution of cyanocobalamin for intranasal administration that has bioavailability of cyanocobalamin of at least about 7% relative to an intramuscular injection of cyanocobalamin. Since the applicants misrepresented the bioavailability of the claimed intranasal cyanocobalamin solution relative to an intramuscular injection of cyanocobalamin and omitted material information that would have corrected this misrepresentation, the inequitable conduct during prosecution of the ‘636 patent taints the prosecution of the ‘714 patent.

169. Accordingly, at least for the reasons discussed above, the ‘714 patent is unenforceable for inequitable conduct.

5. U.S. Patent No. 9,415,007.

170. The ‘007 patent issued from the ‘228 application, which is a continuation of the ‘061 application, which is a continuation of the ‘240 application, which is a division of the ‘399 application, which is a continuation-in-part of the ‘385 application.

171. The material misrepresentations and omission of material information during the prosecution of the ‘636 patent had an immediate and necessary relation to the issuance of the ‘007 patent. The ‘007 patent issued with 20 claims. Each of the claims of the ‘007 patent

recites, *inter alia*, a solution of cyanocobalamin for intranasal administration that has bioavailability of cyanocobalamin of at least about 7% relative to an intramuscular injection of cyanocobalamin. Since the applicants misrepresented the bioavailability of the claimed intranasal cyanocobalamin solution relative to an intramuscular injection of cyanocobalamin and omitted material information that would have corrected this misrepresentation, the inequitable conduct during prosecution of the ‘636 patent taints the prosecution of the ‘007 patent.

172. Accordingly, at least for the reasons discussed above, the ‘007 patent is unenforceable for inequitable conduct.

Fifteenth Defense

Any additional defenses or counterclaims, including any discovery supporting the defenses and counterclaims included herein, that discovery may reveal, as Plaintiff has not begun producing discovery to Perrigo, and Perrigo has not yet had the opportunity to pursue relevant third-party discovery, including regarding patent unenforceability.

PERRIGO UK FINCO LIMITED PARTNERSHIP’S COUNTERCLAIMS

Perrigo UK FINCO Limited Partnership (“Perrigo”), for its Counterclaims against Endo Pharmaceuticals Inc. (“Endo” or “Plaintiff/Counterclaim-Defendant”), alleges as follows:

The Parties

1. Perrigo is a United Kingdom entity, having a place of business at Wrafton, Braunton, Devon, EX33 2DL, United Kingdom.

2. On information and belief, and according to its Complaint, Endo is a corporation organized and existing under the laws of the State of Delaware, having a principal place of business at 1400 Atwater Drive, Malvern, Pennsylvania, 19355.

Jurisdiction and Venue

3. These Counterclaims arise under the Patent Laws of the United States, 35 U.S.C. § 1 *et seq.*; the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202; and the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Pub. L. No. 108-173, 117 Stat. 2066 (2003) (“MMA”) (21 U.S.C. § 355(j) and 35 U.S.C. § 271(e)(5)).

4. This Court has original jurisdiction over the subject matter of these Counterclaims under 28 U.S.C. §§ 1331 and 1338(a); under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202; and under the MMA (21 U.S.C. § 355(j) and 35 U.S.C. § 271(e)(5)).

5. This Court has personal jurisdiction over Plaintiff/Counterclaim-Defendant because it has purposefully availed itself of the rights and privileges of this forum by suing Perrigo in this District, and, on information and belief, because Plaintiff/Counterclaim-Defendant conducts substantial business in, and has regular systematic contact with, this District.

6. Venue is proper under 28 U.S.C. §§ 1391 and 1400.

Background

A. FDA Approval of New Brand-Name Drugs.

7. The Federal Food, Drug, and Cosmetic Act (“FFDCA”), 21 U.S.C. § 301 *et seq.*, as amended by the Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (1984) (commonly known as the “Hatch-Waxman Amendments” or “Hatch-Waxman”), and as further amended by Title XI of the MMA, sets forth the rules that the U.S. Food and Drug Administration (“FDA”) follows when considering whether to approve both brand-name and generic drugs.

8. Under the FFDCA, as amended by Hatch-Waxman and the MMA, an applicant seeking to market a new brand-name drug that has not been previously approved must prepare a New Drug Application (“NDA”) for consideration by FDA. *See* 21 U.S.C. § 355.

9. An NDA includes, among other things, the number of any patent that the NDA holder asserts claims the “drug” or a “method of using [the] drug” for which the NDA was submitted and for which a claim of patent infringement could reasonably be asserted against an unauthorized party. *See* 21 U.S.C. § 355(b)(1), (c)(2); 21 C.F.R. § 314.53(b), (c)(2). The decision to submit patent information to FDA rests solely with the NDA holder.

10. Upon approval of the NDA, FDA publishes patent information for the approved drug in “Approved Drug Products with Therapeutic Equivalence Evaluations,” commonly known as the “Orange Book.” *See* 21 U.S.C. § 355(j)(7)(A)(iii).

B. Generic Competition – Abbreviated New Drug Applications (“ANDAs”).

11. In 1984, Congress enacted the Hatch-Waxman Amendments to the FFDCA. Congress passed Hatch-Waxman, which simplified the procedure for obtaining approval of generic drugs, for the purpose of decreasing the cost of pharmaceuticals through increased competition. Under Hatch-Waxman, a generic manufacturer submits what is called an Abbreviated New Drug Application (“ANDA”).

12. To receive approval of its ANDA, an applicant must, *inter alia*, show that its generic drug is “bioequivalent” to the listed reference drug. *See* 21 U.S.C. § 355(j)(4)(F).

13. When filing an ANDA seeking approval of a generic version of a drug listed in the Orange Book, the ANDA applicant generally must also “certify” that any patent information listed in the Orange Book does not preclude FDA approval of a generic version of the drug. *See* 21 U.S.C. § 355(j)(2)(A)(vii); 21 C.F.R. § 314.94(a)(12).

14. When seeking FDA approval to market prior to patent expiration, an ANDA applicant generally submits a so-called “paragraph IV” certification asserting that the listed patent is invalid, unenforceable, and/or will not be infringed. *See* 21 U.S.C. § 355(j)(2)(A)(vii)(IV).

15. An applicant submitting an ANDA containing a paragraph IV certification must notify both the purported patent holder and NDA holder of its paragraph IV certification. *See* 21 U.S.C. § 355(j)(2)(B).

C. Patents-In-Suit.

16. On or about June 12, 2007, according to the electronic records of the U.S. Patent and Trademark Office (“USPTO”), U.S. Patent No. 7,229,636 (“the ‘636 patent”), entitled “CYANOCOBALAMIN LOW VISCOSITY AQUEOUS FORMULATIONS FOR INTRANASAL DELIVERY,” issued, on its face, to purported named inventors Steven C. Quay, Peter C. Aprile, Zenaida O. Go, and Anthony P. Sileno, and was assigned, on its face, to Natestch Pharmaceutical Company Inc. What purports to be a true and correct copy of the ‘636 patent is attached to Plaintiff’s Complaint as Exhibit A.

17. According to the online records of the USPTO, Endo is the current assignee of the ‘636 patent. Plaintiff/Counterclaim-Defendant asserts that “Endo owns and has exclusive rights to the ‘636 patent, including all rights to sue for infringement thereof.”

18. On or about July 29, 2008, according to the electronic records of the USPTO, U.S. Patent No. 7,404,489 (“the ‘489 patent”), entitled “CYANOCOBALAMIN LOW VISCOSITY AQUEOUS FORMULATIONS FOR INTRANASAL DELIVERY,” issued, on its face, to purported named inventors Steven C. Quay, Peter C. Aprile, Zenaida O. Go, and

Anthony P. Sileno, and was assigned, on its face, to QOL Medical, LLC. What purports to be a true and correct copy of the '489 patent is attached to Plaintiff's Complaint as Exhibit B.

19. According to the online records of the USPTO, Endo is the current assignee of the '489 patent. Plaintiff/Counterclaim-Defendant asserts that "Endo owns and has exclusive rights to the '489 patent, including all rights to sue for infringement thereof."

20. On or about February 1, 2011, according to the electronic records of the USPTO, U.S. Patent No. 7,879,349 ("the '349 patent"), entitled "CYANOCOBALAMIN LOW VISCOSITY AQUEOUS FORMULATIONS FOR INTRANASAL DELIVERY," issued, on its face, to purported named inventors Steven C. Quay, Peter C. Aprile, Zenaida O. Go, and Anthony P. Sileno, and was assigned, on its face, to Par Pharmaceutical, Inc. What purports to be a true and correct copy of the '349 patent is attached to Plaintiff's Complaint as Exhibit C.

21. According to the online records of the USPTO, Endo is the current assignee of the '349 patent. Plaintiff/Counterclaim-Defendant asserts that "Endo owns and has exclusive rights to the '349 patent, including all rights to sue for infringement thereof."

22. On or about August 23, 2011, according to the electronic records of the USPTO, U.S. Patent No. 8,003,353 ("the '353 patent"), entitled "CYANOCOBALAMIN LOW VISCOSITY AQUEOUS FORMULATIONS FOR INTRANASAL DELIVERY," issued, on its face, to purported named inventors Steven C. Quay, Peter C. Aprile, Zenaida O. Go, and Anthony P. Sileno, and was assigned, on its face, to Par Pharmaceutical, Inc. What purports to be a true and correct copy of the '353 patent is attached to Plaintiff's Complaint as Exhibit D.

23. According to the online records of the USPTO, Endo is the current assignee of the '353 patent. Plaintiff/Counterclaim-Defendant asserts that "Endo owns and has exclusive rights to the '353 patent, including all rights to sue for infringement thereof."

24. On or about January 27, 2015, according to the electronic records of the USPTO, U.S. Patent No. 8,940,714 (“the ‘714 patent”), entitled “CYANOCOBALAMIN LOW VISCOSITY AQUEOUS FORMULATIONS FOR INTRANASAL DELIVERY,” issued, on its face, to purported named inventors Steven C. Quay, Peter C. Aprile, Zenaida O. Go, and Anthony P. Sileno, and was assigned, on its face, to Par Pharmaceutical, Inc. What purports to be a true and correct copy of the ‘714 patent is attached to Plaintiff’s Complaint as Exhibit E.

25. According to the online records of the USPTO, Endo is the current assignee of the ‘714 patent. Plaintiff/Counterclaim-Defendant asserts that “Endo owns and has exclusive rights to the ‘714 patent, including all rights to sue for infringement thereof.”

26. On or about August 16, 2016, according to the electronic records of the USPTO, U.S. Patent No. 9,415,007 (“the ‘007 patent”), entitled “CYANOCOBALAMIN LOW VISCOSITY AQUEOUS FORMULATIONS FOR INTRANASAL DELIVERY,” issued, on its face, to purported named inventors Steven C. Quay, Peter C. Aprile, Zenaida O. Go, and Anthony P. Sileno, and was assigned, on its face, to Par Pharmaceutical, Inc. What purports to be a true and correct copy of the ‘007 patent is attached to Plaintiff’s Complaint as Exhibit F.

27. According to the online records of the USPTO, Endo is the current assignee of the ‘007 patent. Plaintiff/Counterclaim-Defendant asserts that “Endo owns and has exclusive rights to the ‘007 patent, including all rights to sue for infringement thereof.”

28. According to the online records of FDA, and as Plaintiff/Counterclaim-Defendant asserts, Endo is the holder of NDA No. 021642 for Nascobal® (cyanocobalamin), Nasal Spray, 500 mcg/spray.

29. On information and belief, the ‘636, ‘489, ‘349, ‘353, ‘714, and ‘007 patents were submitted by Endo to FDA for listing in the Orange Book. By virtue of Endo’s submission,

FDA listed the ‘636, ‘489, ‘349, ‘353, ‘714, and ‘007 patents in the Orange Book in connection with the approved NDA No. 021642 for Nascobal® (cyanocobalamin), Nasal Spray, 500 mcg/spray.

30. On or about March 1, 2019, Plaintiff/Counterclaim-Defendant purports to have brought suit against Perrigo, asserting infringement of the ‘636, ‘489, ‘349, ‘353, ‘714, and ‘007 patents.

D. Perrigo’s Cyanocobalamin Nasal Spray ANDA.

31. Perrigo filed an ANDA with FDA seeking approval for Cyanocobalamin Nasal Spray, 500 mcg/spray (“Perrigo’s ANDA Product”).

32. FDA assigned Perrigo’s ANDA No. 212458.

33. Perrigo’s ANDA references NDA No. 021642 for Nascobal®.

34. Because Perrigo’s ANDA seeks FDA approval to market its generic Cyanocobalamin Nasal Spray, 500 mcg/spray product before expiration of the Orange Book-listed ‘636, ‘489, ‘349, ‘353, ‘714, and ‘007 patents, Perrigo’s ANDA included paragraph IV certifications to the ‘636, ‘489, ‘349, ‘353, ‘714, and ‘007 patents.

35. By letter dated January 24, 2019, in accordance with 21 U.S.C. § 355(j)(2)(B), Perrigo provided, *inter alia*, Endo with written notice that Perrigo submitted an ANDA containing paragraph IV certifications to the ‘636, ‘489, ‘349, ‘353, ‘714, and ‘007 patents (“Perrigo’s January 24, 2019 Notice Letter”).

36. Perrigo’s January 24, 2019 Notice Letter included detailed statements setting forth factual and legal bases as to why the ‘636, ‘489, ‘349, ‘353, ‘714, and ‘007 patents are invalid, unenforceable and/or will not be infringed by the manufacture, use, offer for sale, sale, or importation of the Cyanocobalamin Nasal Spray, 500 mcg/spray product described in

Perrigo's ANDA, and *inter alia*, expressly reserved the right to raise additional defenses in the event that suit was filed.

37. Perrigo's January 24, 2019 Notice Letter set forth at least one factual basis as to why Perrigo's ANDA Product does not infringe any claim of the '636 patent, either literally or under the doctrine of equivalents, directly or indirectly.

38. The claims of the '636 patent are invalid.

39. Perrigo's January 24, 2019 Notice Letter set forth at least one factual basis as to why Perrigo's ANDA Product does not infringe any claim of the '489 patent, either literally or under the doctrine of equivalents, directly or indirectly.

40. The claims of the '489 patent are invalid.

41. Perrigo's January 24, 2019 Notice Letter set forth at least one factual basis as to why Perrigo's ANDA Product does not infringe any claim of the '349 patent, either literally or under the doctrine of equivalents, directly or indirectly.

42. The claims of the '349 patent are invalid.

43. Perrigo's January 24, 2019 Notice Letter set forth at least one factual basis as to why Perrigo's ANDA Product does not infringe any claim of the '353 patent, either literally or under the doctrine of equivalents, directly or indirectly.

44. The claims of the '353 patent are invalid.

45. Perrigo's January 24, 2019 Notice Letter set forth at least one factual basis as to why Perrigo's ANDA Product does not infringe any claim of the '714 patent, either literally or under the doctrine of equivalents, directly or indirectly.

46. The claims of the '714 patent are invalid.

47. Perrigo's January 24, 2019 Notice Letter set forth at least one factual basis as to why Perrigo's ANDA Product does not infringe any claim of the '007 patent, either literally or under the doctrine of equivalents, directly or indirectly.

48. The claims of the '007 patent are invalid.

49. Prior to bringing suit against Perrigo for alleged infringement of the '636, '489, '349, '353, '714, and '007 patents, neither Endo, nor anyone on Endo's behalf, requested access to Perrigo's ANDA.

COUNT I
(Declaration of Non-Infringement of the '636 Patent)

50. Perrigo realleges and incorporates by reference the allegations of Paragraphs 1-49.

51. A present, genuine, and justiciable controversy exists between Endo and Perrigo regarding, *inter alia*, the issues of whether the manufacture, use, offer for sale, sale, or importation of the Cyanocobalamin Nasal Spray, 500 mcg/spray product described in Perrigo's ANDA would infringe any valid and enforceable claim of the '636 patent.

52. The manufacture, use, offer for sale, sale, or importation of the Cyanocobalamin Nasal Spray, 500 mcg/spray product described in Perrigo's ANDA would not infringe any valid and enforceable claim of the '636 patent, either literally or under the doctrine of equivalents, directly or indirectly. For at least the reasons set forth in Perrigo's detailed January 24, 2019 Notice Letter, Perrigo's ANDA Product does not infringe any claim of the '636 patent, either literally or under the doctrine of equivalents, directly or indirectly.

53. Perrigo is entitled to a declaration that the manufacture, use, offer for sale, sale, or importation of the product described in Perrigo's ANDA would not infringe any valid and enforceable claim of the '636 patent.

COUNT II
(Declaration of Invalidity of the ‘636 Patent)

54. Perrigo realleges and incorporates by reference the allegations of Paragraphs 1-53.

55. A present, genuine, and justiciable controversy exists between Endo and Perrigo regarding, *inter alia*, the invalidity of the ‘636 patent.

56. The claims of the ‘636 patent are invalid for failure to satisfy one or more of the conditions for patentability in Title 35 of the United States Code, including, but not limited to 35 U.S.C. §§ 101, 102, 103 and 112, the bases for which include, at the very least, one or more of the following:

a. The alleged invention of the ‘636 patent was known or used by others in this country or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for patent.

b. The alleged invention of the ‘636 patent was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of the application for patent in the United States.

c. The alleged invention of the ‘636 patent does no more than combine familiar elements according to known methods to yield predictable results. Any alleged improvement set forth in the ‘636 patent over the prior art is no more than the predictable use of prior art elements according to their established functions. A person of ordinary skill in the art would have been motivated to combine the teachings of the prior art to achieve the alleged invention of the ‘636 patent and would have had a reasonable expectation of success in doing so.

d. The '636 patent does not contain a written description of the alleged invention, and of the manner and process of making and using it, in such full, clear, concise and exact terms as required by the statutes of the United States to enable any person skilled in the art to practice the invention which the claims purport to cover.

e. The claims of the '636 patent are invalid because they do not inform those skilled in the art about the scope of the invention with reasonable certainty and they do not particularly point out and distinctly claim the subject matter of the alleged invention, as required by 35 U.S.C. § 112.

f. The subject matter claimed in the '636 patent fails to comply with, *inter alia*, 35 U.S.C. §§ 102 and/or 103 at least in that the claimed subject matter as a whole was anticipated by the prior art and/or any differences between the subject matter claimed in the patent and the prior art are such that the subject matter as a whole would have been obvious at the time the alleged invention was made to a person having knowledge of such prior art and having ordinary skill in the art to which the claimed subject matter pertains. By way of non-limiting examples, as set forth in detail in Perrigo's January 24, 2019 Notice Letter, prior art rendering each of the claims of the '636 patent invalid under, at the very least, 35 U.S.C. §§ 102 and/or 103, includes, *but is expressly not limited to*, one or more (or a combination of one or more) of the following references and/or products:

- U.S. Patent No. 4,464,378;
- U.S. Patent No. 5,439,670;
- U.S. Patent No. 5,508,282;
- U.S. Patent No. 5,819,730;
- U.S. Patent No. 5,854,269;
- U.S. Patent No. 5,976,573;

- U.S. Patent Application Publication No. 2002/0132803;
- International Patent Application Publication No. WO 86/05987;
- International Patent Application Publication No. WO 88/04926;
- A.S. Harris, *et al.*, “Effect of Viscosity on the Pharmacokinetics and Biological Response to Intranasal Desmopressin,” *J. Pharm. Sci.*, vol. 78, pp. 470-71 (June 1989);
- D.C. Heimbürger, *et al.*, “Intranasal Cobalamin: A Warning,” Letter to the Ed. & Reply, *J. Am. Med. Assoc.*, vol. 265, p. 2190 (1991);
- V.D. Romeo, *et al.*, “Intranasal Cyanocobalamin,” *J. Am. Med. Assoc.*, vol. 268, p. 1268 (1992);
- H.C. Ansel, *et al.*, PHARMACEUTICAL DOSAGE FORMS AND DRUG DELIVERY SYSTEMS, pp. 415-18 (Williams & Wilkins, 6th ed., 1995);
- J.P.M. Braat, *et al.*, “The lack of effect of benzalkonium chloride on the cilia of the nasal mucosa in patients with perennial allergic rhinitis: a combined functional, light, scanning and transmission electron microscopy study,” *Clinical and Experimental Allergy*, vol. 25, pp. 957-65 (1995);
- C.R. Behl, *et al.*, “Effects of physicochemical properties and other factors on systemic nasal drug delivery,” *Advanced Drug Delivery Reviews*, vol. 29, pp. 89-116 (1998);
- HANDBOOK OF PHARMACEUTICAL EXCIPIENTS (American Pharmaceutical Assoc. and Pharmaceutical Press, 2nd ed. 1994);
- HANDBOOK OF PHARMACEUTICAL EXCIPIENTS (American Pharmaceutical Assoc. and Pharmaceutical Press, 3rd ed. 2000);
- PHYSICIANS’ DESK REFERENCE (Medical Economics Co., 47th ed. 1993) (as well as prior art products identified therein); and
- PHYSICIANS’ DESK REFERENCE (Medical Economics Co., 52nd ed. 1998) (as well as prior art products identified therein).

57. Perrigo is entitled to a declaration that the claims of the ‘636 patent are invalid for failure to satisfy one or more of the conditions for patentability in Title 35 of the United States Code.

COUNT III
(Declaration of Non-Infringement of the ‘489 Patent)

58. Perrigo realleges and incorporates by reference the allegations of Paragraphs 1-57.

59. A present, genuine, and justiciable controversy exists between Endo and Perrigo regarding, *inter alia*, the issues of whether the manufacture, use, offer for sale, sale, or importation of the Cyanocobalamin Nasal Spray, 500 mcg/spray product described in Perrigo’s ANDA would infringe any valid and enforceable claim of the ‘489 patent.

60. The manufacture, use, offer for sale, sale, or importation of the Cyanocobalamin Nasal Spray, 500 mcg/spray product described in Perrigo’s ANDA would not infringe any valid and enforceable claim of the ‘489 patent, either literally or under the doctrine of equivalents, directly or indirectly. For at least the reasons set forth in Perrigo’s detailed January 24, 2019 Notice Letter, Perrigo’s ANDA Product does not infringe any claim of the ‘489 patent, either literally or under the doctrine of equivalents, directly or indirectly.

61. Perrigo is entitled to a declaration that the manufacture, use, offer for sale, sale, or importation of the product described in Perrigo’s ANDA would not infringe any valid and enforceable claim of the ‘489 patent.

COUNT IV
(Declaration of Invalidity of the ‘489 Patent)

62. Perrigo realleges and incorporates by reference the allegations of Paragraphs 1-61.

63. A present, genuine, and justiciable controversy exists between Endo and Perrigo regarding, *inter alia*, the invalidity of the ‘489 patent.

64. The claims of the '489 patent are invalid for failure to satisfy one or more of the conditions for patentability in Title 35 of the United States Code, including, but not limited to 35 U.S.C. §§ 101, 102, 103 and 112, the bases for which include, at the very least, one or more of the following:

a. The alleged invention of the '489 patent was known or used by others in this country or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for patent.

b. The alleged invention of the '489 patent was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of the application for patent in the United States.

c. The alleged invention of the '489 patent does no more than combine familiar elements according to known methods to yield predictable results. Any alleged improvement set forth in the '489 patent over the prior art is no more than the predictable use of prior art elements according to their established functions. A person of ordinary skill in the art would have been motivated to combine the teachings of the prior art to achieve the alleged invention of the '489 patent and would have had a reasonable expectation of success in doing so.

d. The '489 patent does not contain a written description of the alleged invention, and of the manner and process of making and using it, in such full, clear, concise and exact terms as required by the statutes of the United States to enable any person skilled in the art to practice the invention which the claims purport to cover.

e. The claims of the '489 patent are invalid because they do not inform those skilled in the art about the scope of the invention with reasonable certainty and they do

not particularly point out and distinctly claim the subject matter of the alleged invention, as required by 35 U.S.C. § 112.

f. The subject matter claimed in the ‘489 patent fails to comply with, *inter alia*, 35 U.S.C. §§ 102 and/or 103 at least in that the claimed subject matter as a whole was anticipated by the prior art and/or any differences between the subject matter claimed in the patent and the prior art are such that the subject matter as a whole would have been obvious at the time the alleged invention was made to a person having knowledge of such prior art and having ordinary skill in the art to which the claimed subject matter pertains. By way of non-limiting examples, as set forth in detail in Perrigo’s January 24, 2019 Notice Letter, prior art rendering each of the claims of the ‘489 patent invalid under, at the very least, 35 U.S.C. §§ 102 and/or 103, includes, *but is expressly not limited to*, one or more (or a combination of one or more) of the following references and/or products:

- U.S. Patent No. 4,464,378;
- U.S. Patent No. 5,439,670;
- U.S. Patent No. 5,508,282;
- U.S. Patent No. 5,819,730;
- U.S. Patent No. 5,854,269;
- U.S. Patent No. 5,976,573;
- U.S. Patent Application Publication No. 2002/0132803;
- International Patent Application Publication No. WO 86/05987;
- International Patent Application Publication No. WO 88/04926;
- A.S. Harris, *et al.*, “Effect of Viscosity on the Pharmacokinetics and Biological Response to Intranasal Desmopressin,” *J. Pharm. Sci.*, vol. 78, pp. 470-71 (June 1989);

- D.C. Heimburger, *et al.*, “Intranasal Cobalamin: A Warning,” Letter to the Ed. & Reply, *J. Am. Med. Assoc.*, vol. 265, p. 2190 (1991);
- V.D. Romeo, *et al.*, “Intranasal Cyanocobalamin,” *J. Am. Med. Assoc.*, vol. 268, p. 1268 (1992);
- H.C. Ansel, *et al.*, PHARMACEUTICAL DOSAGE FORMS AND DRUG DELIVERY SYSTEMS, pp. 415-18 (Williams & Wilkins, 6th ed., 1995);
- J.P.M. Braat, *et al.*, “The lack of effect of benzalkonium chloride on the cilia of the nasal mucosa in patients with perennial allergic rhinitis: a combined functional, light, scanning and transmission electron microscopy study,” *Clinical and Experimental Allergy*, vol. 25, pp. 957-65 (1995);
- C.R. Behl, *et al.*, “Effects of physicochemical properties and other factors on systemic nasal drug delivery,” *Advanced Drug Delivery Reviews*, vol. 29, pp. 89-116 (1998);
- HANDBOOK OF PHARMACEUTICAL EXCIPIENTS (American Pharmaceutical Assoc. and Pharmaceutical Press, 2nd ed. 1994);
- HANDBOOK OF PHARMACEUTICAL EXCIPIENTS (American Pharmaceutical Assoc. and Pharmaceutical Press, 3rd ed. 2000);
- PHYSICIANS’ DESK REFERENCE (Medical Economics Co., 47th ed. 1993) (as well as prior art products identified therein); and
- PHYSICIANS’ DESK REFERENCE (Medical Economics Co., 52nd ed. 1998) (as well as prior art products identified therein).

65. Perrigo is entitled to a declaration that the claims of the ‘489 patent are invalid for failure to satisfy one or more of the conditions for patentability in Title 35 of the United States Code.

COUNT V

(Declaration of Non-Infringement of the ‘349 Patent)

66. Perrigo realleges and incorporates by reference the allegations of Paragraphs 1-65.

67. A present, genuine, and justiciable controversy exists between Endo and Perrigo regarding, *inter alia*, the issues of whether the manufacture, use, offer for sale, sale, or

importation of the Cyanocobalamin Nasal Spray, 500 mcg/spray product described in Perrigo's ANDA would infringe any valid and enforceable claim of the '349 patent.

68. The manufacture, use, offer for sale, sale, or importation of the Cyanocobalamin Nasal Spray, 500 mcg/spray product described in Perrigo's ANDA would not infringe any valid and enforceable claim of the '349 patent, either literally or under the doctrine of equivalents, directly or indirectly. For at least the reasons set forth in Perrigo's detailed January 24, 2019 Notice Letter, Perrigo's ANDA Product does not infringe any claim of the '349 patent, either literally or under the doctrine of equivalents, directly or indirectly.

69. Perrigo is entitled to a declaration that the manufacture, use, offer for sale, sale, or importation of the product described in Perrigo's ANDA would not infringe any valid and enforceable claim of the '349 patent.

COUNT VI
(Declaration of Invalidity of the '349 Patent)

70. Perrigo realleges and incorporates by reference the allegations of Paragraphs 1-69.

71. A present, genuine, and justiciable controversy exists between Endo and Perrigo regarding, *inter alia*, the invalidity of the '349 patent.

72. The claims of the '349 patent are invalid for failure to satisfy one or more of the conditions for patentability in Title 35 of the United States Code, including, but not limited to 35 U.S.C. §§ 101, 102, 103 and 112, the bases for which include, at the very least, one or more of the following:

a. The alleged invention of the '349 patent was known or used by others in this country or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for patent.

b. The alleged invention of the '349 patent was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of the application for patent in the United States.

c. The alleged invention of the '349 patent does no more than combine familiar elements according to known methods to yield predictable results. Any alleged improvement set forth in the '349 patent over the prior art is no more than the predictable use of prior art elements according to their established functions. A person of ordinary skill in the art would have been motivated to combine the teachings of the prior art to achieve the alleged invention of the '349 patent and would have had a reasonable expectation of success in doing so.

d. The '349 patent does not contain a written description of the alleged invention, and of the manner and process of making and using it, in such full, clear, concise and exact terms as required by the statutes of the United States to enable any person skilled in the art to practice the invention which the claims purport to cover.

e. The claims of the '349 patent are invalid because they do not inform those skilled in the art about the scope of the invention with reasonable certainty and they do not particularly point out and distinctly claim the subject matter of the alleged invention, as required by 35 U.S.C. § 112.

f. The subject matter claimed in the '349 patent fails to comply with, *inter alia*, 35 U.S.C. §§ 102 and/or 103 at least in that the claimed subject matter as a whole was anticipated by the prior art and/or any differences between the subject matter claimed in the patent and the prior art are such that the subject matter as a whole would have been obvious at the time the alleged invention was made to a person having knowledge of such

prior art and having ordinary skill in the art to which the claimed subject matter pertains. By way of non-limiting examples, as set forth in detail in Perrigo's January 24, 2019 Notice Letter, prior art rendering each of the claims of the '349 patent invalid under, at the very least, 35 U.S.C. §§ 102 and/or 103, includes, *but is expressly not limited to*, one or more (or a combination of one or more) of the following references and/or products:

- U.S. Patent No. 4,464,378;
- U.S. Patent No. 5,439,670;
- U.S. Patent No. 5,508,282;
- U.S. Patent No. 5,819,730;
- U.S. Patent No. 5,854,269;
- U.S. Patent No. 5,976,573;
- U.S. Patent Application Publication No. 2002/0132803;
- International Patent Application Publication No. WO 86/05987;
- International Patent Application Publication No. WO 88/04926;
- A.S. Harris, *et al.*, "Effect of Viscosity on the Pharmacokinetics and Biological Response to Intranasal Desmopressin," *J. Pharm. Sci.*, vol. 78, pp. 470-71 (June 1989);
- D.C. Heimburger, *et al.*, "Intranasal Cobalamin: A Warning," Letter to the Ed. & Reply, *J. Am. Med. Assoc.*, vol. 265, p. 2190 (1991);
- V.D. Romeo, *et al.*, "Intranasal Cyanocobalamin," *J. Am. Med. Assoc.*, vol. 268, p. 1268 (1992);
- H.C. Ansel, *et al.*, PHARMACEUTICAL DOSAGE FORMS AND DRUG DELIVERY SYSTEMS, pp. 415-18 (Williams & Wilkins, 6th ed., 1995);
- J.P.M. Braat, *et al.*, "The lack of effect of benzalkonium chloride on the cilia of the nasal mucosa in patients with perennial allergic rhinitis: a combined functional, light, scanning and transmission electron microscopy study," *Clinical and Experimental Allergy*, vol. 25, pp. 957-65 (1995);

- C.R. Behl, *et al.*, “Effects of physicochemical properties and other factors on systemic nasal drug delivery,” *Advanced Drug Delivery Reviews*, vol. 29, pp. 89-116 (1998);
- HANDBOOK OF PHARMACEUTICAL EXCIPIENTS (American Pharmaceutical Assoc. and Pharmaceutical Press, 2nd ed. 1994);
- HANDBOOK OF PHARMACEUTICAL EXCIPIENTS (American Pharmaceutical Assoc. and Pharmaceutical Press, 3rd ed. 2000);
- PHYSICIANS’ DESK REFERENCE (Medical Economics Co., 47th ed. 1993) (as well as prior art products identified therein); and
- PHYSICIANS’ DESK REFERENCE (Medical Economics Co., 52nd ed. 1998) (as well as prior art products identified therein).

73. Perrigo is entitled to a declaration that the claims of the ‘349 patent are invalid for failure to satisfy one or more of the conditions for patentability in Title 35 of the United States Code.

COUNT VII
(Declaration of Non-Infringement of the ‘353 Patent)

74. Perrigo realleges and incorporates by reference the allegations of Paragraphs 1-73.

75. A present, genuine, and justiciable controversy exists between Endo and Perrigo regarding, *inter alia*, the issues of whether the manufacture, use, offer for sale, sale, or importation of the Cyanocobalamin Nasal Spray, 500 mcg/spray product described in Perrigo’s ANDA would infringe any valid and enforceable claim of the ‘353 patent.

76. The manufacture, use, offer for sale, sale, or importation of the Cyanocobalamin Nasal Spray, 500 mcg/spray product described in Perrigo’s ANDA would not infringe any valid and enforceable claim of the ‘353 patent, either literally or under the doctrine of equivalents, directly or indirectly. For at least the reasons set forth in Perrigo’s detailed January 24, 2019

Notice Letter, Perrigo's ANDA Product does not infringe any claim of the '353 patent, either literally or under the doctrine of equivalents, directly or indirectly.

77. Perrigo is entitled to a declaration that the manufacture, use, offer for sale, sale, or importation of the product described in Perrigo's ANDA would not infringe any valid and enforceable claim of the '353 patent.

COUNT VIII
(Declaration of Invalidity of the '353 Patent)

78. Perrigo realleges and incorporates by reference the allegations of Paragraphs 1-77.

79. A present, genuine, and justiciable controversy exists between Endo and Perrigo regarding, *inter alia*, the invalidity of the '353 patent.

80. The claims of the '353 patent are invalid for failure to satisfy one or more of the conditions for patentability in Title 35 of the United States Code, including, but not limited to 35 U.S.C. §§ 101, 102, 103 and 112, the bases for which include, at the very least, one or more of the following:

a. The alleged invention of the '353 patent was known or used by others in this country or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for patent.

b. The alleged invention of the '353 patent was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of the application for patent in the United States.

c. The alleged invention of the '353 patent does no more than combine familiar elements according to known methods to yield predictable results. Any alleged improvement set forth in the '353 patent over the prior art is no more than the predictable

use of prior art elements according to their established functions. A person of ordinary skill in the art would have been motivated to combine the teachings of the prior art to achieve the alleged invention of the '353 patent and would have had a reasonable expectation of success in doing so.

d. The '353 patent does not contain a written description of the alleged invention, and of the manner and process of making and using it, in such full, clear, concise and exact terms as required by the statutes of the United States to enable any person skilled in the art to practice the invention which the claims purport to cover.

e. The claims of the '353 patent are invalid because they do not inform those skilled in the art about the scope of the invention with reasonable certainty and they do not particularly point out and distinctly claim the subject matter of the alleged invention, as required by 35 U.S.C. § 112.

f. The subject matter claimed in the '353 patent fails to comply with, *inter alia*, 35 U.S.C. §§ 102 and/or 103 at least in that the claimed subject matter as a whole was anticipated by the prior art and/or any differences between the subject matter claimed in the patent and the prior art are such that the subject matter as a whole would have been obvious at the time the alleged invention was made to a person having knowledge of such prior art and having ordinary skill in the art to which the claimed subject matter pertains. By way of non-limiting examples, as set forth in detail in Perrigo's January 24, 2019 Notice Letter, prior art rendering each of the claims of the '353 patent invalid under, at the very least, 35 U.S.C. §§ 102 and/or 103, includes, *but is expressly not limited to*, one or more (or a combination of one or more) of the following references and/or products:

- U.S. Patent No. 4,464,378;

- U.S. Patent No. 5,439,670;
- U.S. Patent No. 5,508,282;
- U.S. Patent No. 5,819,730;
- U.S. Patent No. 5,854,269;
- U.S. Patent No. 5,976,573;
- U.S. Patent Application Publication No. 2002/0132803;
- International Patent Application Publication No. WO 86/05987;
- International Patent Application Publication No. WO 88/04926;
- A.S. Harris, *et al.*, “Effect of Viscosity on the Pharmacokinetics and Biological Response to Intranasal Desmopressin,” *J. Pharm. Sci.*, vol. 78, pp. 470-71 (June 1989);
- D.C. Heimbürger, *et al.*, “Intranasal Cobalamin: A Warning,” Letter to the Ed. & Reply, *J. Am. Med. Assoc.*, vol. 265, p. 2190 (1991);
- V.D. Romeo, *et al.*, “Intranasal Cyanocobalamin,” *J. Am. Med. Assoc.*, vol. 268, p. 1268 (1992);
- H.C. Ansel, *et al.*, PHARMACEUTICAL DOSAGE FORMS AND DRUG DELIVERY SYSTEMS, pp. 415-18 (Williams & Wilkins, 6th ed., 1995);
- J.P.M. Braat, *et al.*, “The lack of effect of benzalkonium chloride on the cilia of the nasal mucosa in patients with perennial allergic rhinitis: a combined functional, light, scanning and transmission electron microscopy study,” *Clinical and Experimental Allergy*, vol. 25, pp. 957-65 (1995);
- C.R. Behl, *et al.*, “Effects of physicochemical properties and other factors on systemic nasal drug delivery,” *Advanced Drug Delivery Reviews*, vol. 29, pp. 89-116 (1998);
- HANDBOOK OF PHARMACEUTICAL EXCIPIENTS (American Pharmaceutical Assoc. and Pharmaceutical Press, 2nd ed. 1994);
- HANDBOOK OF PHARMACEUTICAL EXCIPIENTS (American Pharmaceutical Assoc. and Pharmaceutical Press, 3rd ed. 2000);
- PHYSICIANS’ DESK REFERENCE (Medical Economics Co., 47th ed. 1993) (as well as prior art products identified therein); and

- PHYSICIANS' DESK REFERENCE (Medical Economics Co., 52nd ed. 1998) (as well as prior art products identified therein).

81. Perrigo is entitled to a declaration that the claims of the '353 patent are invalid for failure to satisfy one or more of the conditions for patentability in Title 35 of the United States Code.

COUNT IX
(Declaration of Non-Infringement of the '714 Patent)

82. Perrigo realleges and incorporates by reference the allegations of Paragraphs 1-81.

83. A present, genuine, and justiciable controversy exists between Endo and Perrigo regarding, *inter alia*, the issues of whether the manufacture, use, offer for sale, sale, or importation of the Cyanocobalamin Nasal Spray, 500 mcg/spray product described in Perrigo's ANDA would infringe any valid and enforceable claim of the '714 patent.

84. The manufacture, use, offer for sale, sale, or importation of the Cyanocobalamin Nasal Spray, 500 mcg/spray product described in Perrigo's ANDA would not infringe any valid and enforceable claim of the '714 patent, either literally or under the doctrine of equivalents, directly or indirectly. For at least the reasons set forth in Perrigo's detailed January 24, 2019 Notice Letter, Perrigo's ANDA Product does not infringe any claim of the '714 patent, either literally or under the doctrine of equivalents, directly or indirectly.

85. Perrigo is entitled to a declaration that the manufacture, use, offer for sale, sale, or importation of the product described in Perrigo's ANDA would not infringe any valid and enforceable claim of the '714 patent.

COUNT X
(Declaration of Invalidity of the ‘714 Patent)

86. Perrigo realleges and incorporates by reference the allegations of Paragraphs 1-85.

87. A present, genuine, and justiciable controversy exists between Endo and Perrigo regarding, *inter alia*, the invalidity of the ‘714 patent.

88. The claims of the ‘714 patent are invalid for failure to satisfy one or more of the conditions for patentability in Title 35 of the United States Code, including, but not limited to 35 U.S.C. §§ 101, 102, 103 and 112, the bases for which include, at the very least, one or more of the following:

a. The alleged invention of the ‘714 patent was known or used by others in this country or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for patent.

b. The alleged invention of the ‘714 patent was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of the application for patent in the United States.

c. The alleged invention of the ‘714 patent does no more than combine familiar elements according to known methods to yield predictable results. Any alleged improvement set forth in the ‘714 patent over the prior art is no more than the predictable use of prior art elements according to their established functions. A person of ordinary skill in the art would have been motivated to combine the teachings of the prior art to achieve the alleged invention of the ‘714 patent and would have had a reasonable expectation of success in doing so.

d. The '714 patent does not contain a written description of the alleged invention, and of the manner and process of making and using it, in such full, clear, concise and exact terms as required by the statutes of the United States to enable any person skilled in the art to practice the invention which the claims purport to cover.

e. The claims of the '714 patent are invalid because they do not inform those skilled in the art about the scope of the invention with reasonable certainty and they do not particularly point out and distinctly claim the subject matter of the alleged invention, as required by 35 U.S.C. § 112.

f. The subject matter claimed in the '714 patent fails to comply with, *inter alia*, 35 U.S.C. §§ 102 and/or 103 at least in that the claimed subject matter as a whole was anticipated by the prior art and/or any differences between the subject matter claimed in the patent and the prior art are such that the subject matter as a whole would have been obvious at the time the alleged invention was made to a person having knowledge of such prior art and having ordinary skill in the art to which the claimed subject matter pertains. By way of non-limiting examples, as set forth in detail in Perrigo's January 24, 2019 Notice Letter, prior art rendering each of the claims of the '714 patent invalid under, at the very least, 35 U.S.C. §§ 102 and/or 103, includes, *but is expressly not limited to*, one or more (or a combination of one or more) of the following references and/or products:

- U.S. Patent No. 4,464,378;
- U.S. Patent No. 5,439,670;
- U.S. Patent No. 5,508,282;
- U.S. Patent No. 5,819,730;
- U.S. Patent No. 5,854,269;
- U.S. Patent No. 5,976,573;

- U.S. Patent Application Publication No. 2002/0132803;
- International Patent Application Publication No. WO 86/05987;
- International Patent Application Publication No. WO 88/04926;
- A.S. Harris, *et al.*, “Effect of Viscosity on the Pharmacokinetics and Biological Response to Intranasal Desmopressin,” *J. Pharm. Sci.*, vol. 78, pp. 470-71 (June 1989);
- D.C. Heimbürger, *et al.*, “Intranasal Cobalamin: A Warning,” Letter to the Ed. & Reply, *J. Am. Med. Assoc.*, vol. 265, p. 2190 (1991);
- V.D. Romeo, *et al.*, “Intranasal Cyanocobalamin,” *J. Am. Med. Assoc.*, vol. 268, p. 1268 (1992);
- H.C. Ansel, *et al.*, PHARMACEUTICAL DOSAGE FORMS AND DRUG DELIVERY SYSTEMS, pp. 415-18 (Williams & Wilkins, 6th ed., 1995);
- J.P.M. Braat, *et al.*, “The lack of effect of benzalkonium chloride on the cilia of the nasal mucosa in patients with perennial allergic rhinitis: a combined functional, light, scanning and transmission electron microscopy study,” *Clinical and Experimental Allergy*, vol. 25, pp. 957-65 (1995);
- C.R. Behl, *et al.*, “Effects of physicochemical properties and other factors on systemic nasal drug delivery,” *Advanced Drug Delivery Reviews*, vol. 29, pp. 89-116 (1998);
- HANDBOOK OF PHARMACEUTICAL EXCIPIENTS (American Pharmaceutical Assoc. and Pharmaceutical Press, 2nd ed. 1994);
- HANDBOOK OF PHARMACEUTICAL EXCIPIENTS (American Pharmaceutical Assoc. and Pharmaceutical Press, 3rd ed. 2000);
- PHYSICIANS’ DESK REFERENCE (Medical Economics Co., 47th ed. 1993) (as well as prior art products identified therein); and
- PHYSICIANS’ DESK REFERENCE (Medical Economics Co., 52nd ed. 1998) (as well as prior art products identified therein).

89. Perrigo is entitled to a declaration that the claims of the ‘714 patent are invalid for failure to satisfy one or more of the conditions for patentability in Title 35 of the United States Code.

COUNT XI
(Declaration of Non-Infringement of the '007 Patent)

90. Perrigo realleges and incorporates by reference the allegations of Paragraphs 1-89.

91. A present, genuine, and justiciable controversy exists between Endo and Perrigo regarding, *inter alia*, the issues of whether the manufacture, use, offer for sale, sale, or importation of the Cyanocobalamin Nasal Spray, 500 mcg/spray product described in Perrigo's ANDA would infringe any valid and enforceable claim of the '007 patent.

92. The manufacture, use, offer for sale, sale, or importation of the Cyanocobalamin Nasal Spray, 500 mcg/spray product described in Perrigo's ANDA would not infringe any valid and enforceable claim of the '007 patent, either literally or under the doctrine of equivalents, directly or indirectly. For at least the reasons set forth in Perrigo's detailed January 24, 2019 Notice Letter, Perrigo's ANDA Product does not infringe any claim of the '007 patent, either literally or under the doctrine of equivalents, directly or indirectly.

93. Perrigo is entitled to a declaration that the manufacture, use, offer for sale, sale, or importation of the product described in Perrigo's ANDA would not infringe any valid and enforceable claim of the '007 patent.

COUNT XII
(Declaration of Invalidity of the '007 Patent)

94. Perrigo realleges and incorporates by reference the allegations of Paragraphs 1-93.

95. A present, genuine, and justiciable controversy exists between Endo and Perrigo regarding, *inter alia*, the invalidity of the '007 patent.

96. The claims of the '007 patent are invalid for failure to satisfy one or more of the conditions for patentability in Title 35 of the United States Code, including, but not limited to 35 U.S.C. §§ 101, 102, 103 and 112, the bases for which include, at the very least, one or more of the following:

a. The alleged invention of the '007 patent was known or used by others in this country or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for patent.

b. The alleged invention of the '007 patent was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of the application for patent in the United States.

c. The alleged invention of the '007 patent does no more than combine familiar elements according to known methods to yield predictable results. Any alleged improvement set forth in the '007 patent over the prior art is no more than the predictable use of prior art elements according to their established functions. A person of ordinary skill in the art would have been motivated to combine the teachings of the prior art to achieve the alleged invention of the '007 patent and would have had a reasonable expectation of success in doing so.

d. The '007 patent does not contain a written description of the alleged invention, and of the manner and process of making and using it, in such full, clear, concise and exact terms as required by the statutes of the United States to enable any person skilled in the art to practice the invention which the claims purport to cover.

e. The claims of the '007 patent are invalid because they do not inform those skilled in the art about the scope of the invention with reasonable certainty and they do

not particularly point out and distinctly claim the subject matter of the alleged invention, as required by 35 U.S.C. § 112.

f. The subject matter claimed in the '007 patent fails to comply with, *inter alia*, 35 U.S.C. §§ 102 and/or 103 at least in that the claimed subject matter as a whole was anticipated by the prior art and/or any differences between the subject matter claimed in the patent and the prior art are such that the subject matter as a whole would have been obvious at the time the alleged invention was made to a person having knowledge of such prior art and having ordinary skill in the art to which the claimed subject matter pertains. By way of non-limiting examples, as set forth in detail in Perrigo's January 24, 2019 Notice Letter, prior art rendering each of the claims of the '007 patent invalid under, at the very least, 35 U.S.C. §§ 102 and/or 103, includes, *but is expressly not limited to*, one or more (or a combination of one or more) of the following references and/or products:

- U.S. Patent No. 4,464,378;
- U.S. Patent No. 5,439,670;
- U.S. Patent No. 5,508,282;
- U.S. Patent No. 5,819,730;
- U.S. Patent No. 5,854,269;
- U.S. Patent No. 5,976,573;
- U.S. Patent Application Publication No. 2002/0132803;
- International Patent Application Publication No. WO 86/05987;
- International Patent Application Publication No. WO 88/04926;
- A.S. Harris, *et al.*, "Effect of Viscosity on the Pharmacokinetics and Biological Response to Intranasal Desmopressin," *J. Pharm. Sci.*, vol. 78, pp. 470-71 (June 1989);

- D.C. Heimburger, *et al.*, “Intranasal Cobalamin: A Warning,” Letter to the Ed. & Reply, *J. Am. Med. Assoc.*, vol. 265, p. 2190 (1991);
- V.D. Romeo, *et al.*, “Intranasal Cyanocobalamin,” *J. Am. Med. Assoc.*, vol. 268, p. 1268 (1992);
- H.C. Ansel, *et al.*, PHARMACEUTICAL DOSAGE FORMS AND DRUG DELIVERY SYSTEMS, pp. 415-18 (Williams & Wilkins, 6th ed., 1995);
- J.P.M. Braat, *et al.*, “The lack of effect of benzalkonium chloride on the cilia of the nasal mucosa in patients with perennial allergic rhinitis: a combined functional, light, scanning and transmission electron microscopy study,” *Clinical and Experimental Allergy*, vol. 25, pp. 957-65 (1995);
- C.R. Behl, *et al.*, “Effects of physicochemical properties and other factors on systemic nasal drug delivery,” *Advanced Drug Delivery Reviews*, vol. 29, pp. 89-116 (1998);
- HANDBOOK OF PHARMACEUTICAL EXCIPIENTS (American Pharmaceutical Assoc. and Pharmaceutical Press, 2nd ed. 1994);
- HANDBOOK OF PHARMACEUTICAL EXCIPIENTS (American Pharmaceutical Assoc. and Pharmaceutical Press, 3rd ed. 2000);
- PHYSICIANS’ DESK REFERENCE (Medical Economics Co., 47th ed. 1993) (as well as prior art products identified therein); and
- PHYSICIANS’ DESK REFERENCE (Medical Economics Co., 52nd ed. 1998) (as well as prior art products identified therein).

97. Perrigo is entitled to a declaration that the claims of the ‘007 patent are invalid for failure to satisfy one or more of the conditions for patentability in Title 35 of the United States Code.

COUNT XIII
(Declaration of Patent Unenforceability)

98. Perrigo realleges and incorporates by reference the allegations of Paragraphs 1-97.

99. A present, genuine, and justiciable controversy exists between Endo and Perrigo regarding, *inter alia*, the unenforceability of the ‘636, ‘489, ‘349, ‘353, ‘714, and ‘007 patents.

100. The ‘636, ‘489, ‘349, ‘353, ‘714, and ‘007 patents (collectively, the “Patents-in-Suit”) are unenforceable due to inequitable conduct as further described with particularity below.

101. Anthony P. Sileno is listed as a co-inventor of each of the ‘636, ‘489, ‘349, ‘353, ‘714, and ‘007 patents. During the relevant time period, Mr. Sileno was employed by Natestch Pharmaceutical Company Inc. (“Natestch”) as Senior Director of Clinical Affairs and Toxicology.

102. Peter J. Knudsen was an attorney for Natestch representing the patent applicants, including Mr. Sileno, with respect to prosecution of the ‘636 patent and ‘489 patent before the U.S. Patent and Trademark Office (“USPTO”). The assignee listed on the face of the ‘636 patent is Natestch.

103. Messrs. Sileno and Knudsen each owed a duty of candor, duty of good faith, and duty of disclosure to the USPTO.

104. During prosecution of the ‘636 patent, Mr. Knudsen submitted to the USPTO a draft declaration by Mr. Sileno to overcome a rejection by the patent examiner that the pending claims, which recited a comparison of the relative bioavailability of the claimed intranasal solution of cyanocobalamin to an intramuscular injection of cyanocobalamin, were invalid under 35 U.S.C. § 112 for lack of enablement.

105. Upon information and belief, Mr. Sileno knowingly misrepresented in his declaration to the USPTO a clinical trial comparing the bioavailability of the active ingredient cyanocobalamin following administration of an intranasal solution and intramuscular injection of cyanocobalamin, and the U.S. Food and Drug Administration's ("FDA") review of the results of that clinical trial, with intent to deceive.

106. Alternatively, upon information and belief, if Mr. Knudsen submitted Mr. Sileno's unsigned declaration without prior review and approval for filing by Mr. Sileno, Mr. Knudsen knowingly made material misrepresentations in his response to the USPTO, with intent to deceive.

107. Mr. Sileno's declaration presenting the results of that clinical trial and Mr. Knudsen's arguments to the USPTO relying upon Mr. Sileno's declaration were material to overcoming the patent examiner's rejection for lack of enablement and resulted in the issuance of the '636 patent. But for the submission of Mr. Sileno's declaration and/or Mr. Knudsen's arguments relying upon Mr. Sileno's declaration, the '636 patent would not have issued.

108. In addition, upon information and belief, Messrs. Sileno and Knudsen knowingly withheld from the USPTO the FDA-approved label for Nascobal® (cyanocobalamin) nasal spray and the correspondence between Natestch and the FDA relating to review of the application for Nascobal® (cyanocobalamin) nasal spray, with the intent to deceive. These withheld documents address the claimed comparison of the bioavailability of the active ingredient cyanocobalamin following administration by intranasal spray and intramuscular injection. These withheld documents refute the applicants' assertions during prosecution of the '636 patent of the bioavailability of the claimed intranasal solution of cyanocobalamin relative to an intramuscular injection of cyanocobalamin.

109. But for the withholding of the FDA-approved label for Nascobal® (cyanocobalamin) nasal spray and the correspondence between Natestch and the FDA relating to review of the application for Nascobal® (cyanocobalamin) nasal spray, the ‘636 patent would not have issued.

110. The material misrepresentations and omission of material information during the prosecution of the ‘636 patent had an immediate and necessary relation to the issuance of the ‘489 patent, ‘349 patent, ‘353 patent, ‘714 patent, and ‘007 patent.

A. Background On Nascobal® (Cyanocobalamin) Nasal Spray.

111. In November 1996, Natestch received FDA approval of New Drug Application (“NDA”) No. 19-722 for Nascobal® (cyanocobalamin) nasal gel.

112. In December 2003, Natestch filed New Drug Application No. 21-642 seeking FDA approval for Nascobal® (cyanocobalamin) nasal spray.

113. Natestch filed NDA No. 21-642 pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act, as a new dosage form (a nasal spray) for the marketed Nascobal® (cyanocobalamin) nasal gel.

114. To support FDA approval for Nascobal® (cyanocobalamin) nasal spray, Natestch conducted a “three way crossover bioequivalence study comparing the nasal spray to the approved nasal gel (NDA 19-722) and an intramuscular dosage form of cyanocobalamin in normal, healthy subjects.” (New Drug Application No. 21-642, 12/26/2003 Cover Letter, at 2.)

115. Natestch presented the results of the bioequivalence study to the FDA in its NDA No. 21-642. In summarizing the bioequivalence study, Natestch explained that one of the objectives was “to compare the pharmacokinetic profile of a single intranasally-administered spray, single intranasally-administered gel (Nascobal®), and single intramuscular-administered vitamin B12 in a fasted state in normal healthy male and female subjects.” (New Drug

Application No. 21-642, 12/26/2003 Human Pharmacokinetic and Bioavailability Summary, at

1.) Another objective was “to evaluate the bioequivalence of the vitamin B12 nasal gel versus the nasal spray in a fasted state in normal healthy male and female subjects.” (*Id.*).

116. Based on Natestech’s evaluation of the bioequivalence study, Natestech reported to the FDA that the relative bioavailability following administration of a 500 µg cyanocobalamin intranasal spray versus administration of a 100 µg cyanocobalamin intramuscular injection was 0.61 (or 61%) without adjustment for the dosage administered:

Compared to the IN gel formulation, the relative bioavailability for the IN spray formulation was 1.04. Relative bioavailability for Treatment A (spray) versus Treatment C (IM) was 0.61, and 0.63 when comparing Treatment B (gel) versus Treatment C (IM).

(*Id.* at 2.)

117. Based on Natestech’s evaluation of the bioequivalence study, Natestech reported that the intranasal spray was bioequivalent to the intranasal gel:

Bioequivalence between the Vitamin B12 spray formulation and the Vitamin B12 gel formulation was established using 90% confidence intervals for log_e-transformed dose-normalized values of AUC_{0-t} and C_{max}.

(*Id.*).

118. On October 1, 2004, the FDA’s Office of Clinical Pharmacology and Biopharmaceutics completed its review of the bioequivalence study submitted with Natestech’s NDA No. 21-642. The Office of Clinical Pharmacology and Biopharmaceutics summarized its recommendation as follows:

The Office of Clinical Pharmacology and Biopharmaceutics, Division of Pharmaceutical Evaluation II (OCPB/DPE-2) reviewed NDA 21-642 and finds the results unacceptable due to lack of demonstration of bioequivalence between the nasal spray and nasal gel formulations using baseline corrected analysis. The nasal spray had 10% less AUC than the nasal gel using baseline corrected

analysis. Since there are no clinical trials conducted, the clinical significance of the reduced exposure obtained with the nasal spray is not known. Before it is approved, it is recommended to change the formulation of the nasal spray and conduct a bioequivalence trial with baseline corrected analysis.

(Food and Drug Administration, Center for Drug Evaluation and Research, Application Number 21-642, Clinical and Pharmacology and Biopharmaceutics Review(s), at 2.)

119. The FDA's Office of Clinical Pharmacology and Biopharmaceutics found that "pre-dose plasma cyanocobalamin levels contribute significantly to the AUC." (*Id.* at 7.) Accordingly, the Office conducted a baseline corrected analysis of the data from the study. (*Id.*)

120. Based on the FDA's baseline corrected analysis of the data, the FDA concluded that the nasal spray had a bioavailability relative to the intramuscular injection of 0.061 (or 6.1%):

The relative bioavailability (baseline corrected) of the two intranasal formulations as compared to the intramuscular injection was found to be 0.061 (Spray) and 0.071 (Gel).

(*Id.* at 10.)

121. Based on the FDA's baseline corrected analysis of the bioequivalence study, the FDA concluded that the nasal spray and nasal gel were not bioequivalent:

The 90% confidence interval for baseline corrected AUC and C_{\max} was outside the 80-125% range, the intranasal spray had 10% less AUC as compared to the intranasal gel.

(*Id.*).

122. On October 28, 2004, the FDA sent an action letter to Natestch stating that the FDA had completed its review of NDA 21-642. (10/28/2004 Ltr. from FDA re NDA 21-642, at

1.) The FDA informed Natestch that the issue of bioavailability must be addressed:

After correcting for baseline values, the intranasal spray was 10% less bioavailable than the intranasal gel. This product is also less bioavailable than the intramuscular formulation. Since this

product cannot be considered bioequivalent to the reference listed product, clinical use of this product or any cyanocobalamin formulation will require close monitoring of vitamin B₁₂ levels. Patients not achieving adequate vitamin B₁₂ levels will require increased dosing with subsequent blood monitoring.

(*Id.*). Among other things, the FDA recommended that Natestch “[r]evis[e] your package insert (PI) to include a discussion of the difference in pharmacokinetics of the two intranasal products and advice that patients treated with the nasal spray should have vitamin B₁₂ levels closely monitored with dose amount and/or frequency adjusted to achieve adequate levels.” (*Id.*).

123. On November 8, 2004, in response to the FDA’s October 28, 2004 action letter, Natestch requested a telephone conference to clarify the analysis of the bioequivalence study by the FDA’s Clinical Pharmacology and Biopharmaceutics reviewer. (11/8/2004 Ltr. from Natestch re NDA 21-642, at 1.)

124. On November 19, 2004, the FDA held a telephone conference to clarify deficiencies in the clinical and biopharmaceutical review of NDA No. 21-642. (Memorandum of 11/19/2004 T-Con Meeting Minutes, Application Number 21-642, at 1.) Dr. Gordon Brandt, Executive Vice President of Medical Affairs, and Anthony Sileno, Senior Director of Toxicology and Clinical Trials, attended the teleconference as representatives of Natestch. (*Id.*).

125. The November 19, 2004 teleconference meeting minutes reflect that the FDA and Natestch discussed the FDA’s re-analysis of the bioequivalence data submitted by Natestch:

Sponsor: What is the basis for the statement that the spray is 10% less bioavailable than the gel? If this is based on an FDA conducted re-analysis of the bioequivalence data, what is the FDA-determined relative bioavailability of gel vs IM, spray vs IM, and gel vs spray? In the ITT analysis submitted with NDA, the spray had an AUC of 104% relative to the gel with 95% CI of 97.7 – 111.2% (NDA Volume 1.11, page 43). A total of three analyses were submitted with the NDA, and none of them came to the conclusion that the spray was 10% less bioavailable than the gel.

FDA: Baseline corrected analysis was done during the review process. The baseline value was obtained by taking the average of three pre-dose vitamin B12 concentrations in plasma. The relative bioavailability of gel vs. IM, spray vs. IM, and spray vs. gel was found to be 7.1%, 6.1%, and 90.4% respectively. The log transformed 90% confidence intervals for AUC(0-t) and Cmax were 71.71-114.19 and 71.6-118.66 respectively. The spray had 10% less bioavailability as compared to the gel; bioequivalency was not established.

(*Id.* at 2.)

126. On December 1, 2004, Natestch submitted an amendment to NDA No. 21-642 to address the FDA's analysis of the bioequivalence data submitted by Natestch. (NDA No. 21-642, 12/1/2004 Amendment 14, at 3.) In response to the clinical pharmacology and biopharmaceutics reviewer's comments regarding the bioequivalence data, Natestch responded that "[w]e agree with the reviewer's comments, and have made a number of changes to the package insert in response." (*Id.*) For example, with respect to the discussion on the difference in pharmacokinetics, Natestch responded as follows:

The comparative pharmacokinetic data previously included in the package insert has been revised per the reviewer's calculations to compare both gel and spray nasal administrations to intramuscular injection. Additionally, a statement has been added in two places emphasizing that

- nasal formulation have lower absorption than intramuscular formulations, and that
- weekly dosing is therefore required for the nasal products.

(*Id.* at 3-4.)

127. In its December 1, 2004 amendment, Natestch deleted the following passage from the "Pharmacokinetics" section of the proposed label for Nascobal® (cyanocobalamin) nasal spray:

In a pharmacokinetic study comparing B₁₂ nasal spray and B₁₂ nasal gel in 25 healthy male and female subjects, bioequivalence between the B₁₂ spray and gel formulation was established using the 90% confidence intervals for the log_e-transformed pharmacokinetic parameters and fell within the range of 80%-125%.

Compared to the B₁₂ nasal gel, the relative bioavailability for the B₁₂ nasal spray was 1.04. Relative bioavailability for B₁₂ nasal gel and spray versus 100 mcg intramuscular injection was 0.63 and 0.61, respectively.

(*Id.* at 5.) In its place, Natestch added the following statement to its proposed label for Nascobal® (cyanocobalamin) nasal spray:

In a subsequent pharmacokinetic study in 25 healthy subjects, the relative bioavailability for B₁₂ nasal gel and spray versus 100 mcg intramuscular injection was 7% and 6%, respectively.

(*Id.*).

128. On January 20, 2005, Natestch submitted an amendment to NDA No. 21-642 with a revision to its proposed label for Nascobal® (cyanocobalamin) nasal spray. (NDA No. 21-642, 1/20/2005 Amendment 15, at 1.) In its amended proposed label, Natestch deleted the following passages:

In a bioavailability study in 24 pernicious anemia patients comparing B₁₂ nasal gel to intramuscular B₁₂, peak concentrations of B₁₂ after intranasal administration were reached in 1-2 hours. The average peak concentration of B₁₂ after intranasal administration was 1,414 ± 1,003 pg/mL. The bioavailability of the nasal gel relative to an intramuscular injection was found to be 8.9% (90% confidence intervals 7.1-11.2%).

...

In a subsequent pharmacokinetic study in 25 healthy subjects, the relative bioavailability for B₁₂ nasal gel and spray versus 100 mcg intramuscular injection was 7% and 6%, respectively.

(*Id.* at 2.) In their place, Natestch added the following paragraph to its proposed label for Nascobal® (cyanocobalamin) nasal spray:

A three way crossover study in 25 fasting healthy subjects was conducted to compare the bioavailability of the B₁₂ nasal spray to the B₁₂ nasal gel and to evaluate the relative bioavailability of the nasal formulations as compared to the intramuscular injection. The peak concentrations after administration of intranasal spray were reached in 1.25 +/- 1.9 hours. The average peak concentration of B₁₂ obtained after baseline correction following administration of intranasal spray was 757.96 +/- 532.17 pg/mL. The bioavailability of the nasal spray relative to the intramuscular injection was found to be 6.1%. The bioavailability of the B₁₂ nasal spray was found to be 10% less than the B₁₂ nasal gel. The 90% confidence intervals for the log_e-transformed AUC_(0-t) and C_{max} was 71.71% - 114.19% and 71.6% - 118.66% respectively.

(*Id.*).

129. On January 31, 2005, Nascotech received FDA approval of NDA No. 21-642 for Nascobal® (cyanocobalamin) nasal spray.

130. The originally approved label for Nascobal® (cyanocobalamin) nasal spray states that “[t]he bioavailability of the nasal spray relative to the intramuscular injection was found to be 6.1%.” (Nascobal® (cyanocobalamin) nasal spray Prescribing Information at 1.)

B. Patents-In-Suit.

131. U.S. Patent Application No. 10/787,385 (“the ‘385 application”) was filed on February 26, 2004, and issued as the ‘636 patent on June 12, 2007.

132. U.S. Patent Application No. 10/814,399 (“the ‘399 application”) was filed on March 31, 2004, and issued as the ‘489 patent on July 29, 2008.

133. U.S. Patent Application No. 12/079,875 (“the ‘875 application”) was filed on March 27, 2008, and issued as the ‘349 patent on February 1, 2011.

134. U.S. Patent Application No. 12/142,240 (“the ‘240 application”) was filed on June 19, 2008, and issued as the ‘353 patent on August 23, 2011.

135. U.S. Patent Application No. 13/189,061 (“the ‘061 application”) was filed on July 22, 2011, and issued as the ‘714 patent on January 27, 2015.

136. U.S. Patent Application No. 14/485,228 (“the ‘228 application”) was filed on September 12, 2014, and issued as the ‘007 patent on August 16, 2016.

137. Each of the ‘636 patent, ‘489 patent, ‘349 patent, ‘353 patent, ‘714 patent, and ‘007 patent derive from and are related to the ‘385 application.

138. The named inventors for all of the Patents-in-Suit are Steven C. Quay, Peter C. Aprile, Zenaida O. Go, and Anthony P. Sileno.

C. Prosecution History Of U.S. Patent Application No. 10/787,385.

139. On February 26, 2004, Mr. Sileno and the other co-inventors filed the ‘385 application with the USPTO.

140. The ‘385 application was originally filed with 31 claims. Claims 1, 23, 24, 30, and 31 of the ‘385 application, as originally filed, recited as follows:

1. A stable pharmaceutical aqueous solution of cyanocobalamin comprised of cyanocobalamin and water wherein said solution of cyanocobalamin is suitable for intranasal administration, has a viscosity less than about 1000 cPs, and wherein said solution of cyanocobalamin has a bioavailability of cyanocobalamin when administered intranasally of at least about 7% relative to an intramuscular injection of cyanocobalamin with the proviso that the solution contains no mercury or mercury compounds.

23. A stable pharmaceutical aqueous solution of cyanocobalamin comprised of cyanocobalamin at a concentration of about 0.5% of total weight of solution, citric acid at a concentration of about 0.12%, sodium citrate at a concentration of about 0.32% glycerin at a concentration of about 2.23%, benzalkonium chloride at concentration of about 0.02% and water wherein said solution of cyanocobalamin is suitable for intranasal administration, has a viscosity less than about 1000 cPs, and wherein said solution of cyanocobalamin has a bioavailability of cyanocobalamin when administered intranasally of at least about 7% relative to an intramuscular injection of cyanocobalamin with the proviso that mercury and mercury containing compounds are not present.

24. A method for administering cyanocobalamin comprised of infusing the nose with an aqueous solution of cyanocobalamin, wherein the solution of cyanocobalamin has a viscosity of less than 1000 cPs, and wherein said solution of cyanocobalamin has a bioavailability of cyanocobalamin of about 7% relative to an intramuscular injection of cyanocobalamin, with the proviso that mercury and mercury containing compounds are not present in the solution.

30. A method for administering cyanocobalamin comprised of infusing the nose with an aqueous solution of cyanocobalamin wherein said aqueous solution of cyanocobalamin is comprised of cyanocobalamin at a concentration of about 0.5% of total weight of solution, citric acid at a concentration of about 0.12%, sodium citrate at a concentration of about 0.32%, glycerin at a concentration of about 2.23%, benzalkonium chloride at concentration of about 0.02% and water wherein said solution of cyanocobalamin is suitable for intranasal administration, has a viscosity less than about 1000 cPs, and wherein said solution of cyanocobalamin has a bioavailability of cyanocobalamin when administered intranasally of at least about 7% relative to an intramuscular injection of cyanocobalamin, with the proviso that the solution of cyanocobalamin contains no mercury or mercury-containing compounds.

31. A method for elevating the vitamin B 12 levels in the cerebral spinal fluid (CSF) comprising administering intranasally a sufficient amount of a solution of cyanocobalamin so that the average ratio of vitamin B12 in the CSF to that in the blood serum ($B12\text{ CSF}/B12\text{ Serum} \times 100$) is increased to at least about 1.1, wherein said aqueous solution of cyanocobalamin is comprised of cyanocobalamin at a concentration of about 0.5% of total weight of solution, citric acid at a concentration of about 0.12%, sodium citrate at a concentration of about 0.32%, glycerin at a concentration of about 2.23%, benzalkonium chloride at concentration of about 0.02% and water wherein said solution of cyanocobalamin is suitable for intranasal administration, has a viscosity less than about 1000 cPs, and wherein said solution of cyanocobalamin has a bioavailability of cyanocobalamin when administered intranasally of at least about 7% relative to an intramuscular injection of cyanocobalamin, with the proviso that the cyanocobalamin solution contains no mercury or mercury-containing compounds.

(‘636 Patent Prosecution History (“PH”), 2/26/2004 Claims, at 23-26.)

141. On April 27, 2005, the patent examiner issued an Office Action with a non-final rejection. The patent examiner rejected pending claims 1, 23, 24, 30, and 31 under 35 U.S.C. § 112 as failing to comply with the enablement requirement, because the specification does not provide “all of the data necessary to calculate the bioavailability claimed relative to that of an intramuscular injection.” The patent examiner stated as follows:

Claims 1, 23, 24, 30 and 31 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contains [*sic*] subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The aforementioned claims are directed to a solution that, when administered intranasally, have a bioavailability of at least 7% relative to an intramuscular injection. An adequate representation regarding the bioavailability claimed would be one that provides all of the data necessary to calculate the bioavailability claimed relative to that of an intramuscular injection.

(‘636 Patent PH, 4/27/2005 Office Action at 7.)

142. On September 22, 2005, the applicants filed their Amendment and Response to the April 27, 2005 Office Action. The applicants acknowledged that “[t]he central factual basis for this rejection asserted by the Office is that the disclosure allegedly lacks ‘sufficient AUC data’ to support Applicants’ claims to a solution of cyanocobalamin providing ‘a bioavailability of cyanocobalamin, when administered nasally, of at least about 7% relative to an intramuscular injection of cyanocobalamin.’” (‘636 Patent PH, 9/22/2005 Amendment and Response at 6.)

143. In the September 22, 2005 Amendment and Response, the applicants “concede[d] the Office’s point that explicit AUC data are not provided for bioavailability of cyanocobalamin delivered via intramuscular injection.” (*Id.*).

144. In the September 22, 2005 Amendment and Response, the applicants stated that “the subject data are directly derivable from comparative data provided in the application, which fully support the subject, ‘at least 7%’ relative bioavailability functional limitation recited in Applicants’ claims.” (*Id.*). The applicants explained as follows:

Despite that these data do not expressly provide comparative AUC values for IM [intramuscular] bioavailability of cyanocobalamin from Applicants’ studies, these values are readily and accurately derivable from the data that are presented. In particular, the comparative bioavailability study results presented above demonstrate that the ‘relative bioavailability’ ratio of the spray versus IM, and gel versus IM, is 0.6105, and 0.6284, respectively. These values represent ratios of the natural log of geometric means of the AUC based on nominal doses (see, e.g., page 17). These data were dose normalized according to conventional practice to the appropriate dose multiple based on a dose of 500 µg given intranasal and 100 µg given by IM (see, e.g., page 12).

The skilled artisan will readily comprehend these data and fully appreciate that the dose normalized data yield a ratio of bioavailability between Applicants’ IN [intranasal] cyanocobalamin solution and IM-administration that reasonably corresponds to the claimed value of “at least about 7%”. This determination requires nothing more than a standard mathematical operation to derive the dose normalized relative AUC values for the IN spray and IM injection. In the example provided on page 17, this standard operation/result is $0.6105 \times 100 \mu\text{g}/500\mu\text{g} \times 100 = 12\%$; or a ratio of the AUC between the IN spray and IM injection of 0.12. In addition to these clearly founded values, the actual arithmetic AUC are provided on page 17 of the specification for the spray and gel as 92000 and 97000 pg*hr/mL, respectively. These data likewise fully evince the corresponding AUC for the IM injected study comparator, according to Applicants’ disclosure. For example, the arithmetic mean of the AUC for IM is calculated as 147155 pg*hr/mL (as readily derived by reverse mathematical operation from the ratios given-for example for the spray $92000/147155 = 0.62$ ratio). When dose normalized according to the disclosure, these data correspond directly to an exemplary relative bioavailability value within Applicants’ described range of at least 7% and preferably 9, 10, 11 or 12 % for the Spray versus IM.

(*Id.* at 7-8.)

145. On July 31, 2006, the patent examiner issued an Office Action with a final rejection. The patent examiner maintained the rejection of claims 1, 23, 24, 30, and 31 under 35 U.S.C. § 112, first paragraph, for failing to comply with the enablement requirement.

146. In the July 31, 2006 Office Action, the patent examiner explained that the specification does not provide the necessary data to calculate the claimed bioavailability of the intranasal spray relative to that intramuscular injection:

The claims are directed to a solution that, when administered intranasally, have a bioavailability of at least 7% relative to an intramuscular injection. An adequate representation regarding the bioavailability claimed would be one that provides all of the data necessary to calculate the bioavailability claimed relative to that of an intramuscular injection.

Additionally, there are several methods of assessing bioavailability in humans and other animals. The selection of methods depends on the nature of the drug product and makes use of such parameters as time of peak plasma concentration, peak plasma concentration and area under the plasma-time curve (AUC). However, Applicant does not provide any AUC data for bioavailability of cyanocobalamin delivered via intramuscular injection.

Further, Applicant discloses several examples in the specification to demonstrate the relative bioavailability relating to the compositions and methods claims. However, in order to demonstrate relative bioavailability, Applicant must provide four variables for the bioavailability equation. Applicant's disclosure fails to demonstrate relative bioavailability in its examples and does not disclose any AUC data for either route of administration. Thus, as a result of this finding and the lack of adequate representations in the specification, Applicant has not enabled this aspect of the claimed composition or methods for using the same. The skilled artisan in this field would not accept the representations set forth in the instant disclosure as sufficient to enable cyanocobalamin compositions and methods of using the composition based on the bioavailability of about 7% relative to and intramuscular injection of cyanocobalamin.

Moreover, pharmacokinetic profiles are predictable and are routinely demonstrated when an applicant claims that a

formulation has a specific relative bioavailability. Thus, it would be expected that the applicant could demonstrate that the formulations and methods claimed have a bioavailability of cyanocobalamin, when administered nasally, of at least 7% relative to an intramuscular injection of cyanocobalamin, and in demonstrating this, Applicant would provide the data necessary to calculate the relative bioavailability.

Thus, in order to accomplish the showing that the bioavailability of cyanocobalamin, when administered nasally, is at least 7% relative to an intramuscular injection of cyanocobalamin, the Applicant would have to show the AUC and those administered for both the intranasal and intramuscular routes to calculate the bioavailability. Therefore, the rejection of the claims under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and as set forth herein.

(‘636 Patent PH, 7/31/2006 Office Action at 2-4 (emphasis added).)

147. An interview between the patent examiner and the applicants was scheduled for October 4, 2006.

148. On October 3, 2006, in advance of the interview, Mr. Knudsen submitted to the patent examiner a draft response to the July 31, 2006 Office Action and a draft declaration by Mr. Sileno.

149. Mr. Sileno’s declaration identified that he is “presently employed by Natestech Pharmaceutical Inc. . . . as Senior Director of Clinical Affairs and Toxicology.” (‘636 Patent PH, 10/3/2006 Sileno Declaration, ¶ 1.)

150. Mr. Sileno states that “I have designed and implemented pre-clinical studies at Natestech to assess pharmacokinetics and pharmacodynamics for formulations, methods and devices for intranasal drug delivery—including the formulations, methods and devices for intranasal drug delivery of cyanocobalamin described in the above- referenced United States Patent Application Serial No. 10/787,385 entitled CYANOCOBALAMIN LOW VISCOSITY

AQUEOUS FORMULATIONS FOR INTRANASAL DELIVERY, filed on February 26, 2004.”
(*Id.*).

151. Mr. Sileno’s declaration identifies himself as a named inventor of the ‘385 application and affirms that he has “carefully reviewed and analyzed the complete file history of the ‘385 application”:

2. I am a named inventor in the ‘385 application, and I have carefully reviewed and analyzed the complete file history of the ‘385 application. In particular, I have reviewed and fully understand the ‘385 specification and all claims presented in this application, including the currently pending claims 1-31 (as set forth in the Current Listing of Claims presented in the Response to Office Action filed contemporaneously herewith). I have also reviewed all substantive Office Actions in the ‘385 application, including the most recent Office Action mailed July 31, 2006 (Paper No./Mail Date 20060722), to which my remarks herein, below are directed.

(*Id.* ¶ 2.)

152. Mr. Sileno’s declaration states, in response to the patent examiner’s rejection for lack of enablement, that “I consider that a person of ordinary skill in the art would view the instant disclosure as fully enabling for the subject matter of the current pending claims. In particular, a person of ordinary skill in the art, would consider that the instant specification provides clear evidence that the claimed cyanocobalamin compositions achieve ‘a bioavailability of cyanocobalamin when administered nasally of at least about 7% relative to an intramuscular injection of cyanocobalamin.”” (*Id.* ¶ 5.)

153. Mr. Sileno’s declaration states that “the specification provides explicit methodology and results, in the form of detailed comparative bioavailability studies and data presented in the Examples, which demonstrate the relative bioavailability characteristics of the claimed solutions. The data from these examples clearly and comprehensively support this

relative bioavailability characteristic in a manner that would be readily understood and practiced by persons of ordinary skill in the art.” (*Id.* ¶ 8.) As an example, Mr. Sileno’s declaration quotes the following section of the specification under the heading “Pharmacokinetic Results”:

The relative bioavailability for the two IN formulations was 0.9715. Bioavailability when comparing treatment A (Spray) versus treatment C (IM) was 0.6105, and 0.6284 when comparing Treatment B (gel) versus Treatment C (IM).

* * *

The pharmacokinetic profiles of the spray formulation and the gel formulation are similar for C_{max} (1480 pg/mL, 1670 pg/mL, respectively) and AUC_{0-t} (9200 pg*hr/mL, 9700 pg*hr/mL, respectively). Additionally, the median difference for T_{max} between the spray and gel IN formulation was less than 15 minutes (-0.24). The C_{max} value for the IM formulation was significantly higher than the C_{max} values for the two IN formulations ($p < 0.0001$).

Relative Bioavailability was assessed by examining the ratio of the nasal B12 spray group mean to the reference group mean with regard to AUC. The ratio is derived by dividing the AUC IN by the AUC IM, therefore, the IM AUC is used in the equation to calculate the relative bioavailability, even if it’s not present in the application. The ratio of the AUC is an appropriate way to represent bioavailability, for example 12% bioavailability is just a 0.12 ratio of the AUC and multiplied by 100 is 12%.

(*Id.* ¶ 9 (quoting page 17 of the specification).)

154. Mr. Sileno’s declaration acknowledged that “these data do not expressly provide comparative AUC values for IM bioavailability of cyanocobalamin from the described studies.” (*Id.* ¶ 10.) However, Mr. Sileno’s declaration asserted that “these values are readily and accurately derivable from the data that are presented.” (*Id.*).

155. Mr. Sileno’s declaration stated that “[p]ersons of ordinary skill in the art would readily discern this aspect of the description, and no experimentation beyond the results provided in the disclosure would be necessary to determine the subject, relative AUC values.” (*Id.*) Mr.

Sileno's declaration asserted that comparative bioavailability between the administration of an intranasal solution and intramuscular injection may be derived as follows from the data presented in the specification:

11. The comparative bioavailability study results cited from the specification above, demonstrate that the "relative bioavailability" ratio of the spray versus IM, and gel versus IM, is 0.6105, and 0.6284, respectively. As the disclosure clearly indicates, these ratios were obtained by dividing the AUC of the spray, or gel, by the AUC of IM-administered cyanocobalamin. Therefore, the AUC for the IM is readily discerned based on the ratios 0.6105 and 0.6284—a simple mathematical calculation from the AUC of spray and gel and the AUC for the IM is obtained as 15000 pg*hr/mL. As the specification also clearly indicates, these data were dosed normalized according to conventional practice (to the appropriate dose multiple based on a dose of 500 µg given intranasal and 100 µg given by IM; see, e.g., pages 12-16).

12. The skilled artisan would have readily understood these data and fully appreciated that the dose normalized data fully evinced a ratio of bioavailability between the IN cyanocobalamin solutions of the invention and IM-administered cyanocobalamin—which ratio as exemplified in the disclosure is shown to correspond reasonably to the claimed value of "at least about 7%." This determination requires nothing more than a standard mathematical operation to derive the dose normalized relative AUC values for the IN spray and IM injection. In the example provided on page 17, this standard operation/result is $0.6105 \times 100 \mu\text{g}/500 \mu\text{g} \times 100 = 12\%$; or a ratio of the AUC between the IN spray and IM injection of 0.12. In addition to these clearly founded values, the actual arithmetic AUC are provided on page 17 of the specification for the spray and gel as 92000 and 97000 pg*hr/mL, respectively. These data, cross referenced to the corresponding data for IM administration, likewise fully evince the corresponding AUC for the IM injected study comparator.

13. As such, the arithmetic mean of the AUC for IM is readily calculated as 15000 pg*hr/mL (derived quite simply by reverse mathematical operation from the ratios given—for example for the spray $92000/\text{AUC IM} = 0.61$ ratio). When dose normalized according to the disclosure, these data correspond directly to an exemplary relative bioavailability value within the described ranges set forth in the specification (e.g., as described at page 8, lines 32-35—"wherein the solution of cyanocobalamin has a bioavailability of at least 7%, more preferably at least about 8, 9,

10, 11, 12% or more of the bioavailability of an intramuscular injection of cyanocobalamin.”).

(*Id.* ¶¶ 11-13.)

156. Mr. Sileno’s declaration states that “[t]he comprehensiveness and accuracy of the instant disclosure regarding relative bioavailability of the claimed intranasal cyanocobalamin solutions (compared to IM delivery), is further evinced by a Phase I Pharmacokinetic Study completed on behalf of Natestech in September, 2002 (see Appendix B, attached hereto).” (*Id.* ¶ 15.) Appendix B was not attached to Mr. Sileno’s declaration that was submitted to the USPTO.

157. Mr. Sileno’s declaration asserts that “[t]he FDA reviewed and accepted these relative bioavailability data and findings” in approval of Natestech’s Nascobal® (cyanocobalamin) nasal spray product:

The resulting Phase I Pharmacokinetic Study Report was submitted and favorably reviewed by the U.S. Food and Drug Administration (FDA). The FDA specifically reviewed and considered relative bioavailability data and findings between intranasal and intramuscular delivery formulations and methods, as a key aspect of this Report. The FDA reviewed and accepted these relative bioavailability data and findings, and ultimately approved Natestech’s New Drug Application (NDA) for an intranasal cyanocobalamin solution (currently marketed as Nascobal®, a widely prescribed treatment for Vitamin B₁₂ deficiency). The relative bioavailability characteristics of the approved Nascobal® product compared to IM cyanocobalamin formulations and methods, are fully supported by the ‘385 specification, and accurately recited in the currently pending claims.

(*Id.*). Mr. Sileno’s declaration does not cite or attach any document reflecting that the FDA had accepted the relative bioavailability data and findings presented by Mr. Sileno.

158. Mr. Sileno's declaration attested that he "designed, directed, monitored, and reviewed the Phase I Pharmacokinetic Study and Report (Appendix B), and thereafter participated in its submission and review by the FDA." (*Id.* ¶ 16.)

159. Mr. Sileno's declaration asserts that "[t]here are no substantive/technical deficiencies in the relative bioavailability methods and results described in the '385, compared to the corresponding bioavailability methods and results presented in the Phase I Pharmacokinetic Study Report. Although some material from the Phase I Pharmacokinetic Study Report was not incorporated into the '385 specification, such material was omitted for purposes of economy, and is in no way essential for describing or implementing the invention set forth in the pending claims." (*Id.* ¶ 18.)

160. Mr. Sileno's declaration concludes that "the data and conclusions provided in the '385 specification are for all purposes *equivalent* to the data and conclusions provided in the Phase I Pharmacokinetic Study Report—which the FDA expressly relied upon to conclude that Nascobal® achieves high, therapeutically effective, relative bioavailability compared to IM cyanocobalamin formulations and methods, consistent with the relative bioavailability terms presented in the instant disclosure and recited in the pending claims." (*Id.* ¶ 19 (emphasis in original).)

161. Mr. Sileno's declaration was unsigned when it was submitted to the USPTO by Mr. Knudsen on October 3, 2006.

162. Contemporaneously with the submission of Mr. Sileno's declaration, on October 3, 2006, Mr. Knudsen submitted a Response to the patent examiner's July 31, 2006 Office Action. The October 3, 2006 Response was signed by Mr. Knudsen, with a certification that the response is being filed electronically with the USPTO.

163. At the time of the October 3, 2006 Response, Mr. Knudsen was Intellectual Property Counsel for Natestch and was an attorney for the applicants with respect to prosecution of the ‘385 application.

164. In the October 3, 2006 Response, Mr. Knudsen, on behalf of the applicants, asserted that “[d]espite that explicit AUC values may not be expressed in Applicant’s disclosure for IM- treated subjects, the specification nonetheless fully describes and enables these results. In particular, the data provided in the working examples of Applicant’s disclosure encompass all essential data necessary to demonstrate relative AUC values.” (‘636 Patent PH, 10/3/2006 Response at 9.)

165. In the October 3, 2006 Response, Mr. Knudsen, on behalf of the applicants, stated that “[t]o assist the Office in further considering the enablement issues in this case, Applicant submits herewith the Declaration of co-inventor, Anthony Sileno, M.S.” (*Id.* at 10.) In support of the response to the patent examiner’s rejection, Mr. Knudsen cites and/or quotes to paragraphs 7- 20 of Mr. Sileno’s declaration. (*Id.* at 10-12.)

166. In the October 3, 2006 Response, Mr. Knudsen, on behalf of applicants, relied upon Mr. Sileno’s declaration to assert that the specification provides “all essential data necessary to determine relative AUC values”:

The findings and conclusions presented in Mr. Sileno’s Declaration strongly support Applicant’s position—that their disclosure provides all essential data necessary to determine relative AUC values, for both IN- and IM- administered cyanocobalamin, and that the disclosure fully demonstrates that Applicant’s formulations and methods achieve “bioavailability of at least 7% of the bioavailability of an intramuscular (IM) injection of cyanocobalamin.”

(*Id.* at 14.)

167. In the October 3, 2006 Response, Mr. Knudsen, on behalf of applicants, further emphasized that the “similar focus and positive outcome of the FDA’s review of Nascobal®” demonstrated that specification enabled the claimed bioavailability limitations:

In addition to the foregoing facts and authority, Mr. Sileno provides additional evidence relating to enablement, by reference to a Phase I Pharmacokinetic Study that he designed, directed, monitored, and reviewed for an IN cyanocobalamin formulation according to the pending claims (Sileno Declaration at ¶¶ 16-20; Phase I Pharmacokinetic Study Report, Appendix B). Mr. Sileno also participated in submission and review of these Study results before the FDA.

As noted in ¶ 16 of Mr. Sileno’s Declaration, the FDA specifically reviewed and considered relative bioavailability data and findings between intranasal and intramuscular cyanocobalamin formulations and methods, “as a key aspect of this Report.”

The FDA accepted these relative bioavailability data and findings, and ultimately approved Natestch’s New Drug Application (NDA) for an intranasal cyanocobalamin solution (currently marketed as Nascobal®, a widely prescribed treatment for Vitamin B₁₂ deficiency). The relative bioavailability characteristics of the approved Nascobal® product compared to IM cyanocobalamin formulations and methods, are fully supported by the ‘385 specification, and accurately recited in the currently pending claims (id., underscore added)

Considering the similar focus and positive outcome of the FDA’s review of Nascobal® to the instant enablement issues, it is most significant that the relative bioavailability methods and results described in the ‘385 specification “were taken directly from the Phase I Pharmacokinetic Study” (Sileno Declaration, at ¶ 18; comparing pages 12-18 of specification, to pages 27-42 of the Phase I Pharmacokinetic Study Report, Appendix B).

(*Id.* (annotations in original).)

168. In the October 3, 2006 Response, Mr. Knudsen, on behalf of applicants, concluded that “[i]n view of the evidence and authority presented above, Applicant respectfully

submits that its disclosure fully supports the pending claims. In this regard, the disclosure is ‘reasonably correlated’ with the scope of the claims, such that skilled artisans would have been able to practice the invention commensurate with the claims, without ‘undue experimentation.’ Accordingly, the rejection of claims 3, 14, 20, 31, and 37 under 35 U.S.C. § 112 is respectfully submitted to be overcome.” (*Id.* at 15.)

169. On October 4, 2006, the patent examiner held an interview with Mr. Knudsen. The October 4, 2006 Interview Summary reflects that an agreement with respect to the claims had been reached. The interview is described as follows:

Applicant will submit an amendment to narrow independent claims, which will include adding a buffer *Markush* group and a preservative *Markush* group. If Applicant determines that client does not want to make the changes suggested, Examiner will withdraw the finality of last Office Action and issue a new Office Action based on U.S.C. 112, first paragraph scope of enablement.

(‘636 Patent PH, 10/4/2006 Interview Summary at 1.)

170. On November 29, 2006, Mr. Knudsen, on behalf of applicants, filed a Response to the July 31, 2006 Office Action. Mr. Knudsen explained that the patent examiner had withdrawn the original enablement rejection based on the October 4, 2006 interview:

The current Office Action presents a rejection of claims 1, 23, 24, 30, and 31 under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement. This rejection was specifically addressed in an Examiner Interview on October 4, 2006, between Applicant’s representative, Peter Knudsen, and Examiner Paul Ward and Supervisory Primary Examiner Thurman Page (see, Interview Summary Paper No. 20061004).

During the course of this Interview, Examiner indicated that the original enablement rejection (relating to determining bioavailability) presented in the current Office Action would be withdrawn, and that a new group for rejection was being considered relating to scope/enablement. In the context of discussing this new ground for rejection, Examiner indicated that the claims would be allowable over such scope rejection if

amended to include “a buffer Markush group and a preservative Markush group” (see, Interview Summary).

Applicant has amended the claims herein in accordance with Examiner’s suggestions to include an exemplary buffer Markush group and an exemplary preservative Markush group, in accordance with the teachings of the specification as detailed above. Applicant thereby respectfully submits that all groups for rejection under 35 U.S.C. § 112, first paragraph, have been overcome.

(‘636 Patent PH, 11/29/2006 Response at 8.)

171. On December 13, 2006, the USPTO issued a Notice of Allowance of the ‘385 application, which issued as the ‘636 patent on June 12, 2007. (‘636 Patent PH, 12/13/2006 Notice of Allowance at 1; ‘636 Patent PH, 6/12/2007 Issue Notification at 1.)

172. The ‘636 patent issued with 31 claims. Each of the claims of the ‘636 patent recites, *inter alia*, a solution of cyanocobalamin for intranasal administration that has bioavailability of cyanocobalamin of [at least] about 7% relative to an intramuscular injection of cyanocobalamin.

D. Inventor Anthony Sileno Made Material Misrepresentations And Intentionally Withheld Material Information With An Intent To Deceive.

1. Mr. Sileno’s Material Misrepresentations To The USPTO.

173. Mr. Sileno’s declaration to the USPTO included several misrepresentations of the clinical trial comparing the bioavailability of the active ingredient cyanocobalamin following administration of an intranasal solution and intramuscular injection of cyanocobalamin.

a. The Relative Bioavailability Of The Intranasal Cyanocobalamin Solution To The Intramuscular Cyanocobalamin Injection Is Not 12%.

174. Mr. Sileno declared that, based on the data presented in the specification, a skilled artisan could determine that the bioavailability of the intranasal cyanocobalamin solution relative to the intramuscular cyanocobalamin injection is 12% (*i.e.*, “a ratio of the AUC between the IN

spray and IM injection of 0.12”). (‘636 Patent PH, 10/3/2006 Sileno Declaration, ¶ 12.) Based on this calculation, Mr. Sileno declared that “the data provided in the specification directly evince that the formulations and methods claimed yield a bioavailability of cyanocobalamin, when administered nasally, of at least 7% relative to an intramuscular injection of cyanocobalamin.” (*Id.* ¶ 14.)

175. Mr. Sileno’s calculation of relative bioavailability is misleadingly false.

176. Mr. Sileno’s calculation did not baseline-correct for the pre-existing levels of cyanocobalamin in the blood plasma.

177. The specification states that the “[b]ioavailability of the intranasal spray relative to an intramuscular injection of cyanocobalamin’ means the percent amount of a dose of the intranasal taken up by the systemic vascular system in comparison to the same amount of cyanocobalamin injected.” (‘636 Patent at col. 3, ll. 56-61.) This comparison of the bioavailability of the intranasal spray relative to an intramuscular injection of cyanocobalamin requires the measurement of bioavailability to be baseline-corrected (*i.e.*, to exclude the pre-existing levels of cyanocobalamin in the blood plasma) to determine the amount of cyanocobalamin that is “taken up by the systemic vascular system” from administration of the nasal spray or intramuscular injection.

178. When the bioavailabilities of cyanocobalamin following administration of an intranasal solution and intramuscular injection of cyanocobalamin are corrected for baseline levels of cyanocobalamin, as analyzed by the FDA and agreed upon by Natestch in seeking approval of its NDA No. 21-642, the bioavailability of the intranasal cyanocobalamin solution relative to the intramuscular cyanocobalamin injection is only 6.1%, a fact which Mr. Sileno knew from his participation in meetings with FDA.

b. The FDA Reviewed And Rejected The Relative Bioavailability Data And Findings That Were Presented To The USPTO By Mr. Sileno.

179. Mr. Sileno declared that “[t]he comprehensiveness and accuracy of the instant disclosure regarding relative bioavailability of the claimed intranasal cyanocobalamin solutions (compared to IM delivery), is further evinced by a Phase I Pharmacokinetic Study completed on behalf of Natestech in September, 2002 (see Appendix B, attached hereto). The resulting Phase I Pharmacokinetic Study Report was submitted and favorably reviewed by the U.S. Food and Drug Administration (FDA). FDA specifically reviewed and considered relative bioavailability data and findings between intranasal and intramuscular delivery formulations and methods, as a key aspect of this Report.” (‘636 Patent PH, 10/3/2006 Sileno Declaration, ¶ 15.) Mr. Sileno declared that “[t]he FDA reviewed and accepted these relative bioavailability data and findings, and ultimately approved Natestech’s New Drug Application (NDA) for an intranasal cyanocobalamin solution (currently marketed as Nascobal®, a widely prescribed treatment for Vitamin B₁₂ deficiency).” (*Id.*).

180. Mr. Sileno’s assertion that, following FDA review, FDA “accepted these relative bioavailability data and findings” is misleadingly false.

181. FDA did not accept that the bioavailability of the intranasal cyanocobalamin solution relative to the intramuscular cyanocobalamin injection was 12%.

182. When FDA reviewed the Phase I Pharmacokinetic Study, the FDA initially disagreed with Natestech’s conclusion that the “[r]elative bioavailability for Treatment A (spray) versus Treatment C (IM) was 0.61, and 0.63 when comparing Treatment B (gel) versus Treatment C (IM).” (Phase I Pharmacokinetic Study Synopsis at 7; Food and Drug Administration, Center for Drug Evaluation and Research, Application Number 21-642, Clinical and Pharmacology and Biopharmaceutics Review(s), at 2.) Further, at FDA’s request, Natestech

deleted from its proposed label for Nascobal® (cyanocobalamin) nasal spray the statement that the “[r]elative bioavailability for B₁₂ nasal gel and spray versus 100 mcg intramuscular injection was 0.63 and 0.61, respectively.” (NDA No. 21-642, 12/1/2004 Amendment 14, at 5.) Mr. Sileno’s calculation that the bioavailability of the intranasal cyanocobalamin solution relative to the intramuscular cyanocobalamin injection is 12% relies on results of the bioequivalence study that were expressly rejected by the FDA.

183. Instead, when FDA reviewed the Phase I Pharmacokinetic Study, FDA concluded that the “pre-dose plasma cyanocobalamin levels contribute significantly to the AUC.” (Food and Drug Administration, Center for Drug Evaluation and Research, Application Number 21-642, Clinical and Pharmacology and Biopharmaceutics Review(s), at 7.) Accordingly, FDA conducted a baseline corrected analysis of the data from the study. FDA found that, in its baseline corrected analysis, “[t]he two intranasal formulations had a relative bioavailability of 0.061 (spray) and 0.071 (gel) to the intramuscular injection formulation used as a reference.” (*Id.*). Further, FDA’s approved label for Nascobal® (cyanocobalamin) nasal spray states that “[t]he bioavailability of the nasal spray relative to the intramuscular injection was found to be 6.1%.” (Nascobal® (cyanocobalamin) nasal spray Prescribing Information at 1.)

c. The Specification Does Not Provide Sufficient Data To Calculate The Relative Bioavailability.

184. Mr. Sileno declared that “[t]he relative bioavailability methods and results described in the ‘385 specification, referenced above, were taken directly from the Phase I Pharmacokinetic Study.” (‘636 Patent PH, 10/3/2006 Sileno Declaration, ¶ 17.) Mr. Sileno declared that “[t]here are no substantive/technical deficiencies in the relative bioavailability methods and results described in the ‘385, compared to the corresponding bioavailability methods and results presented in the Phase I Pharmacokinetic Study Report.” (*Id.* ¶ 18.) Mr.

Sileno declared that “the data and conclusions provided in the ‘385 specification are for all purposes *equivalent* to the data and conclusions provided in the Phase I Pharmacokinetic Study Report—which the FDA expressly relied upon to conclude that Nascobal® achieves high, therapeutically effective, relative bioavailability compared to IM cyanocobalamin formulations and methods, consistent with the relative bioavailability terms presented in the instant disclosure and recited in the pending claims.” (*Id.* ¶ 19 (emphasis in original).)

185. Mr. Sileno’s assertion that “the data and conclusions provided in the ‘385 specification are for all purposes *equivalent* to the data and conclusions provided in the Phase I Pharmacokinetic Study Report—which the FDA expressly relied upon to conclude that Nascobal® achieves high, therapeutically effective, relative bioavailability compared to IM cyanocobalamin formulations and methods, consistent with the relative bioavailability terms presented in the instant disclosure and recited in the pending claims” is misleadingly false.

186. The data and conclusions provided in the specification do not present data sufficient to conduct FDA’s baseline corrected analysis of the bioavailability of the intranasal cyanocobalamin solution relative to the intramuscular cyanocobalamin injection.

187. When FDA reviewed the Phase I Pharmacokinetic Study, the FDA concluded that the “pre-dose plasma cyanocobalamin levels contribute significantly to the AUC.” (Food and Drug Administration, Center for Drug Evaluation and Research, Application Number 21-642, Clinical and Pharmacology and Biopharmaceutics Review(s), at 7.) FDA baseline corrected the data “by taking the average of the individual baseline levels (3 points in the study) and subtracting it from the observed values at each time point for each treatment.” (*Id.*).

188. The specification does not provide sufficient data to calculate the pre-dose plasma cyanocobalamin levels for each of the treatment groups.

189. The specification does not provide sufficient data to calculate the baseline-corrected AUC following administration of the claimed intranasal cyanocobalamin solution or the intramuscular cyanocobalamin injection.

190. The specification does not provide sufficient data to calculate the baseline-corrected bioavailability of the intranasal cyanocobalamin solution relative to the intramuscular cyanocobalamin injection.

191. FDA relied upon data from the Phase I Pharmacokinetic Study that were not presented in the patent specification to calculate the pre-dose plasma cyanocobalamin levels for each of the treatment groups, the baseline-corrected AUC following administration of the claimed intranasal cyanocobalamin solution or the intramuscular cyanocobalamin injection, and the baseline-corrected bioavailability of the intranasal cyanocobalamin solution relative to the intramuscular cyanocobalamin injection.

192. Each of the misrepresentations of the relative bioavailability contained in Mr. Sileno's declaration, alone and collectively, were material to issuance of the '385 application.

193. The patent examiner relied upon Mr. Sileno's declaration to understand how a person of ordinary skill in the art would have reviewed the clinical data in the specification, how the FDA reviewed the clinical data, and how the specification supports the scope of the claims.

194. The patent examiner withdrew its enablement rejection based on the opinions by Mr. Sileno regarding support for the relative bioavailability limitations in the specification.

195. But for Mr. Sileno's declaration, the '385 application would not have been granted as the '636 patent.

2. Mr. Sileno's Material Omissions To The USPTO.

196. Mr. Sileno failed to disclose material information to the USPTO reflecting the FDA's calculation of the intranasal cyanocobalamin solution relative to the intramuscular cyanocobalamin injection, and Natestech's adoption of that calculation.

a. Nascobal® (Cyanocobalamin) Nasal Spray Prescribing Information.

197. The Nascobal® (cyanocobalamin) nasal spray prescribing information was not submitted to the USPTO during prosecution of the '385 application or during the prosecution of any of the Patents-in-Suit.

198. The Nascobal® (cyanocobalamin) nasal spray prescribing information reflects that "[t]he bioavailability of the nasal spray relative to the intramuscular injection was found to be 6.1%." (Nascobal® (cyanocobalamin) nasal spray Prescribing Information at 1.)

199. The Nascobal® (cyanocobalamin) nasal spray prescribing information was publicly available during the prosecution of the '385 application, including prior to the submission of Mr. Sileno's October 3, 2006 Declaration.

200. The Nascobal® (cyanocobalamin) nasal spray prescribing information was material to the prosecution of the '385 application in light of the arguments made by Mr. Knudsen and the declaration by Mr. Sileno responding to the patent examiner's rejection.

201. Prior to the submission of Mr. Sileno's declaration, the patent examiner issued a final rejection for lack of enablement, because the specification did not support a showing that "the bioavailability of cyanocobalamin, when administered nasally, is at least 7% relative to an intramuscular injection of cyanocobalamin." ('636 Patent PH, 7/31/2006 Office Action at 4.) The statement in the Nascobal® (cyanocobalamin) nasal spray prescribing information that "[t]he bioavailability of the nasal spray relative to the intramuscular injection was found to be

6.1%” shows that the claimed intranasal cyanocobalamin solution does not achieve a bioavailability of at least 7% relative to an intramuscular injection of cyanocobalamin.

202. After the submission of Mr. Sileno’s declaration, the statement in the Nascobal® (cyanocobalamin) nasal spray prescribing information that “[t]he bioavailability of the nasal spray relative to the intramuscular injection was found to be 6.1%” refutes Mr. Sileno’s calculation of the bioavailability of the intranasal cyanocobalamin solution relative to the intramuscular cyanocobalamin injection. But at no point during prosecution of the ‘636 patent or any of the other Patents-in-Suit did Mr. Sileno submit the Nascobal® (cyanocobalamin) nasal spray prescribing information to the USPTO.

203. The Nascobal® (cyanocobalamin) nasal spray prescribing information would not have been cumulative to the information that had been submitted to the USPTO. The USPTO was not informed that the FDA had determined, and Natestech had agreed, that “[t]he bioavailability of the nasal spray relative to the intramuscular injection was found to be 6.1%.”

204. But for the fact that the Nascobal® (cyanocobalamin) nasal spray prescribing information had not been submitted for review by the USPTO, the ‘385 application would not have been granted as the ‘636 patent.

b. Correspondence Between FDA And Natestech In Review Of NDA No. 21-642 Regarding Calculation Of Relative Bioavailability.

205. The correspondence between FDA and Natestech in the review of NDA No. 21-642 regarding the appropriate measure of the bioavailability of an intranasal cyanocobalamin solution relative to an intramuscular cyanocobalamin injection were not submitted to the USPTO during prosecution of the ‘385 application or during the prosecution of any of the Patents-in-Suit. For example, the October 1, 2004 Review by FDA’s Office of Clinical Pharmacology and Biopharmaceutics of NDA No. 21-642 was not submitted to the USPTO during prosecution of

the '385 application or during the prosecution of any of the Patents-in-Suit. As another example, the November 19, 2004 Teleconference Meeting Minutes between FDA and Natestch was not submitted to the USPTO during prosecution of the '385 application or during the prosecution of any of the Patents-in-Suit.

206. The correspondence between FDA and Natestch in the review of NDA No. 21-642 reflect FDA's conclusion that, based on the data from the Phase I Pharmacokinetic Study submitted by Natestch, the bioavailability of an intranasal cyanocobalamin solution relative to an intramuscular cyanocobalamin injection was 6.1%.

207. Upon information and belief, certain correspondence between FDA and Natestch in the review of NDA No. 21-642, including the October 1, 2004 Review by FDA's Office of Clinical Pharmacology and Biopharmaceutics of NDA No. 21-642 and the November 19, 2004 Teleconference Meeting Minutes between the FDA and Natestch were publicly available during the prosecution of the '385 application, including prior to the submission of Mr. Sileno's October 3, 2006 Declaration.

208. The correspondence between FDA and Natestch in the review of NDA No. 21-642 were material to the prosecution of the '385 application in light of the arguments made by Mr. Knudsen and the declaration by Mr. Sileno responding to the patent examiner's rejection.

209. Prior to the submission of Mr. Sileno's declaration, the patent examiner issued a final rejection for lack of enablement, because the specification did not support a showing that "the bioavailability of cyanocobalamin, when administered nasally, is at least 7% relative to an intramuscular injection of cyanocobalamin." ('636 Patent PH, 7/31/2006 Office Action at 4.) The correspondence from FDA reflecting that, based on the data from the Phase I Pharmacokinetic Study submitted by Natestch, the bioavailability of an intranasal

cyanocobalamin solution relative to an intramuscular cyanocobalamin injection was 6.1% shows that the claimed intranasal cyanocobalamin solution does not achieve a bioavailability of at least 7% relative to an intramuscular injection of cyanocobalamin.

210. After the submission of Mr. Sileno's declaration, the correspondence from FDA reflecting that, based on the data from the Phase I Pharmacokinetic Study submitted by Natestch, the bioavailability of an intranasal cyanocobalamin solution relative to an intramuscular cyanocobalamin injection was 6.1% refute Mr. Sileno's calculation of the bioavailability of the intranasal cyanocobalamin solution relative to the intramuscular cyanocobalamin injection. But at no point during prosecution of the '636 patent or any of the other Patents-in-Suit did Mr. Sileno submit any of the correspondence between FDA and Natestch in the review of NDA No. 21-642 regarding the appropriate measure of the bioavailability of an intranasal cyanocobalamin solution relative to an intramuscular cyanocobalamin injection.

211. The correspondence between FDA and Natestch in the review of NDA No. 21-642 regarding the appropriate measure of the bioavailability of an intranasal cyanocobalamin solution relative to an intramuscular cyanocobalamin injection would not have been cumulative to the information that had been submitted to the USPTO. The USPTO was not informed that FDA had determined, and Natestch had agreed, that the bioavailability of an intranasal cyanocobalamin solution relative to an intramuscular cyanocobalamin injection was 6.1%.

212. But for the fact that the correspondence between FDA and Natestch in the review of NDA No. 21-642 regarding the appropriate measure of the bioavailability of an intranasal cyanocobalamin solution relative to an intramuscular cyanocobalamin injection had not been submitted to the USPTO for review, the '385 application would not have been granted as the '636 patent.

3. Mr. Sileno Knowingly Made Material Misrepresentations To The USPTO And Withheld Material Information From The USPTO With An Intent To Deceive.

213. Upon information and belief, Mr. Sileno had knowledge of the results of the Phase I Pharmacokinetic Study and FDA's calculation of the bioavailability of the intranasal cyanocobalamin solution relative to the intramuscular cyanocobalamin injection based on that study.

214. In his October 3, 2006 Declaration, Mr. Sileno declared that he was the "Senior Director of Clinical Affairs and Toxicology" at Natestech. ('636 Patent PH, 10/3/2006 Sileno Declaration, ¶ 1.) Mr. Sileno declared that "[w]ithin my professional knowledge and duties described above, I designed, directed, monitored, and reviewed the Phase I Pharmacokinetic Study and Report (Appendix B), and *thereafter participated in its submission and review by the FDA.*" ('636 Patent PH, 10/3/2006 Sileno Declaration, ¶ 16.)

215. Upon information and belief, prior to the submission of his declaration, Mr. Sileno was aware of the correspondence and discussions between FDA and Natestech in the review of NDA No. 21-642 regarding the appropriate measure of the bioavailability of an intranasal cyanocobalamin solution relative to an intramuscular cyanocobalamin injection. For example, Mr. Sileno participated in the November 19, 2004 telephone conference with FDA to discuss the FDA's clinical and biopharmaceutical review of the Phase I Pharmacokinetic Study. (Memorandum of 11/19/2004 T-Con Meeting Minutes, Application Number 21-642, at 1.) At the meeting, FDA discussed the need to baseline correct the bioequivalence data. (*Id.* at 2-3.) FDA also presented its calculation that the bioavailability of the intranasal cyanocobalamin solution relative to the intramuscular cyanocobalamin injection was 6.1%. (*Id.*).

216. Upon information and belief, prior to the submission of his declaration, Mr. Sileno was aware of FDA approval of Nascobal® (cyanocobalamin) nasal spray and the FDA-

approved label's statement that "[t]he bioavailability of the nasal spray relative to the intramuscular injection was found to be 6.1%." (Nascobal® (cyanocobalamin) nasal spray Prescribing Information at 1.)

217. Upon information and belief, at the time of his declaration, Mr. Sileno had knowledge of the importance of the calculation of relative bioavailability to the prosecution of the '385 application.

218. In his October 3, 2006 Declaration, Mr. Sileno declared to the USPTO that he was a named inventor of the '385 application and affirmed that he has "carefully reviewed and analyzed the complete file history of the '385 application":

2. I am a named inventor in the '385 application, and I have carefully reviewed and analyzed the complete file history of the '385 application. In particular, I have reviewed and fully understand the '385 specification and all claims presented in this application, including the currently pending claims 1-31 (as set forth in the Current Listing of Claims presented in the Response to Office Action filed contemporaneously herewith). I have also reviewed all substantive Office Actions in the '385 application, including the most recent Office Action mailed July 31, 2006 (Paper No./Mail Date 20060722), to which my remarks herein, below are directed.

('636 Patent PH, 10/3/2006 Sileno Declaration, ¶ 2.)

219. Upon information and belief, despite understanding the importance of the calculation of relative bioavailability to the prosecution of the '385 application, at the time of his declaration, Mr. Sileno made several misrepresentations relating to the clinical trial comparing the bioavailability of the active ingredient cyanocobalamin following administration of an intranasal solution and intramuscular injection of cyanocobalamin, and FDA's review of the clinical trial.

220. Upon information and belief, Mr. Sileno misrepresented to the USPTO that the bioavailability of the intranasal cyanocobalamin solution relative to the intramuscular

cyanocobalamin injection was 12%, despite knowing that FDA had determined, as agreed by Natestch, that the relative bioavailability is only 6.1%.

221. Upon information and belief, Mr. Sileno misrepresented to the USPTO that FDA had “accepted these relative bioavailability data and findings” in approving the new drug application for Nascobal® (cyanocobalamin) nasal spray, despite knowing that the clinical data from which he calculated the relative bioavailability (*e.g.*, the relative bioavailability of 500 µg cyanocobalamin nasal spray to 100 µg cyanocobalamin intramuscular injection was 0.61) had been rejected by FDA and deleted from the draft label for Nascobal® (cyanocobalamin) nasal spray.

222. Upon information and belief, Mr. Sileno misrepresented to the USPTO that “the data and conclusions provided in the ‘385 specification are for all purposes *equivalent* to the data and conclusions provided in the Phase I Pharmacokinetic Study Report—which the FDA expressly relied upon to conclude that Nascobal® achieves high, therapeutically effective, relative bioavailability compared to IM cyanocobalamin formulations,” despite knowing that the data and conclusions provided in the specification do not present sufficient data to conduct FDA’s baseline corrected analysis of the relative bioavailability.

223. Upon information and belief, Mr. Sileno knowingly withheld disclosure of the Nascobal® (cyanocobalamin) nasal spray prescribing information, despite knowing that the prescribing information reported the bioavailability of the intranasal cyanocobalamin solution relative to the intramuscular cyanocobalamin injection and knowing that this information was material to the prosecution of the ‘385 application.

224. Upon information and belief, Mr. Sileno knowingly withheld the correspondence between FDA and Natestch in the review of NDA No. 21-642 regarding the appropriate measure

of the bioavailability of an intranasal cyanocobalamin solution relative to an intramuscular cyanocobalamin injection, despite knowing that this information was material to the prosecution of the ‘385 application.

225. For at least the reasons above, the single most reasonable inference able to be drawn from the evidence is that Mr. Sileno intended to deceive the USPTO by misrepresenting the bioavailability of the claimed intranasal cyanocobalamin solution relative to the prior art intramuscular cyanocobalamin injection, in order to obtain allowance of the ‘385 application.

226. For at least the reasons above, the single most reasonable inference able to be drawn from the evidence is that Mr. Sileno intended to deceive the USPTO by withholding the FDA approved label for Nascobal® (cyanocobalamin) nasal spray and correspondence between FDA and Natestch in the review of NDA No. 21-642 in order to obtain allowance of the ‘385 application.

227. Accordingly, at least for the reasons discussed above, the ‘636 patent which issued from the ‘385 application is unenforceable for inequitable conduct.

E. Alternatively, Prosecuting Attorney Peter Knudsen Made Material Misrepresentations And Intentionally Withheld Material Information With An Intent To Deceive.

1. If Mr. Knudsen Submitted Mr. Sileno’s Unsigned Declaration Without Prior Review And Approval For Filing By Mr. Sileno, Mr. Knudsen Made Material Misrepresentations To The USPTO.

228. On October 3, 2006, Mr. Knudsen submitted to the USPTO a draft declaration from Mr. Sileno that was unsigned. To the extent that Mr. Knudsen submitted Mr. Sileno’s declaration without prior review and approval for filing by Mr. Sileno, Mr. Knudsen made material misrepresentations to the USPTO with intent to deceive.

229. In the October 3, 2006 Response submitted during the prosecution of the ‘385 application, Mr. Knudsen, on behalf of applicants, stated that “[t]o assist the Office in further

considering the enablement issues in this case, Applicant submits herewith the Declaration of co-inventor, Anthony Sileno, M.S.” (‘636 Patent PH, 10/3/2006 Response at 10.) In this response, Mr. Knudsen repeatedly cited and quoted Mr. Sileno’s declaration to overcome the USPTO’s rejection for lack of enablement.

230. To the extent that Mr. Knudsen submitted Mr. Sileno’s declaration without prior review and approval for filing by Mr. Sileno, the submission of Mr. Sileno’s declaration was a material misrepresentation to the USPTO. By submitting Mr. Sileno’s declaration, Mr. Knudsen was representing to the USPTO that Mr. Sileno, a named co-inventor of the ‘385 application and a proclaimed person of ordinary skill in the art, had reviewed and agreed with the facts and opinions contained in the declaration.

231. To the extent that Mr. Knudsen submitted Mr. Sileno’s declaration without prior review and approval for filing by Mr. Sileno, this misrepresentation was material to the issuance of the ‘385 application. Mr. Sileno’s declaration included several assertions regarding the clinical trial comparing the bioavailability of the active ingredient cyanocobalamin following administration of an intranasal solution and intramuscular injection of cyanocobalamin. Upon information and belief, had Mr. Sileno reviewed his declaration, he would have known that the draft declaration included several material misrepresentations. Based on Mr. Knudsen’s representation that Mr. Sileno had reviewed and approved the declaration, the patent examiner relied upon Mr. Sileno’s declaration to understand how a person of ordinary skill in the art would have reviewed the clinical data in the specification, how FDA reviewed the clinical data, and how the specification supports the scope of the claims. The patent examiner withdrew its enablement rejection based on the arguments by Mr. Knudsen that relied upon the opinions by Mr. Sileno regarding support for the relative bioavailability limitations in the specification. But

for Mr. Sileno's declaration and Mr. Knudsen's arguments based on that declaration, the '385 application would not have been granted as the '636 patent.

2. Mr. Knudsen's Material Omissions To The USPTO.

232. Mr. Knudsen failed to disclose material information to the USPTO reflecting FDA's calculation of the intranasal cyanocobalamin solution relative to the intramuscular cyanocobalamin injection, and Natestch's adoption of that calculation.

233. As discussed above, the Nascobal® (cyanocobalamin) nasal spray prescribing information was not submitted to the USPTO during prosecution of the '385 application or during prosecution of any of the Patents-in-Suit. This was material to the prosecution of the '385 application in light of the arguments made by Mr. Knudsen and the declaration by Mr. Sileno responding to the patent examiner's rejection. This would not have been cumulative to the information that had been submitted to the USPTO. But for the fact that the Nascobal® (cyanocobalamin) nasal spray prescribing information had not been submitted for review by the USPTO, the '385 application would not have been granted as the '636 patent.

234. As discussed above, the correspondence between FDA and Natestch in the review of NDA No. 21-642 regarding the appropriate measure of the bioavailability of an intranasal cyanocobalamin solution relative to an intramuscular cyanocobalamin injection were not submitted to the USPTO during prosecution of the '385 application or during prosecution of any of the Patents-in-Suit. These correspondences were material to the prosecution of the '385 application in light of the arguments made by Mr. Knudsen and the declaration by Mr. Sileno responding to the patent examiner's rejection. This would not have been cumulative to the information that had been submitted to the USPTO. But for the fact that the correspondence between FDA and Natestch in the review of NDA No. 21-642 regarding the appropriate measure of the bioavailability of an intranasal cyanocobalamin solution relative to an intramuscular

cyanocobalamin injection had not been submitted to the USPTO for review, the '385 application would not have been granted as the '636 patent.

3. Mr. Knudsen Knowingly Made Material Misrepresentations To The USPTO And Withheld Material Information From The USPTO With An Intent To Deceive.

235. Upon information and belief, to the extent that Mr. Knudsen submitted Mr. Sileno's declaration without prior review and approval for filing by Mr. Sileno, Mr. Knudsen knowingly misrepresented the nature of Mr. Sileno's declaration.

236. Upon information and belief, Mr. Knudsen knew that, upon submission of Mr. Sileno's declaration, the patent examiner would infer that Mr. Sileno had previously reviewed and approved for filing his declaration.

237. For at least the reasons above, to the extent that Mr. Knudsen submitted Mr. Sileno's declaration without prior review and approval for filing by Mr. Sileno, the single most reasonable inference able to be drawn from the evidence is that Mr. Sileno intended to deceive the USPTO by misrepresenting the nature of Mr. Sileno's declaration, in order to obtain allowance of the '385 application.

238. Upon information and belief, Mr. Knudsen had knowledge of the results of the Phase I Pharmacokinetic Study and the FDA's calculation of the bioavailability of the intranasal cyanocobalamin solution relative to the intramuscular cyanocobalamin injection based on that study.

239. In his October 3, 2006 Response, Mr. Knudsen identified himself as Intellectual Property Counsel at Natestch.

240. In his October 3, 2006 Response, Mr. Knudsen explains that "the FDA specifically reviewed and considered relative bioavailability data and findings between intranasal and intramuscular cyanocobalamin formulations and methods." ('636 Patent PH, 10/3/2006

Response at 14.) Mr. Knudsen further asserted that “[c]onsidering the similar focus and positive outcome of the FDA’s review of Nascobal® to the instant enablement issues, it is most significant that the relative bioavailability methods and results described in the ‘385 specification ‘were taken directly taken [*sic*] from the Phase I Pharmacokinetic Study.’” (*Id.*).

241. Upon information and belief, prior to the submission of his October 3, 2006 Response, Mr. Knudsen was aware of FDA approval of Nascobal® (cyanocobalamin) nasal spray and the FDA-approved label’s statement that “[t]he bioavailability of the nasal spray relative to the intramuscular injection was found to be 6.1%.” (Nascobal® (cyanocobalamin) nasal spray Prescribing Information at 1.)

242. Upon information and belief, prior to the submission of his October 3, 2006 Response, Mr. Knudsen was aware of the correspondence and discussions between the FDA and Nasteck in the review of NDA No. 21-642 regarding the appropriate measure of the bioavailability of an intranasal cyanocobalamin solution relative to an intramuscular cyanocobalamin injection.

243. Upon information and belief, as the prosecuting attorney, Mr. Knudsen had knowledge of the importance of the calculation of relative bioavailability to the prosecution of the ‘385 application.

244. Upon information and belief, Mr. Knudsen knowingly withheld disclosure of the Nascobal® (cyanocobalamin) nasal spray prescribing information, despite knowing that the prescribing information reported the bioavailability of the intranasal cyanocobalamin solution relative to the intramuscular cyanocobalamin injection and knowing that this information was material to the prosecution of the ‘385 application.

245. Upon information and belief, Mr. Knudsen knowingly withheld the correspondence between the FDA and Natestch in the review of NDA No. 21-642 regarding the appropriate measure of the bioavailability of an intranasal cyanocobalamin solution relative to an intramuscular cyanocobalamin injection, despite knowing that this information was material to the prosecution of the '385 application.

246. For at least the reasons above, the single most reasonable inference able to be drawn from the evidence is that Mr. Knudsen intended to deceive the USPTO by withholding the FDA approved label for Nascobal and correspondence between the FDA and Natestch in the review of NDA No. 21-642 in order to obtain allowance of the '385 application.

247. Accordingly, at least for the reasons discussed above, the '636 patent which issued from the '385 application is unenforceable for inequitable conduct.

F. The Material Misrepresentations And Omissions During Prosecution Of The '636 Patent Taint Each Of The Patents-in-Suit.

248. The acts of inequitable conduct described herein taint all of the patent applications within this patent family, including under the doctrine of infectious unenforceability. Because all of the patent applications that led to each of the Patents-in-Suit derive from and are related to the '385 application, each of the Patents-in-Suit is unenforceable as a result of inequitable conduct.

1. U.S. Patent No. 7,404,489.

249. The '489 patent issued from the '399 application, which was filed as a continuation-in-part of the '385 application. Paul Ward, who was patent examiner for the '385 application, also examined the '489 patent.

250. On April 21, 2005, during the prosecution of the '399 application, the patent examiner issued an Office Action that included a non-final rejection. The patent examiner

rejected the pending claims as obvious over the prior art, including Wenig (U.S. Patent No. 4,724,231), Grychowski (U.S. Patent No. 6,745,760), Slot *et al.*, Garcia-Arieta *et al.*, and Harris *et al.* (‘489 Patent PH, 4/21/2005 Office Action at 2-8.) The patent examiner also rejected claims 3, 14, 20, 31, and 37 as failing to comply with the enablement requirement with respect to the claimed bioavailability of the intranasal cyanocobalamin solution relative to an intramuscular cyanocobalamin injection. (*Id.* at 8-14.)

251. On September 22, 2005, the applicants filed an Amendment and Response to the April 21, 2005 Office Action. (‘489 Patent PH, 9/22/2005 Amendment and Response.) In response to the obviousness rejection, the applicants argued, *inter alia*, that “the art of record fails to evince practical motivation coupled with a reasonable expectation for developing the instant formulations and methods specifically characterized as providing a bioavailability ‘when administered intranasally of at least about 7% relative to an intramuscular injection of cyanocobalamin.’” (*Id.* at 23.)

252. In the September 22, 2005 Amendment and Response, in response to the enablement rejection, the applicants repeated the same arguments as raised in the September 22, 2005 Amendment and Response filed with the ‘385 application. (*Id.* at 9-12.) For example, the applicants argued that “[t]he skilled artisan will readily comprehend these data and fully appreciate that the dose normalized data yield a ratio of bioavailability between Applicants’ IN cyanocobalamin solution and IM-administration that reasonably corresponds to the claimed value of ‘at least about 7%.’” (*Id.* at 11.) The applicants repeated that, based on a standard mathematical operation of the data presented in the specification, the bioavailability of an intranasal cyanocobalamin solution relative to an intramuscular cyanocobalamin injection is 12%. (*Id.*)

253. On July 11, 2006, the patent examiner issued an Office Action with a final rejection. (‘489 Patent PH, 7/11/2006 Amendment and Response.) The patent examiner accepted that the applicants had overcome the obviousness rejection. (*Id.* at 2.) Thus, the applicant’s argument that “the art of record fails to evince practical motivation coupled with a reasonable expectation for developing the instant formulations and methods specifically characterized as providing a bioavailability ‘when administered intranasally of at least about 7% relative to an intramuscular injection of cyanocobalamin’” was material to overcoming the patent examiner’s obviousness rejection. The patent examiner further maintained his enablement rejection. (*Id.* at 2-4.)

254. On June 11, 2007, the applicants filed an Amendment and Response to the July 11, 2006 Final Office Action. (‘489 Patent PH, 6/11/2007 Amendment and Response.) The applicants overcame the final enablement rejection by amending the claims to delete the relative bioavailability limitation. (*Id.* at 9.)

255. On May 8, 2008, the patent examiner issued a Notice of Allowance of the ’399 application.

256. The material misrepresentations and omission of material information during the prosecution of the ‘636 patent had an immediate and necessary relation to the issuance of the ‘489 patent. The applicants overcame the obviousness rejection by arguing that “the art of record fails to evince practical motivation coupled with a reasonable expectation for developing the instant formulations and methods specifically characterized as providing a bioavailability ‘when administered intranasally of at least about 7% relative to an intramuscular injection of cyanocobalamin.’” Since the applicants misrepresented the bioavailability of the claimed intranasal cyanocobalamin solution relative to an intramuscular injection of cyanocobalamin and

omitted material information that would have corrected this misrepresentation, the inequitable conduct during prosecution of the '636 patent taints the prosecution of the '489 patent.

257. Accordingly, at least for the reasons discussed above, the '489 patent is unenforceable for inequitable conduct.

2. U.S. Patent No. 7,879,349.

258. The '349 patent issued from the '875 application, which is a continuation of the '399 application, which is a continuation-in-part of the '385 application. Paul Ward, who was patent examiner for the '385 application, also examined the '349 patent.

259. The material misrepresentations and omission of material information during the prosecution of the '636 patent had an immediate and necessary relation to the issuance of the '349 patent. The '349 patent issued with 17 claims. Each of the claims of the '349 patent recites, *inter alia*, a solution of cyanocobalamin for intranasal administration that has bioavailability of cyanocobalamin of at least about 7% relative to an intramuscular injection of cyanocobalamin. Since the applicants misrepresented the bioavailability of the claimed intranasal cyanocobalamin solution relative to an intramuscular injection of cyanocobalamin and omitted material information that would have corrected this misrepresentation, the inequitable conduct during prosecution of the '636 patent taints the prosecution of the '349 patent.

260. Accordingly, at least for the reasons discussed above, the '349 patent is unenforceable for inequitable conduct.

3. U.S. Patent No. 8,003,353.

261. The '353 patent issued from the '240 application, which is a division of the '399 application, which is a continuation-in-part of the '385 application. Paul Ward, who was patent examiner for the '385 application, also examined the '353 patent.

262. On November 26, 2010, the patent examiner issued an Office Action with a non-final rejection. (‘353 Patent PH, 11/26/2010 Office Action.) The patent examiner rejected all of the pending claims for obviousness-type double patenting over claim 30 of the ‘636 patent. (*Id.* at 3.) The patent examiner found that “the subject matter claimed in the instant application is fully disclosed in the [‘636] patent and is covered by the patent since the patent and the application are claiming common subject matter.” (*Id.*). The patent examiner did not issue any other rejections based on obviousness or enablement.

263. On February 23, 2011, the applicants filed a terminal disclaimer to overcome the patent examiner’s rejection on the ground of obviousness-type double patenting over claim 30 of the ‘636 patent. (‘353 Patent PH, 2/23/2011 Response at 2.)

264. On May 4, 2011, the patent examiner issued a Notice of Allowance.

265. The material misrepresentations and omission of material information during the prosecution of the ‘636 patent had an immediate and necessary relation to the issuance of the ‘353 patent. The patent examiner found that the ‘353 patent claimed “common subject matter” as the ‘636 patent, which required a terminal disclaimer to overcome the obviousness-type double patenting rejection. Upon information and belief, since the applicants had overcome the obviousness and enablement rejections in the earlier applications to which the ‘353 patent derived, the patent examiner did not renew any obviousness or enablement rejections. Since the applicants misrepresented the bioavailability of the claimed intranasal cyanocobalamin solution relative to an intramuscular injection of cyanocobalamin and omitted material information that would have corrected this misrepresentation to obtain issuance of the ‘636 patent, the inequitable conduct during prosecution of the ‘636 patent taints the prosecution of the ‘353 patent.

266. Accordingly, at least for the reasons discussed above, the '353 patent is unenforceable for inequitable conduct.

4. U.S. Patent No. 8,940,714.

267. The '714 patent issued from the '061 application, which is a continuation of the '240 application, which is a division of the '399 application, which is a continuation-in-part of the '385 application.

268. The material misrepresentations and omission of material information during the prosecution of the '636 patent had an immediate and necessary relation to the issuance of the '714 patent. The '714 patent issued with 11 claims. Each of the claims of the '714 patent recites, *inter alia*, a solution of cyanocobalamin for intranasal administration that has bioavailability of cyanocobalamin of at least about 7% relative to an intramuscular injection of cyanocobalamin. Since the applicants misrepresented the bioavailability of the claimed intranasal cyanocobalamin solution relative to an intramuscular injection of cyanocobalamin and omitted material information that would have corrected this misrepresentation, the inequitable conduct during prosecution of the '636 patent taints the prosecution of the '714 patent.

269. Accordingly, at least for the reasons discussed above, the '714 patent is unenforceable for inequitable conduct.

5. U.S. Patent No. 9,415,007.

270. The '007 patent issued from the '228 application, which is a continuation of the '061 application, which is a continuation of the '240 application, which is a division of the '399 application, which is a continuation-in-part of the '385 application.

271. The material misrepresentations and omission of material information during the prosecution of the '636 patent had an immediate and necessary relation to the issuance of the '007 patent. The '007 patent issued with 20 claims. Each of the claims of the '007 patent

recites, *inter alia*, a solution of cyanocobalamin for intranasal administration that has bioavailability of cyanocobalamin of at least about 7% relative to an intramuscular injection of cyanocobalamin. Since the applicants misrepresented the bioavailability of the claimed intranasal cyanocobalamin solution relative to an intramuscular injection of cyanocobalamin and omitted material information that would have corrected this misrepresentation, the inequitable conduct during prosecution of the ‘636 patent taints the prosecution of the ‘007 patent.

272. Accordingly, at least for the reasons discussed above, the ‘007 patent is unenforceable for inequitable conduct.

REQUEST FOR RELIEF

WHEREFORE, Perrigo respectfully requests that this Court enter a Judgment and Order in its favor and against Plaintiff/Counterclaim-Defendant Endo as follows:

- (a) Declaring that the manufacture, sale, offer for sale, use or importation of the Cyanocobalamin Nasal Spray, 500 mcg/spray product described in Perrigo’s ANDA No. 212458 does not and will not infringe (either literally or under the doctrine of equivalents), directly or indirectly (either by inducement or contributorily), any valid and enforceable claim of the ‘636 patent;
- (b) Declaring that the claims of the ‘636 patent are invalid;
- (c) Declaring that the ‘636 patent is unenforceable;
- (d) Declaring that the manufacture, sale, offer for sale, use or importation of the Cyanocobalamin Nasal Spray, 500 mcg/spray product described in Perrigo’s ANDA No. 212458 does not and will not infringe (either literally or under the doctrine of equivalents), directly or indirectly (either by inducement or contributorily), any valid and enforceable claim of the ‘489 patent;
- (e) Declaring that the claims of the ‘489 patent are invalid;
- (f) Declaring that the ‘489 patent is unenforceable;
- (g) Declaring that the manufacture, sale, offer for sale, use or importation of the Cyanocobalamin Nasal Spray, 500 mcg/spray product described in Perrigo’s ANDA No. 212458 does not and will not infringe (either literally or under the doctrine of equivalents), directly or indirectly (either by inducement or contributorily), any valid and enforceable claim of the ‘349 patent;

- (h) Declaring that the claims of the '349 patent are invalid;
- (i) Declaring that the '349 patent is unenforceable;
- (j) Declaring that the manufacture, sale, offer for sale, use or importation of the Cyanocobalamin Nasal Spray, 500 mcg/spray product described in Perrigo's ANDA No. 212458 does not and will not infringe (either literally or under the doctrine of equivalents), directly or indirectly (either by inducement or contributorily), any valid and enforceable claim of the '353 patent;
- (k) Declaring that the claims of the '353 patent are invalid;
- (l) Declaring that the '353 patent is unenforceable;
- (m) Declaring that the manufacture, sale, offer for sale, use or importation of the Cyanocobalamin Nasal Spray, 500 mcg/spray product described in Perrigo's ANDA No. 212458 does not and will not infringe (either literally or under the doctrine of equivalents), directly or indirectly (either by inducement or contributorily), any valid and enforceable claim of the '714 patent;
- (n) Declaring that the claims of the '714 patent are invalid;
- (o) Declaring that the '714 patent is unenforceable;
- (p) Declaring that the manufacture, sale, offer for sale, use or importation of the Cyanocobalamin Nasal Spray, 500 mcg/spray product described in Perrigo's ANDA No. 212458 does not and will not infringe (either literally or under the doctrine of equivalents), directly or indirectly (either by inducement or contributorily), any valid and enforceable claim of the '007 patent;
- (q) Declaring that the claims of the '007 patent are invalid;
- (r) Declaring that the '007 patent is unenforceable;
- (s) Ordering that Plaintiff/Counterclaim-Defendant's Complaint be dismissed with prejudice and judgment entered in favor of Perrigo;
- (t) Declaring that this is an exceptional case under 35 U.S.C. § 285 and awarding Perrigo attorneys' fees, costs, and expenses in this action; and
- (u) Awarding Perrigo any further and additional relief as the Court deems just and proper.

Dated: March 25, 2019

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