UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

SHIRE LLC and SHIRE US INC., Plaintiffs,	)	
v.	)	CIVIL ACTION NO. 15-13909-WGY
ABHAI, LLC, Defendant.	)	

YOUNG, D.J. March 22, 2018

FINDINGS OF FACT, RULINGS OF LAW, AND ORDER FOR JUDGMENT

I. INTRODUCTION

On November 20, 2015, the plaintiffs Shire LLC and Shire US Inc. (collectively, "Shire"), brought this action against the defendant Abhai, LLC ("Abhai"), for patent infringement of the United States Reissued Patent No. RE42,096 (the "'096 Patent"), in violation of 35 U.S.C. § 271(e)(2)(A) (count I), and patent infringement of the United States Reissued Patent No. RE41,148 (the "'148 Patent") in violation of 35 U.S.C. § 271(e)(2)(A) (count II). Compl. ¶¶ 1, 20-33.

This is an Abbreviated New Drug Application ("ANDA") patent case. Abhai is pursuing an ANDA with the Food and Drug Administration ("FDA"). Compl. ¶ 1. Controlling statutory law encourages such applications and rewards successful, first-to-

file applicants as a means toward controlling pharmaceutical prices. See generally FTC v. Actavis, Inc., 570 U.S. 136 (2013). At the same time, the law protects existing patent rights and encourages prompt litigation to assay the limits of those rights. See generally In re Nexium (Esomeprazole) Antitrust Litig., 842 F.3d 34 (1st Cir. 2016). This is such litigation.

The challenge for Abhai here is to design a pharmaceutical product that falls just beyond the reach of Shire's patents yet is sufficiently bioequivalent and therapeutically equivalent to Shire's product to satisfy the FDA of its efficacy.

On February 3, 2016, Abhai filed an amended answer to the complaint and counterclaims requesting a declaration of non-infringement of the '096 Patent (count I), and a declaration of non-infringement of the '148 Patent (count II). Def.'s Am. Answer, Defenses, & Countercls. ("Def.'s Am. Answer") ¶¶ 18-29, ECF No. 35. On February 17, 2016, Shire filed its answer to Abhai's counterclaims. Counterdefs.' Answer, ECF No. 38.

On March 1, 2016, the case was referred to mediation, provided by Judge Marianne B. Bowler. Elec. Clerk's Notes, ECF Nos. 44-46. The case returned to this session's running trial list on January 13, 2017 after both parties failed to come to an agreement. Elec. Clerk's Notes, ECF Nos. 93-94; Report Alternative Dispute Resolution Provider, ECF No. 96.

The bench trial began on March 27, 2017. Elec. Clerk's Notes, ECF No. 148. On April 4, 2017, after four days of trial, Abhai filed a motion to amend its pretrial memorandum to include eight new trial exhibits. Def.'s Mot. Amend Pretrial Mem., ECF No. 153; Def.'s Mem. Supp. Mot. Amend Pretrial Mem., ECF No. 154. The exhibits purported to show that the dissolution tests reported by Abhai on its product were performed incorrectly and the data was invalid. Def.'s Mem. Supp. Mot. Amend Pretrial Mem. 1. The Court held a hearing on the motion on April 4, 2017. Elec. Clerk's Notes, ECF No. 157. The Court, after hearing from counsel, suspended the proceedings for 90 days and entered an order requiring full discovery on the incorrect data and tests. Id. The fifth day of trial resumed on September 5, 2017. Elec. Clerk's Notes, ECF No. 282. The ninth and final day of trial was on September 15, 2017. Elec. Clerk's Notes, ECF No. 328. Closing arguments were held on October 18, 2017. Elec. Clerk's Notes, ECF No. 336. The Court now makes the following findings of fact and rulings of law.

II. FINDINGS OF FACT

A. The Parties

Shire LLC is a limited liability company located in Florence, Kentucky. Am. Joint Pretrial Mem. ("Admitted Facts") ¶ 1, ECF No. 139. Shire LLC is a direct, wholly-owned subsidiary of Shire US Inc., a New Jersey corporation whose

principal place of business is in Lexington, Massachusetts. Id. at ¶ 3; Compl. ¶ 3. Shire LLC is the owner and assignee of the '096 and '148 Patents. Admitted Facts ¶ 2. Shire Development LLC, an affiliate of Shire, is the holder of the New Drug Application ("NDA") No. 21-303, for delayed-release capsules containing dextroamphetamine sulfate, dextroamphetamine saccharate, amphetamine aspartate monohydrate, and amphetamine sulfate. Id. at ¶ 15. Shire markets this drug under the name Adderall XR. Id. at ¶ 16. Adderall XR is marketed for the treatment of Attention-Deficit/Hyperactivity Disorder ("ADHD"). Id. at ¶ 17. The '096 Patent and the '148 Patent are listed in the FDA's Approved Drug Products with Therapeutic Equivalence Evaluations for Adderall XR. Id. at ¶ 19.

Abhai is a limited liability company located in Saint Augustine, Florida. Id. at ¶ 4. Abhai seeks approval from the FDA to market its Abbreviated New Drug Application No. 207489 ("ANDA Product"). Id. at ¶ 5. Adderall XR is the Reference Listed Drug for Abhai's ANDA Product. Id. at ¶ 7. Abhai's ANDA Product has the same active ingredients and is bioequivalent to Adderall XR. Id. at ¶¶ 8-9.

B. The Patents

The '096 Patent, titled "Oral Pulsed Dose Drug Delivery System," was issued by the United States Patent and Trademark Office ("PTO") on February 1, 2011. Admitted Facts ¶ 20. U.S.

Application No. 11/091,011, later issued as the '096 Patent, was filed with the PTO on March 24, 2005. Id. at ¶ 21. The '096 Patent is a reissue of U.S. Patent No. 6,322,819 (the "'819 Patent'"). Id. at ¶ 22. The '819 Patent was issued by the PTO on November 27, 2001. Id. U.S. Application No. 09/176,542, issued as the '819 Patent, was filed with the PTO on October 21, 1998. Id. at ¶ 23.

The '148 Patent, also titled "Oral Pulsed Dose Drug Delivery System," was issued by the PTO on February 23, 2010. Id. at ¶ 25. U.S. Application No. 11/091 was issued as the '148 Patent. Id. at ¶ 26. The '148 Patent claims priority to PCT/US99/24554, which was filed on October 29, 1999. Id. at ¶ 27. Its PCT Publication Number is WO00/23055 and its PCT Publication Date is April 27, 2000. Id. The '148 Patent is a reissue of U.S. Patent No. 6,605,300 (the "'300 Patent"). Id. at ¶ 28. U.S. Application No. 09/807,462, which led to the '300 Patent, was filed with the PTO on July 19, 2001. Id. at ¶ 29. The '300 Patent is a continuation-in-part of the '819 Patent. Id. at ¶ 30. Beth A. Burnside, Xiaodi Guo, Kimberly Fiske, Richard A. Couch, Rong-Kun Chang, Donald J. Treacy, Charlotte M. McGuiness, and Edward M. Rudnic are listed as inventors of the '096 and '148 Patents. Id. at ¶¶ 24, 31.

C. The Asserted Claims

Shire asserts that Abhai's ANDA Product infringes on Claim 1 of the '096 Patent. Admitted Facts at 1. Shire asserts that Abhai's ANDA Product infringes Claims 1, 11 (as it depends from Claims 1, 2, and 7), and 13 of the '148 Patent. Id. Abhai raises one affirmative defense, asserting that Shire cannot meet its burden of proof to prove that Abhai's ANDA product will infringe any enforceable claims of the '096 and '148 Patents. Def.'s Am. Answer at 6. Abhai advances two counterclaims: (1) Abhai's ANDA Product did not infringe the '096 Patent and it is entitled to a declaration asserting that there is no infringement; and(2) Abhai's ANDA Product did not infringe on the '148 Patent and it is entitled to a declaration asserting that there is no infringement. Id. at ¶¶ 18-29. Shire asserts as an affirmative defense to the counterclaims that Abhai's counterclaims fail to state claims upon which relief can be granted. Counterdefs.' Answer at 7.

D. Shire's Adderall XR

The FDA approved Shire's product, Adderall XR, on October 11, 2001, and it is indicated for the treatment of ADHD. Admitted Facts ¶ 17. Adderall XR is marketed in six dosage strengths: 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, and 30 mg. Id. at ¶ 18. The drug contains a combination of amphetamine sulfate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and dextroamphetamine saccharate. Id. at ¶ 15. Adderall XR has

the same active ingredients as Abhai's ANDA Product. Trial Tr. Day 9 at 53:19-22; Admitted Facts ¶ 8. Adderall XR contains two types of drug-containing beads designed to provide a "double-pulsed delivery of amphetamines." Trial Tr. Day 9 at 53:23-54:4; Trial Ex. 61 at 1.

The different dosage strengths of Adderall XR contain "Immediate-Release (IR) pellets" (the "IR Beads") and "Delayed-Release (DR) pellets" (the "DR Beads"). Trial Tr. Day 9 at 54:10-14; Trial Ex. 24 at 48. The IR and DR Beads in Shire's Adderall XR start with a sugar sphere, which is then covered with a drug layer containing dextroamphetamine sulfate, dextroamphetamine saccharate, amphetamine aspartate monohydrate, and amphetamine sulfate, mixed with hydroxypropyl methylcellulose, a binder. Admitted Facts ¶ 15; Trial Tr. Day 9 at 54:15-23; Trial Ex. 24 at 48. This drug layer is covered with a coating of Opadry Beige. Trial Tr. Day 9 at 54:22-24; Trial Ex. 24 at 48. In the DR Beads, the drug layer and Opadry Beige layer are covered with a coating containing Eudragit L30D-55, triethyl citrate, and talc. Trial Tr. Day 9 at 54:21-55:1; Trial Ex. 24 at 48-49. Shire calls this layer the "polymeric layer" or "polymeric coating." Trial Ex. 24 at 48-49, Trial Ex. 365 at 279. Abhai refers to this as the enteric coating. Trial Tr. Day 9 at 56:18-25. The DR Beads in Adderall XR contain the same ingredients as Abhai's ANDA Product. Trial Tr. Day 9 at

55:7-19. They both contain the same enteric coating polymer. Id. The IR Beads in Adderall XR also contain the same ingredients as Abhai's ANDA Product. Trial Tr. Day 9 at 55:2-4.

The DR Beads in Adderall XR are manufactured by covering the IR Beads with the enteric coating. Trial Ex. 365 at 279; Trial Ex. 391 at 3. This is similar to the manufacturing process of DR Beads in Abhai's ANDA Product. Trial Ex. 391 at 3. No other change is made to the IR Beads. Trial Ex. 365 at 279. Shire manufactured its Adderall XR using an 18" Wurster Column in a Glatt GPCG-30 fluid bed processor. Trial Ex. 365 at 279, 282. As part of its NDA, Shire indicated that the commercial batches of Adderall XR sold after product approval would be manufactured using a Glatt GPCG-200 fluid bed processor equipped with a 46" Wurster column. Trial Ex. 365 at 279, 286. The difference is due in part to the fact that the larger commercial batches of Adderall XR require equipment with larger capacity. Trial Ex. 365 at 279.

Shire measured the coating thickness of the polymeric layer in Adderall XR and found it to be an average of 40 microns. Trial Ex. 386 at 3; Trial Tr. Day 9 at 56:23-25.

E. Abahi's ANDA Product

Abhai's ANDA Product is designed to be available in five dosage strengths: 10 mg, 15 mg, 20 mg, 25mg, and 30 mg. Admitted Facts ¶ 32. Each dosage strength contains a

combination of amphetamine sulfate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and dextroamphetamine saccharate. Id.

Abhai's ANDA Product is a capsule filled with two types of beads: IR Beads and DR Beads. Admitted Facts ¶ 38. The IR Beads contain a core particle, which consists of sugar spheres, 30 to 50 mesh, NF white. Trial Tr. Day 8 at 16:25-17:3. The core particle is then surrounded by a drug layer, consisting of four active ingredients and a binder. Id. at 17:5-13. The active ingredients are dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate. Id. at 17:8-12; Trial Ex. 28. Hydroxypropyl methyl cellulose, Methocel E5 Premium LV, acts as the binder. Trial Ex. 28. The drug layer is covered by a seal coating comprised of Opadry Beige YS-1-17274-A. Trial Tr. Day 8 17:13-16; Trial Ex. 28. The IR Beads in all strengths contain the same ingredients. Trial Tr. Day 8 at 17:17-22. The DR Beads contain the same core particle, drug layer, and seal coating as the IR Beads. Id. at 18:6-13. On top of the seal coating in the DR Beads, there is a delayed release coating polymer ("DR Polymer Layer") made up of an acid/methacrylic acid copolymer dispersion (Eudragit L30D55). Id. at 18:13-17. It is plasticized with triethyl citrate and followed by antistatic agents talc and silicon dioxide. Id. at 18:17-19; Trial Ex. 28.

The DR Beads in all strengths contain the same ingredients. Id. at 18:20-24. The DR beads are created by covering IR Beads with the DR Polymer Layer. Trial Ex. 26 at 36.

F. Dissolution Testing and the FDA-Recommended Method Used by Abhai

Using an in vitro dissolution method, Abhai tested all strengths of its ANDA Product to determine the amount of drug release at different time points. Trial Exs. 11 at 23; 10 at 5; 9 at 3, 8. The method used is recommended by the FDA for Adderall XR and any generic equivalent. Trial Ex. 8 at 1; Trial Tr. Day 2 at 5:12-21; Trial Tr. Day 5 at 14:10-24; Trial Tr. Day 8 at 25:16-26:1. The method includes: (1) placing capsules in the vessels of an apparatus called USP Apparatus II (commonly known as a "paddle apparatus") and stirring the paddle at 50 rpm; (2) using 750 milliliters of dilute hydrochloric acid (with a pH of 1.1) for the first two hours of testing; (3) after two hours, adding 200 milliliters of 200 mM phosphate buffer to bring the pH up to 6.0 for the remainder of the test (for a total volume of 950 milliliters); and (4) sampling the drug release at 0.5, 1, 2, 3, and 4 hours. Trial Tr. Day 5 at 14:25–15:4, 16:16–17:5; Trial Tr. Day 8 at 26:4–21; Trial Tr. Day 2 at 7:5–19; Trial Ex. 8 at 1.

The FDA-recommended two-stage test attempts to replicate the conditions under which a product similar to Adderall XR or

Abhai's ANDA Product performs in the body. Trial Tr. Day 8 at 30:2-13; Trial Tr. Day 1 at 125:10-19. The pH of 1.1 in the first stage of the FDA-recommended test simulates the lower end of the observed pH in the stomach. Trial Tr. Day 1 at 66:14-18; Trial Tr. Day 8 at 27:7-11; Trial Tr. Day 1 at 117:21-22. The IR Beads in Abhai's ANDA Product will release their active ingredients when they hit the stomach. Trial Tr. Day 1 at 117:14-17. The DR Beads will leave the stomach and travel into the small intestine, where they will release their active ingredients. Id. at 117:17-21. The higher pH of 6.0 used in the second stage of the dissolution tests simulates the pH in the upper small intestine. Trial Tr. Day 1 at 66:19–21, 117:23–24; Trial Tr. Day 8 at 27:12–16; Trial Ex. 12 at 6; Namburi 2016 Dep. 81:6-16. Switching the pH levels at two hours simulates the initiation of the "delayed pulsed enteric release" in Claim 1 of the '096 Patent. Trial Tr. Day 9 at 25:5–15. This is point at which the DR Beads move from the stomach to the intestines. Id. The FDA-recommended two-stage test is two hours at the pH 6.0 stage because it resembles the approximate transit time through the upper part of the small intestine. Trial Tr. Day 8 at 28:15–19, 29:22–30:1; Trial Ex. 18 at 5 (fig. 2).

The USP II (Paddle) apparatus used in the FDA-recommended two-stage test has six vessels. Trial Tr. Day 5 at 16:12–15.

At specific times, aliquots of the dissolution medium are removed and analyzed to determine the amount of drug released from the formulation. Trial Tr. Day 5 at 20:17–21:1 (discussing sampling); Trial Ex. 319 (Lab Notebook 3004) at 8, 11, 14, 18, 27.

Shen Yung Luk, Ph.D. ("Dr. Luk") performed dissolution tests on Abhai's ANDA Product for Shire.[1] Dr. Luk used high performance liquid chromatography ("HPLC") with ultraviolet light absorption spectroscopy to analyze the dissolution media and determine the amount of drug release from the formulation. Trial Tr. Day 5 at 13:15–22, 23:22–25. This is a common method used in the pharmaceutical industry. Id. at 23:23-25. Ultraviolet light absorption spectroscopy measures the amount of light absorbed by a solution. Trial Tr. Day 5 at 25:10–16. The measurements obtained using the ultraviolet light absorption spectroscopy method are compared against solutions of known concentration to calculate the concentration of the compound

[1] Dr. Luk is the Chief Scientific Officer of Juniper Pharma. Trial Tr. Day 1 at 31:7-8. Dr. Luk's experience and background includes research in the fields of polymer science, fine chemicals, and pharmaceutical materials analysis. Id. at 31:24-34:19. In the last twelve years, he as investigated the analysis of complex pharmaceutical products. Trial Ex. 41.

Dr. Luk testified about the coating thickness elements of the '148 Patent and about the in vitro dissolution testing he performed on Abhai's ANDA Product in October of 2016. Trial Tr. Day 1 at 35:10-16. He also testified about additional in vitro dissolution testing he performed on Abhai's ANDA Product again in May of 2016. Trial Tr. Day 5 at 12:20-13:4.

dissolved. Id. HPLC is used with ultraviolet light absorption spectroscopy to separate a compound from any other substances in the sample. Trial Tr. Day 5 at 13:15–22. The separation occurs when the sample solution is passed over a tube or "column" containing fine particles, to which the different compounds in the solution adsorb (stick to) in varying degrees. Trial Tr. Day 5 at 23:22–24:10. Liquid ("eluent") is passed through the column and extracts different compounds from the column. Id. Due to the differences in adsorption, each compound is drawn through the column at a different and characteristic time (otherwise known as the retention time), allowing each compound to be measured separately. Id. The output from the HPLC and UV analysis is a plot of UV light absorbance versus time called a chromatogram. Id. at 25:8–18; Luk Supp. Report ¶¶ 26-28Each peak corresponds to different compounds. Id. The height or area of a resulting peak is measured, and it is proportional to the amount of material in the sample. Trial Tr. Day 5 at 27:21–22; Trial Ex. 320.

G. Stability Dissolution Testing on Abhai's ANDA Product

Abhai reported dissolution data over the proposed shelf life of its ANDA Product, for each of its five dosage strengths. Trial Ex. 130 at 43, 46, 50, 54, 57, 60, 64, 67. Abhai is seeking an expiration date for its ANDA Product of 24 months, based on the stability data generated for dextroamphetamine

saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate and amphetamine sulfate extended-release capsules. Trial Ex. 131 at 2; 192 at 1. Abhai conducted various testings, including dissolution testing, to support its proposed expiration date. Trial Exs. 130, 240. Abhai is representing to the FDA, based on the stability testing on its ANDA Product, that a person can take its ANDA Product effectively up until 24 months. Trial Tr. Day 2 at 96:7-10.

1. Original, Now-Repudiated, Stability Testing in Abhai's ANDA Product

Abhai tested its ANDA Product at seven sample ages (initial, three months, six months, nine months, twelve months, eighteen months, and twenty-four months) and at five sample times (0.5 hours, one hour, two hours, three hours, four hours). Trial. Ex. 130 at 43, 46, 50, 54, 57, 60, 64, 67. The following batches were tested: D0482 (10 mg), D0537 (15 mg), D0480 (20 mg), D0541 (25 mg), and D0449 (30 mg). Id. These were the same batches used in the batch dissolution testing. See Trial Exs. 9 at 3, 8; 10 at 5, 13; 11 at 23. At the time of the March trial, no 24 month stability dissolution testing had been conducted on the 15 mg and 25 mg strengths of Abhai's ANDA Product. Trial Ex. 130. For the following strengths, 10 mg, 20 mg, and 30 mg, 24 month stability dissolution testing was conducted but only

the 2-hour and 3-hour sample times were recorded. Trial Ex. 130 at 46, 57, and 67.

2. Errors in Original Stability Testing on Abhai's ANDA Product

After a Rule 30(b)(6) deposition of Abhai, conducted on October 14, 2016, Abhai discovered that it incorrectly performed its 18 month dissolution test for the 15 mg and 25 mg sample dosage, and it incorrectly performed its 24 month dissolution test for the 10, 20, and 30 mg sample dosage for its ANDA Product. Def's Mem. Supp. Mot. Amend Pretrial Mem. 5; Trial Ex. 240 at 4, 6, 8, 10, 18, 20, 22, 24, 32, 34; Trial Tr. Day 9 at 13:18-14:1. Abhai conducted its original 18-month stability testing on the 15 mg strength from May 25 to May 31, 2016. Trial Ex. 225 at 3. Abhai conducted its original 18 month stability testing on the 25 mg strength from May 25 to May 31, 2016. Trial Ex. 226 at 3. Abhai conducted its original 24 month stability dissolution testing on the 30 mg strength from March 29 to April 4, 2016. Trial Ex. 230 at 36. Abhai conducted its original 24 month stability dissolution testing on the 10 mg strength on April 6, 2016. Trial Ex. 227 at 36. Abhai conducted its original 24 month stability dissolution testing on the 20 mg strength on April 5, 2016. Trial Ex. 229 at 55.

Five out of the thirty-three sets of dissolution testing completed prior to the discovery of the incorrect testing were performed incorrectly. Trial Tr. Day 6 at 126:24-130:20. The original 24 month dissolution test for the 10, 20, and 30 mg strengths and 18 month dissolution test for the 15 and 25 mg strengths were performed incorrectly. Trial Tr. Day 9 13:18-14:1; Trial Ex. 220 at 9-12. Technicians collected samples from the dissolution medium after the ANDA Product had been in the buffer solution (pH 6.0) for three hours (5 hours after testing began), instead of one hour (3 hours after testing began). Id.

After an investigation of the testing was conducted, Abhai determined that "poor method clarity" was the "root cause" of the testing errors. Trial Tr. Day 9 at 32:19-22; Trial Ex. 220 at 9-10. The 30 mg strength had been tested using Finished Product Test Method MOA No. 142, Rev No. 05. Trial Ex. 220 at 9. The analysts used similar testing methods for the 10 mg, 15 mg, 20 mg, and 25 mg, dosage strengths. Id. at 11. Shorter testing durations comprised another part of the testing error. Id. Samples were also taken later than called for in the revised stability dissolution method: at five hours, instead of three. Trial Tr. Day 9 at 34:3-9. The mistakes made in Abhai's stability dissolution testing indicate that neither the analysts nor their supervisors understood the FDA-recommended two-stage dissolution method. Trial Tr. Day 9 at 38:18-39:5. Abhai

revised its dissolution procedure for each strength of its ANDA Product following the investigation. Trial Ex. 220 at 11. The revised test methods are dated October 25, 2016. Trial Ex. 220 at 18-27.

3. Revised Stability Testing on Abhai's ANDA Product

The 15 mg strength was manufactured in August 2014. Trial Ex. 240 at 8; Trial Ex. 130 at 50. Re-testing of the 15 mg strength at the "18-month" storage age was conducted from November 7 to November 9, 2016. Trial Ex. 225 at 14. The 15 mg samples were 27 months old at the time. Trial Tr. Day 9 at 14:16-20. The 15 mg samples were tested for the "24 month" storage age at the same time they were re-tested for the 18-month storage age. Trial Ex. 225 at 14.

The 25 mg strength was originally manufactured in October 2014. Trial Ex. 240 at 22; Trial Ex. 130 at 60. Re-testing of the 25 mg strength for the "18-month" storage age was conducted from November 8 to November 9, 2016. Trial Ex. 212 at 3. The 25 mg samples were 25 months old at the time of re-testing. Trial Tr. Day 9 at 14:16-20. The 25 mg samples were tested for the "24-month" storage age at the same time they were re-tested for the "18-month" storage age. Trial Ex. 212 at 3. The 10 mg strength was manufactured in February 2014. Trial Ex. 240 at 1; Trial Ex. 130 at 43. Retesting of the 10 mg strength for the "24-month" storage age took place from November 7 to November 9,

2016. Trial Ex. 213 at 3. At the time of the retesting, the 10 mg samples were 33 months old. Trial Day 9 at 14:9-15. The original 20 mg strength was manufactured in February 2014. Trial Ex. 240 at 15; Trial Ex. 130 at 54. Retesting of the 20 mg strength for the "24-month" storage age took place from November 8 to November 9, 2016. Trial Ex. 214 at 3. The 20 mg samples were 33 months old at the time of the retesting. Trial Tr. Day 9 at 14:9-15. The 30 mg strength was manufactured in February 2014. Trial Ex. 240 at 29; Trial Ex. 130 at 64. Re-testing of the 30 mg strength for the "24-month" storage age took place from November 8 to November 9, 2016. The 30 mg samples were 33 months old during retesting. Trial Tr. Day 9 at 14:9-15. Results from the re-testing were submitted to FDA as the "18-month" results for the 15 and 25 mg strengths, and as the "24-month" results for the 10, 20, and 30 mg strengths. Trial Ex. 240 at 4, 8, 18, 22, 32.

H. Bioequivalence Studies on Abhai's ANDA Product

Abhai performed and submitted to the FDA three bioequivalence studies of its ANDA Product. Trial Exs. 68-70. As part of the studies, Abhai administered its ANDA Product to adult volunteer subjects. Trial Exs. 68 at 3; 69 at 3; 70 at 3. Blood samples were then taken at specific time points, from times zero to 60 hours. Trial Exs. 68 at 36; 69 at 38; 70 at 35. Abhai analyzed the blood samples to measure the amount of

d-amphetamine and l-amphetamine in the subject's blood plasma. Trial Exs. 68 at 44; 69 at 45; 70 at 43. Abhai then collected and presented the data in its ANDA, along with graphs of the drug concentration data over time. Trial Exs. 71, 75, 81. The clinical studies were performed during the following gastric states: (i) Fasted, meaning the subjected fasted for ten hours prior to dosing; (ii) Fed, meaning the subjects consumed a standardized high-fat breakfast thirty minutes prior to dosing; and (iii) Sprinkled, meaning the subjects consumed one tablespoon of applesauce on which the contents of one capsule were sprinkled. Trial Exs. 68 at 3; 69 at 3; 70 at 3. Twenty-eight individual subjects participated in Abhai's Fasted ANDA Study; 40 individual subjects participated in Abhai's Fed ANDA Study, and 28 individual subjects participated in Abhai's Sprinkled ANDA Study. Trial Exs. 68 at 6; 69 at 7; 70 at 6.

III. RULINGS OF LAW

A. Abhai's Proposed ANDA Product Infringes Claim 1 of the '096 Patent

Claim 1 of the '096 patent includes:

> A pharmaceutical composition for delivery of one or more pharmaceutically active amphetamine salts, comprising: (a) one or more pharmaceutically active amphetamine salts covered with an immediate release coating; and (b) one or more pharmaceutically active amphetamine salts that are covered with an enteric release coating that provides for delayed pulsed enteric release, wherein said enteric release coating releases essentially all of said one or more pharmaceutically active amphetamine salts coated with

> said enteric coating within about 60 minutes after initiation of said delayed pulsed enteric [release] release; wherein the pharmaceutically active amphetamine salts in (a) and (b) comprise mixed amphetamine salts.
>
> Trial Ex. 1 at Claim 1.

Abhai admits that its ANDA Product meets the following limitations of claim 1 of the '096 Patent: (1) "a pharmaceutical composition for delivery of one or more pharmaceutically active amphetamine salts"; (2) "one or more pharmaceutically active amphetamine salts covered with an immediate release coating"; and (3) "the pharmaceutically active amphetamine salts . . . comprise mixed amphetamine salts." Admitted Facts ¶¶ 37, 42, 47; see also Trial Ex. 1 at Claim 1. Abhai only disputes that its ANDA Product meets the following limitations of claim 1: (1) "one or more pharmaceutically active amphetamine salts that are covered with an enteric release coating the provides for delayed pulsed enteric release"; and (2) "wherein said enteric release coating releases essentially all of said one or more pharmaceutically active amphetamine salts coated with said enteric coating within about 60 minutes after initiation of said delayed pulsed enteric release."

The active ingredients in Abhai's ANDA Product are amphetamine sulfate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and dextroamphetamine saccharate. Admitted Facts ¶ 35. These are pharmaceutically active

amphetamine salts. Id. at ¶ 36; Trial Tr. Day 8 at 20:4-9. They are contained in the drug layer of the DR Beads. Trial Tr. Day 8 at 20:12-15; Trial Exs. 26 at 34; 28 at 2; 29 at 1. The drug layer is then covered by a seal coat, then a DR Polymer Layer. Trial Tr. Day 8 at 18:11-19; Trial Ex. 26 at 34. The DR Polymer Layer is made up of Eudragit L30D-55, triethyl citrate, and talc. Trial Tr. Day 8 at 18:13-19; Trial Ex. 26 at 28. Eudragit L30D-55 is used for the enteric coating. Trial Tr. Day 8 at 21:1-5; Trial Exs. 26 at 38; 32 at 22; 26 at 39; 2 at 10:59-11:1. According to the '096 Patent, enteric polymers include Eudragit L30D-55 and can be used in enteric coatings. Trial Ex. 1 at 17.

The purpose of the enteric coating is to prevent release of the drug in the stomach, while still ensuring that drug release from the dosage form will occur at some point in the digestive tract distal to the stomach. Trial Exs. 5 at 36; 6 at 13. Eudragit L30D-55 is designed to delay release of active ingredients until the pH of gastric juices reaches above 5.5, indicative of the small intestine. Trial Ex. 15 at 6; Trial Tr. Day 8 at 19:20-20:1, 28:6-14; Trial Ex. 12 at 6; Namburi 2016 Dep. 80:9-15, 81:21-24.

The Eudragit L30D-55 in Abhai's ANDA Product is manufactured by Evonik. Trial Ex. 30 at 32. Evonik describes Eudragit L30D-55 as an "effective and stable enteric coating[]

with a fast dissolution in the upper Bowel." Trial Ex. 7 at 1. During his deposition, Ranga Namburi, Ph.D. ("Dr. Namburi")[2] admitted that the Eudragit L30D-55 in Abhai's ANDA Product was used as an enteric coating. Namburi 2016 Dep. 114:12-15. Therefore, the DR Polymer Layer in Abhai's ANDA Product, comprising Eudragit L30D-55, constitutes an "enteric release coating." Trial Tr. Day 8 at 22:12-14; Trial Ex. 1 at Claim 1. This "enteric release coating" covers the one or more pharmaceutically active amphetamine salts in the DR Beads of Abhai's ANDA Product. Trial Tr. Day 8 at 22:17-22.

The parties agree that "delayed pulsed enteric release" as used in the patent means "rapid and complete release of drug (after a first dose by immediate release) designed to be delayed until the drug has passed through the stomach into the intestines." Am. Joint Claim Construction Statement at A-1, ECF No. 77. Testifying for Shire, Jennifer Dressman, Ph.D. ("Dr.

[2] Dr. Namburi, Abhai's 30(b)(6) witness and the director of research and development at KVK Tech, Inc. ("KVK"), testified by deposition about the formulation and development of Abhai's ANDA Product, KVK's discovery of the errors in Abhai's ANDA Product, and his knowledge of the issues and arguments in the litigation. Namburi 2016 Dep. 6:8-230:20. KVK is a U.S.-based manufacturer of high quality generic pharmaceuticals and the contract development partner for Abhai. Trial Tr. Day 7 at 46:12-13; 47:11. KVK does the initial development of the product and when and if the product becomes commercialized, KVK handles all the manufacturing of the product. Id. at 47:11-14.

Dressman")[3] explained that she applied a standard for complete release that required release of 75-80% from the enteric coated dosage form, based on guidance from the FDA and chapters from the U.S. Pharmacopeia ("USP"), as well as the specifications and claims of the asserted patents. Trial Tr. Day 8 at 31:2-8; Trial Exs. 5, 19, 21. The FDA allows manufacturers to end sampling from their dissolution testing after 80% drug release. Trial Ex. 5 at 10. This threshold is applied to dissolution testing of enteric-coated dosage forms. Trial Ex. 5 at 35-36;

[3] Dr. Dressman is a Professor of Pharmaceutical Technology and the Director of the Institute of Pharmaceutical Technology at the Johann Wolfgang Goethe University in Frankfurt, Germany. Trial. Tr. Day 8 at 4:24-5:3. Dr. Dressman has taught and written on a variety of subjects concerning pharmaceutics, including the design, composition, manufacture, and evaluation of pharmaceutical dosage forms, including coated dosage forms, dissolution testing, prediction of oral drug absorption, and in vitro in vivo correlation. Trial Tr. Day 8 at 6:10-15, 9:4-10:6.

Dr. Dressman testified to the elements in the '096 and '148 Patents. Trial Tr. Day 8 at 11:10-12:3. The elements of Claim 1 of the '096 Patent state: "One or more pharmaceutically active amphetamine salts that are covered with an enteric release coating," and a "delayed pulsed enteric release," and the element "wherein said enteric release coating releases essentially all of said one or more pharmaceutically active amphetamines salts coated with said enteric coating within about 60 minutes after initiation of said delayed pulsed enteric release." Id. at 11:16-23. The element of Claims 1, 11, and 13 of the '148 Patent states: "A delayed enteric release dosage form that provides delayed release upon oral administration to said patient." Id. at 11:24-12:3. Dr. Dressman also testified that Dr. Luk's dissolution testing results were more reliable than Abhai's and should therefore be credited. Id. at 13:17-20.

Trial Tr. Day 8 at 31:21-32:24. This suggests that complete release has occurred. Trial Tr. Day 8 at 32:25-34:1.

The FDA's guidance, provided to the PTO during prosecution of the '096 Patent, anticipates that enteric-coated dosage forms need to release 80% of the drug in order for the release to be considered "complete" as required in "delayed pulsed enteric release." Trial Tr. Day 8 at 31:18-20, 32:25-33:13; Trial Ex. 3 at 3168-3219. According to the USP, 75-80% of the label claim is the typical acceptance value for dissolution specifications. Trial Tr. Day 8 at 35:16-36:1; Trial Ex. 19 at 8. This represents an essentially complete release of the drug. Id. Therefore, the FDA and USP guidance confirm that "complete" release means that at least 75-80% of the enteric coated drug has been released.

In its Claim Construction Order, the Court construed the term "a delayed enteric release dosage form that provides delayed release upon oral administration," as "a dosage form that provides rapid and complete release of drug (after a first dose by immediate release) intended to be delayed until the drug has passed through the stomach into the intestines after oral administration." Claim Construction Order at 13, ECF No. 85. The term occurs in Claims 1, 11, and 13 of the '148 patent and parallels the construction of "delayed pulsed enteric release" in the '096 Patent. The Court specifically noted that Figure 6

of the ’096 and ’148 Patents supports a pulsed release invention. Claim Construction Order at 11–12. The Court rejected Shire’s argument that Figure 6 supported a sustained release invention in the ’148 Patent. Claim Construction Order at 11–12. Therefore, Figure 6 of the asserted patents illustrates the rapid and complete (“pulsed”) release claimed in both the ’096 and ’148 Patents. Claim Construction Order at 11–12.

The ‘096 and ‘148 Patents describe Figure 6 as “illustrat[ing] the drug release profile of coated pellets described in Example 4 which exemplifies the delayed release components of the present invention.” Trial Ex. 1 at 6:49–52; Trial Tr. Day 8 at 41:18–24. Example 4 of the ‘096 Patent describes the formulation for enteric-coated mixed amphetamine salts pellets. Trial Ex. 1 at 11:45–12:13. Figure 6 shows a staged in vitro dissolution test where the pellets were exposed to pH 1.1 for two hours. See, e.g., Trial Ex. 1 at Fig. 6; Trial Ex. 1 at 11:45–12:13; 6:49-52; 11:45–12:13. The pH was then increased to pH 6.0 for one hour to represent the movement of the dosage form from the stomach into the intestines, initiating the delayed enteric release. Trial Tr. Day 8 at 41:25-42:5. The pH was increased to 7.5 for the remainder of the test. Trial Ex. 1 at Fig. 6; id. at 11:45-12:13. The enteric release continues for at least six hours after it is

initiated, and over time about 80% of the enteric-coated drug is released. Trial Ex. 1 at Fig. 6; Trial Tr. Day 8 at 42:9-16. Therefore, a "rapid and complete" release according to the construction for "delayed pulsed enteric release" may take as long as six hours and is consistent with release of about 80% of the enteric-coated drug. Trial Ex. 1 at Fig. 6; Claim Construction Order at 11-12. The term "delayed pulsed enteric release" does not require release of 100% of the drug within about 30-60 minutes. Trial Tr. Day 8 at 38:6-13, 40:13-17.

Claim 13 of the '096 Patent, which claims a "protective layer over the enteric release coating," also requires that the composition provide a "rapid and complete release," regardless of the protective layer, because the construction of "delayed pulsed enteric release," which is part of Claim 13, requires "rapid and complete release." Trial Tr. Day 6 at 40:9-18; Trial Tr. Day 7 at 23:19-24:4; Trial Ex. 1 at Claim 13. Abhai claimed that Figure 6 is an embodiment of Claim 20 of the '148 Patent, which requires "a protective coating layer." Trial Tr. Day 7 at 25:10–14; Trial Ex. 2 at Claim 20. Claim 20 is a dependent claim that depends from Claim 1. Trial Ex. 2 at Claim 20. Claim 1 requires "a delayed enteric release dosage form that provides delayed release upon oral administration," and the Court has construed it to include a "rapid and complete" release. Trial Tr. Day 7 at 26:12–21; Trial Ex. 2 at Claim 1.

Therefore, as a dependent claim, Claim 20 of the ’148 Patent requires a rapid and complete release. Thus, by admitting that Figure 6 embodies Claim 20, Abhai has admitted that “rapid and complete” release is shown in Figure 6. The Patents’ specifications and Abhai’s expert Diane Burgess, Ph.D. (“Dr. Burgess”)[4] recognize that the recited “protective layer” can provide for rapid and complete release. Trial Tr. Day 6 at 40:22–25;; Trial Ex. 2 at 5:44–46.

The data submitted at trial shows rapid and complete release. The parties first “normalize” the data to measure the amount of drugs released from the DR Beads. Trial Tr. Day 6 at 14:23-15:9. “Normalization” refers to the calculations that experts from both parties performed to estimate the amount of amphetamine in the DR Beads and the percent released from those beads, while excluding the amount of amphetamine released from the IR Beads. Id.

In order to calculate the amount of drug released from the DR Beads in the first hour of exposure to pH 6.0, Dr. Dressman first divided the amount of drug released after the first hour in pH 6.0 by the amount of the label claim released over the

[4] Dr. Burgess is a Professor of Pharmaceutics at the University of Connecticut. Trial Tr. Day 1 at 108:18-109:7. She testified concerning Abhai’s alleged non-infringement of the ’096 and ’148 Patents. See generally Trial Tr. Day 1 at 106:7–127:4, Day 2 at 5:3–124:20, Day 5 at 124:23– 126:13, Day 6 at 5:4–168:2, Day 7 at 4:9–39:4.

full two hours in pH 6.0. Trial Tr. Day 9 at 6:17–7:17. The results were multiplied by 100% to calculate the percentage. Id. This is referred to as "4-hour normalization." Trial Tr. Day 9 at 5:22–6:1; Trial Tr. Day 6 at 63:5–6.

Both parties' experts use the "Assay Normalization" when dissolution data is not available at the four-hour mark. Trial Ex. 399; Trial Tr. Day 9 at 51:19-20. An assay is a method of determining the percentage of label claim or the amount of drug present (on average) in a given batch, compared to the amount of drug listed on the label. Trial Tr. Day 1 at 124:14–19. The assay value is used to calculate the amount of drug released from the DR Beads in the first hour of exposure to pH 6.0. See generally Trial Ex. 399. This type of normalization method assumes that the assay amount for a given batch of product is the actual amount of drug contained in each capsule of that product. Trial Tr. Day 2 at 13:25–14:2

Dr. Burgess also used a different of four-hour normalization method where time points subsequent to three hours indicate that a plateau has been reached. She then chose the highest release value observed and treated it as the capsule content. Trial Tr. Day 6 at 17:22–18:10.

"Label claim normalization" is also used when no four-hour dissolution value is available. Trial Tr. Day 9 at 20:1-3. Using this method, normalization is achieved by dividing the

amount of release in the first hour of exposure to pH 6.0 by 50%, which represents the expected amount of amphetamine in the DR Beads. Trial Tr. Day 9 at 19:24–20:4; Trial Ex. 394.

The most appropriate method to normalize release data from extended release mixed amphetamine salt dosage forms is to use the four-hour normalization method. Trial Tr. Day 9 at 8:14–20. Observed release data after four hours shows that a drug release plateau is reached at the beginning of the fourth hour. Trial Tr. Day 9 at 7:20–8:21. This means that drug release will be complete by the end of the fourth hour. Id. The result of Dr. Dressman's four-hour normalization and Dr. Burgess's "highest percentage release" normalization methods thus will be approximately the same. Id.; Trial Tr. Day 6 at 18:1–10, 63:4–10.

In May of 2017, Dr. Luk performed dissolution testing on each strength of Abhai's ANDA Product. Trial Tr. Day 5 at 12:24-13:4. His testing showed a plateau that began at four hours, which meant that release from the DR Beads in Abhai's ANDA Product had finished after four hours. Trial Tr. Day 9 at 7:20–8:20. Dr. Luk's testing of Abhai's ANDA Product back in October 2016 also showed a drug release plateau starting at four hours. Trial Ex. 199. Shire's testing of NDA batches of Adderall XR also showed a similar amount of release at the end of four hours (two hours in pH 6.0) as at the end of five hours.

Trial Exs. 25 at 231, 236, 241; 382 at 34, 39, 44. Teva's testing of Adderall XR in 2006 also showed a similar amount of drug release at four hours (two hours in pH 6.0) as at 4.5 hours. Trial Ex. 358 at 26, 30, 34, 38, 42, 46; Trial Tr. Day 9 at 43:6-10. Andrx's testing of Adderall XR in 2007 similarly showed a plateau in drug release between four hours (two hours in pH 6.0) and 6 hours. Trial Ex. 390 at 1, 2, 3, 4, 5, 6; Trial Tr. Day 9 at 44:11-17.

Abhai claims that the four-hour normalization is not accurate because, after conducting a dissolution test on the 20 and 30 mg strengths of Abhai's ANDA Product, with the second stage conducted at a pH of 6.8 instead of the FDA-recommended pH of 6.0, the total release observed was higher than the release observed in other tests conducted according to the FDA-recommended two stage method. Trial Tr. Day 6 at 92:5-93:1. Therefore, Abhai argues, there must have been additional, unreleased drugs in the capsules that were tested according to the FDA-recommended method. Trial Tr. Day 6 at 92:5-93:1. The pH 6.8 testing, however, was conducted on different capsules than those used in the testing that Dr. Luk performed according to the FDA-recommended two-stage method, and the contents of each individual capsule varied substantially. Trial Tr. Day 5 at 111:13–112:5. As Dr. Dressman explained, it is not a fair comparison, and it is misleading to compare the two sets of data

because the content of each capsule was different. Trial Tr. Day 5 at 103:20-104:18.

Abhai's testing of its ANDA Product shows rapid and complete release. Abhai tested 12 capsules of each strength of its ANDA Product using the FDA's recommended in vitro dissolution method. Trial Exs. 9 at 3, 8; 10 at 5, 13; 11 at 23. Applying four-hour normalization to Abhai's batch dissolution data, the results showed rapid and complete release from the DR Beads. Trial Tr. Day 9 at 12:14-17. For the 10 mg strength, the percent release was 84.9%; for the 15 mg strength, the percent release was 85.7%; for the 20 mg strength, the percent release was 76.1%; for the 25 mg strength, the percent release was 87.5%; and for the 30 mg strength, the percent release was 73.8%. Trial Exs. 26 at 98, 89, 80; 32 at 55, 64.

Abhai's retest of its ANDA Product also shows rapid and complete release. Abhai normalized its results using the four-hour, assay value, and label-claim normalization methods. Trial Exs. 394; 240 at 1, 4, 8, 11, 15, 18, 22, 25, 29, 32; Trial Tr. Day 9 at 19:19-24:4, 22:6-15. Under these methods, Abhai obtained many values exceeding both 75% and 80%, and over 90% in some instances. Trial Tr. Day 9 at 19:19-20:4, 20:16-22:1, 22:6-15, 22:25-23:4; Trial Exs. 330; 240 at 1, 4, 8, 11, 15, 18, 22, 25, 29, 32; 394. These numbers show rapid and complete

release of the drug from the DR Beads over the first hour of exposure to pH 6.0. Trial Tr. Day 9 at 22:2-5, 23:5-9.

Dr. Luk's dissolution testing also shows rapid and complete release. Trial Tr. Day 9 at 10:22-25. In May of 2017, Dr. Luk performed dissolution testing on six capsules of all strengths of Abhai's ANDA Product using steel sinkers conforming to the USP dissolution monograph specification. Trial Ex. 319 at 3, 7, 10, 13, 17, 26; Trial Tr. Day 5 at 37:17-24, 39:18-40:1; Trial Ex. 20 at 4. Dr. Luk placed the capsules in a dissolution media, first prepared on May 12, 2017. Trial Ex. 319 at 1. He also used a USP II (Paddle) dissolution apparatus, set to 50 rmp. Trial Tr. Day 5 at 16:12-15, 61:1-24. The dissolution bath was started at pH 1.1, and one capsule was added. Trial Tr. Day 5 at 18:25–19:12; Trial Ex. 319 (Lab Notebook 3004) at 8, 11, 14, 18, 27. Capsules were then added at intervals of five minutes. Trial Tr. Day 5 at 19:13–19. A five-minute interval was used to allow sufficient time for the addition of the 200 mM phosphate buffer and adjustment of pH to 6.0 at the two-hour time point. Trial Tr. Day 5 at 20:4–14, 22:2-4. The testing mirrored Abhai's dissolution testing procedures. Trial Tr. Day 5 at 21:7-9; Trial Exs. 40 at 18; 284 at 17.

Dr. Luk took samples at additional time points beyond those required by the FDA prior to the pH being adjusted to 6.0, and then again after it was adjusted. Trial Tr. Day 5 at 23:2-7.

The results from each sample collected were compared against the results from a standard solution with a known concentration of amphetamine. Trial Tr. Day 5 at 25:8-16.

Dr. Luk conducted two dissolution tests on Abhai's ANDA Product. Trial Ex. 392. His first test, conducted on October 2016, showed rapid and complete release from the DR Beads for the 20 mg and 30 mg strengths. Trial Tr. Day 1 at 57:11-16, 64:15-20; Trial Exs. 195; 8 at 1. Over 90% of the drug from the DR Beads was released after the first hour of exposure to pH 6.0. Trial Tr. Day 9 at 10:22-11:5. It is of no consequence that the samples tested by Dr. Luk were beyond the 2-month shelf life because all the testing performed met the dissolution specifications provided in Abhai's ANDA Product. Trial Tr. Day 2 at 109:4-110:22; Trial Exs. 199; 130 at 57-59, 67-69.

Dr. Luk's second test, performed on May of 2017 on all dosage strengths, showed rapid and complete release of the drug from the DR Beads for the first hour of exposure to pH 6.0. Trial Ex. 392. He obtained values for percent release of drug from the DR Beads that exceeded 90% for the first hour of exposure to pH 6.0 for each strength. Trial Tr. Day 9 at 11:2-5. Using sinkers to perform the dissolution testing did not distort the results because industry standard dictates that a sinker should be used whenever the dosage form would float without the use of the sinker, and Abhai's ANDA Product floats

when placed in dissolution media. Trial Tr. Day 5 at 32:18-33:6, 33:14-18, 34:2-4, 41:8-20; 42:1-6, 44:22-45:7; Trial Exs. 20 at 4; 324 at 7; 318 at 11; 289 at 3; 306 at ¶ 4.

Moreover, using HPLC instead of ultra-high performance liquid chromatography ("UPLC") as the analytical method when performing dissolution testing did not affect the results because both are based on the same process, and by using HPLC, Dr. Luk used the same methods of USP. Trial Tr. Day 5 at 13:15-22; 51:23-52:2; 52:22-24. Using a different dissolution media did not have an effect on the analysis. Trial Tr. Day 5 at 49:6-18.

Abhai's dissolution testing results are unreliable. Abhai conducted dissolution testing on commercial batches of Adderall XR, in accordance with the FDA-recommended testing methods for its ANDA submission. Trial Exs. 26, at 80, 89, 98; 32 at 55, 64; 11 at 15, 19; Trial Tr. Day 9 at 39:9-15, 40:20-23. Other generic drug companies also conducted dissolution testing on commercial batches of Adderall XR for their own submissions. Trial Tr. Day 9 at 42:18-46:23. When compared to the dissolution rates obtained by the other generic drug companies testing Adderall XR, Abhai's dissolution rates were lower. Trial Tr. Day 9 at 46:13-23, 48:12-18; Trial Ex. 397. Abhai also obtained lower dissolution testing results than Shire when testing Adderall XR. Compare Trial Exs. 396; 26 at 98, 89, 80;

32 at 55, 64; 30 at 6; 121 at 6, with Trial Exs. 25 at 231, 234, 236, 239, 241; 382 at 31, 34, 36, 39, 41, 44. When applying the four-hour and assay normalization to Abhai's dissolution testing results for Adderall XR, the normalized percent release of drugs from the DR Beads during the first hour of exposure to pH 6.0 is as follows: 85.4% and 90.9% for the 10 mg strength; 83.7% and 86.1% for the 15 mg strength; 79.2% and 82.1% for the 20 mg strength; 81.3% and 81.3% for the 25 mg strength; and 76.1% and 73.5% for the 30 mg strength. Trial Exs. 396; 26 at 98, 89, 80; 32 at 55, 64; 30 at 6; 121 at 6. When applying the four-hour and assay normalization to Shire's dissolution testing results for Adderall XR, the normalized percent release of drugs from the DR Beads during the first hour of exposure to pH 6.0 is as follows: 94.4% and 104.9% for the 10 mg strength; 96.2% and 106.2% for the 15 mg strength; 88.7% and 99.8% for the 20 mg strength; 96.2% and 104.6% for the 25 mg strength; and 89.6% and 87.4% for the 30 mg strength. Trial Exs. 25 at 231, 234, 236, 239, 241; 382 at 31, 34, 36, 39, 41, 44.

Abhai's ANDA Product contains an enteric release coating that releases "essentially all of said one or more pharmaceutically active amphetamine salts coated with said enteric coating within about 60 minutes after initiation of said delayed pulsed enteric release," as stated in the '096 Patent. Trial Ex. 1 at 12:62-65. Dissolution and stability data from

Abhai's ANDA product, as well as Dr. Luk's testing, confirm that within 60 minutes after the initiation of the delayed pulsed enteric release, essentially all of the amphetamine in the DR Beads of Abhai's ANDA Product is released, and each strength exhibits complete release from the DR Beads within 60 minutes. Trial Tr. Day 9 at 25:16-24. Therefore, "essentially all" of the contents of the DR Beads are released within about 60 minutes. Thus Abhai's ANDA Product infringes claim 1 of the '096 Patent.

B. Abhai's ANDA Product Infringes Claims 1, 11, and 13 of the '148 Patent

Claim 1 of the '148 Patent is an independent claim. Trial Ex. 2 at 13:28–55. Claim 11 is a dependent claim that depends from Claim 10, which is a multiple dependent claim depending from Claims 1–4, 6, or 7. Id. at 14:11–18. Shire asserts Claim 11 only as it depends from Claims 1, 2, and 7. Admitted Facts at 1. Claim 13 is a dependent claim that depends from Claim 12. Trial Ex. 2 at 14:46–47.

Claim 1 of the '148 patent includes:

> A pharmaceutical formulation for delivery of a mixture of amphetamine base salts effective to treat ADHD in a human patient comprising: an immediate release dosage form that provides immediate release upon oral administration to said patient; a delayed enteric release dosage form that provides delayed release upon oral administration to said patient; and a pharmaceutically acceptable carrier; wherein said amphetamine base salts comprise dextroamphetamine sulfate, dextroamphetamine saccharate, amphetamine

> aspartate monohydrate and amphetamine sulfate; wherein said pharmaceutical formulation is sufficient to maintain an effective level of amphetamine base salts in the patient over the course of at least 8 hours without further administration of amphetamine base salt, and the peak plasma concentration of amphetamine base salts reached after release of said delayed enteric release dosage form exceeds the peak plasma concentration previously reached after release of said immediate release dosage form; and wherein said pharmaceutical formulation, when containing about a total dose of 20 mg, will produce in a human individual a plasma concentration versus time curve (ng/ml versus hours) having an area under the curve (AUC) of about 467 to about 714 ng hr/ml.

Id. at 13:28-55.

Claim 10 recites: "A formulation of one of claims 1-4, 6 or 7 wherein said delayed enteric release dosage form comprises a coating of a thickness of [at least] greater than 20 μm which comprises dried about 30% (dry substance) aqueous dispersion of an anionic copolymer based on methacrylic acid and acrylic acid ethyl ester, said coating being soluble at a pH of about 5.5 upwards." Id. at 14:10–16. Claim 11 recites: "A formulation of claim 10 wherein said thickness is at least 25 μm." Id. at 14:17-18. Claim 2, which is incorporated into asserted Claim 11 through Claim 10, provides: "A formulation of claim 1 wherein said plasma concentration curve has a maximum concentration (Cmax) of about 22.5 to about 40 ng/ml for about a total dose of 20 mg." Id. at 13:56–58. Claim 7, which is incorporated into asserted Claim 11 through Claim 10, provides: "A formulation of claim 2 wherein Cmax is about 40 ng/ml." Id. at 14:4–5.

Claim 12 provides:

> A pharmaceutical formulation for delivery of a mixture of amphetamine base salts effective to treat ADHD in a human patient comprising: an immediate release dosage form that provides immediate release upon oral administration to said patient; a delayed enteric release dosage form that provides delayed release upon oral administration to said patient, wherein said enteric release dosage form comprises a coating of a thickness of [at least] greater than 20 µm which comprises dried aqueous dispersion of an anionic copolymer based on methacrylic acid and acrylic acid ethyl ester, said coating being soluble at a pH of about 5.5 upwards; and a pharmaceutically acceptable carrier; wherein said amphetamine base salts comprise dextroamphetamine sulfate, dextroamphetamine saccharate, amphetamine aspartate monohydrate and amphetamine sulfate; wherein said pharmaceutical formulation is sufficient to maintain an effective level of amphetamine base salts in the patient over the course of at least 8 hours without further administration of amphetamine base salt, and the peak plasma concentration of amphetamine base salts reached after release of said delayed enteric release dosage form exceeds the peak plasma concentration of said salts previously reached after release of said immediate release dosage form.

Id. at 14:19–45.

Claim 13 provides: "[a] formulation of claim 12 wherein said thickness is at least 25 µm." Id. at 14:46–47. Claim 13 does not contain any limitation relating to AUC or Cmax. Id. at 14:19–47.

Abhai admits that its ANDA Product meets the following limitations of the asserted claims of the '148 Patent: (1) "Abhai admits that its ANDA Product meets the following limitations of claim 1 of the '096 Patent"; (2) "an immediate

release dosage form that provides immediate release upon oral administration to said patient"; (3) "a pharmaceutically acceptable carrier"; (4) "wherein said amphetamine base salts comprise dextroamphetamine sulfate, dextroamphetamine saccharate, amphetamine aspartate monohydrate and amphetamine sulfate"; (5) "a coating . . . which comprises dried about 30% (dry substance) aqueous dispersion of an anionic copolymer based on methacrylic acid and acrylic acid ethyl ester"; and (6) "said coating being soluble at a pH of about 5.5 upwards." Admitted Facts ¶¶ 48-51, 54; Trial Ex. 2 at Claims 1, 10, and 12.

Abhai disagrees that its ANDA Product meets the following limitations in the asserted claims of the '148 Patent: (1) "a delayed enteric release dosage form that provides delayed release upon oral administration to said patient" (Claims 1, 11, and 13); (2) "wherein said pharmaceutical formulation is sufficient to maintain an effective level of amphetamine base salts in the patient over the course of at least 8 hours without further administration of amphetamine base salt" (Claims 1, 12); (3) "the peak plasma concentration of amphetamine base salts reached after release of said delayed enteric release dosage form exceeds the peak plasma concentration previously reached after release of said immediate release dosage form" (Claims 1, 12)"; (4) "will produce in a human individual a plasma concentration versus time curve (ng/ml versus hours) having an

area under the curve (AUC) of about 467 to about 714 ng hr/ml" (Claims 1, 11); (5) "said plasma concentration curve has a maximum concentration (Cmax) of about 22.5 to about 40 ng/ml for about a total dose of 20 mg" (Claim 11); "wherein Cmax is about 40 ng/ml" (Claim 11); and (6) "a thickness of greater than 20 μm" (Claims 10, 12)/ "said thickness is at least 25 μm" (Claims 11, 13). Trial Ex. 2 at Claims 1, 10, 11, 12, 13.

Abhai's ANDA Product contains "a delayed enteric release dosage form that provides delayed release upon oral administration," thus infringing on claims 1, 11 and 13 of the '148 Patent. This Court construed the language "delayed enteric release dosage form that provides delayed release upon oral administration" as "a dosage form that provides rapid and complete release of drug (after a first dose by immediate release) intended to be delayed until the drug has passed through the stomach into the intestines after oral administration." Claim Construction Order at 13. The construction of "delayed pulsed enteric release" and the construction of "a delayed enteric release dosage form that provides delayed release upon oral administration" mirror each other. Trial Tr. Day 9 at 27:3-11; Am. Joint Claim Construction Statement at A-1; Claim Construction Order at 13. Both require a rapid and complete release of the drug from the enteric coated dosage form in Abhai's ANDA Product (the DR Beads), following a

dose by immediate release, that is intended or designed to be delayed until the drug has passed into the intestines. Trial Tr. Day 9 at 27:12–14; Am. Joint Claim Construction Statement at A-1; Claim Construction Order at 13. As stated above, Abhai's ANDA Product has "a delayed enteric release dosage form that provides delayed release upon oral administration." Supra at 30. The term "a delayed enteric release dosage form that provides delayed release upon oral administration" does not require release of 100% of the drug within 30–60 minutes. Trial Tr. Day 8 at 38:6-13; Trial Ex. 2 at Claims 1, 12. There is no requirement that "essentially all" of the drug be released within an hour of exposure to pH 6.0. Trial Tr. Day 9 at 27:15-21. As explained above, Figure 6 in both asserted patents supports a pulsed release invention. Supra at 32.

When applying assay normalization to Abhai's revised stability data, the percent release from the DR Beads after two hours of exposure to pH 6.0 shows rapid and complete release. Trial Exs. 395; 130 at 43, 50, 54, 60, 64; Trial Tr. Day 9 at 28:18-29:2, 30:2-4. At the initial storage age, the percent release from the DR Beads was 100.59% for the 10 mg strength; 96.27% for the 15 mg strength; 93.36% for the 20 mg strength; 96.71% for the 25 mg strength; and 86.42% for the 30 mg strength. Trial Exs. 395; 130 at 43, 50, 54, 60, 64; Trial Tr. Day 9 at 28:18-29:2. For the 3, 6, 9, 12, 18, and 24 months

storage age, the percent values were above 75% for each of the dosage strengths, except for those where the release was not measured. Id. For some of the dosage strengths for some of the sample ages, there is over 95% release from the DR Beads during the first two hours of exposure to pH 6.0, and in some cases 100% release or more. Trial Tr. Day 9 at 29:12–19. Therefore, Abhai's ANDA Product has "a delayed enteric release dosage form that provides delayed release upon oral administration."

Abhai's ANDA Product also meets the "effective level" imitation in claims 1, 11, and 13 of the '148 Patent. The "effective level" limitation of the '148 Patent requires that the pharmaceutical formulation be "sufficient to maintain an effective level of amphetamine base salts in the patient over the course of at least 8 hours without further administration of amphetamine base salt." Trial Ex. 2 at 13:42-45. Abhai's ANDA Product infringes on this claim for the following reasons: (1) Abhai's label demonstrates that its ANDA Product is a long-acting, once-daily product that can be substituted for a twice-daily dosing regimen of Adderall and has been demonstrated to reduce symptoms over the course of at least 8 hours; (2) Abhai's ANDA Product is a therapeutic equivalent of Adderall XR, which has been shown to reduce ADHD symptoms over the course of 8 hours; and (3) Abhai's studies show that its ANDA Product will have a rapid onset of effects that will continue for at least 4

hours after maximum concentration is reached, meaning that the product will reduce ADHD symptoms over the course of at least 8 hours.

Abhai's proposed label for its ANDA Product states that it is an "extended-release" product, with direction to the patient to take the medication "once daily." Trial Ex. 31 at 8; Trial Tr. Day 3 at 8:22-9:6. It also states that those patients who are "taking divided doses of immediate-release" Adderall "may be switched [to Abhai's ANDA Product] at the same total daily dose taken once daily." Trial Ex. 31 at 8; Trial Tr. Day 3 at 9:7-10:3. In its initial form, before Adderall XR came to be, Adderall treatment required multiple doses throughout the day in order to provide relief from ADHD symptoms for at least 8 hours. Trial Ex. 2 at 3:16-40; Trial Tr. Day 2 at 143:22-147:4; Trial Tr. Day 3 at 16:12-18:7 Trial Ex. 86. Therefore, the proposed label demonstrates that one daily dosage of Abhai's ANDA Product would provide the same relief from ADHD symptoms for at least 8 hours, as two dosages of Adderall. The proposed label confirms that Abhai's ANDA Product is created to produce long-lasting effects after it is administered. Trial Ex. 31 at 8; Trial Tr. Day 3 at 9:2-6.

Abhai's ANDA Product is also the therapeutic equivalent to Adderall XR and meets the "effective level" limitation. When submitting its ANDA to the FDA, Abhai stated that "[t]he active

ingredient, indications, including route of administration, dosage form and qualitative composition [of its ANDA Product] are the same as that of Adderall XR." Trial Ex. 145 at 1; Trial Tr. Day 3 at 4:14–5:19. Abhai also requested that FDA designate its product as a "therapeutic equivalen[t]" to Adderall XR and represented that its product "is of the same pharmacological and therapeutic class as that of [Adderall XR] and can be expected to have the same therapeutic effect as [Adderall XR] when administered per label claims." Id. In doing so, Abhai represented to the FDA that its product will have the same duration effect as Adderall XR. Trial Tr. Day 3 at 4:14-5:19.

Abhai's ANDA Product is also bioequivalent to Adderall XR, meaning the two produce plasma concentration versus time curves that are sufficiently equivalent. Trial Tr. Day 3 at 7:5-17; 8:13-18. In its proposed label, Abhai cites to studies, also cited in Adderall XR's label, that report a reduction of ADHD symptoms over the course of at least 8 hours. Trial Ex. 117; Trial Tr. Day 3 at 22:24-23:5. The FDA allows Abhai to cite to those studies without requiring it to perform its own safety and efficacy clinical trials, because the similarity between the pharmacokinetic profiles of the two products means that Abhai's ANDA Product will have the same therapeutic effect as Adderall XR. Trial Ex. 31 at 29-31; Trial Tr. Day 3 at 9:7-10:3. Being therapeutically equivalent means that both products will have

the same duration of efficacy in humans and will be treated interchangeably. Trial Tr. Day 3 at 9:7-10:3, 54:19-55:2.

Abhai cites to a number of studies in its proposed label including James T. McCracken et al., Analog Classroom Assessment of Once-Daily Mixed Amphetamine Formulation, SLI381 (ADDERALL XR), in Children with ADHD, 42 J. Am. Acad. Child Adolesc. Psychiatry, 673-683 (2003) (the "McCracken study"), and Joseph Bierderman et al., A Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study of SLI381 (ADDERALL XR) in Children with Attention-Deficit/Hyperactivity Disorder, 110 Pediatrics, 258-266 (2002) (the "Bierderman study"). Trial Ex. 117; Trial Tr. Day 3 at 22:24-23:5, 51:16-53:17; Trial Ex. 118; see also Trial Exs. 119 at 2, 3, 5-6, 9, 12; 120. The McCracken study stands for the proposition that Adderall XR provides efficacy over the course of the entire day. Trial Tr. Day 3 at 31:14-33:7. Abhai cited the McCracken study in its proposed label without citing any alleged design flaws or issues. Trial Ex. 31 at 30; Trial Tr. Day 3 at 36:7-12. The Bierderman study stands for the proposition that Adderall XR reduces ADHD symptoms over the course of 8 hours. Trial Tr. Day 3 at 46:22-51:15; Trial Ex. 118. The authors state that "SLI381 [Adderall XR] is a safe and effective once-daily dosage form of stimulant medication that lasts throughout the school day and into the early evening"; that "dosing the morning before the child left

for school would ensure protection against ADHD symptoms during and beyond the school day"; and that "the duration of action of SLI381 should allow for pharmacological support of homework activity, after school athletic and social activities, as well as family life." Trial Ex. 118 at 7; Trial Tr. Day 3 at 48:17–50:11. Other studies cited by Abhai in its proposed label indicate that Adderall XR is an effective once-daily treatment, designed to reduce ADHD symptoms over the course of an entire day. Trial Exs. 119 at 2; 120 at 1; Trial Tr. Day 3 at 51:19-53:7; Trial Ex. 31 at 30. Therefore, like Adderall XR, Abhai's ANDA Product reduces ADHD symptoms over the course of 8 hours. Trial Tr. Day 4 at 19:3-22:22.

Abhai argues that these studies are not relevant to the analysis of whether its ANDA Product meets the "effective level limitation" claim because the claim requires the "pharmaceutical formulation" to provide an effective level of amphetamine over the course of 8 hours without the assistance of residual amphetamine in the blood stream, and the studies cited did not account for residual amphetamine in the blood stream. See generally Trial Tr. Day 3 at 150:10-151:4. This argument is without merit. It is contrary to the plain language of the claim, standard clinical practice, and the '148 Patent itself. The plain language of the claim does not contain any wording which requires that the pharmaceutical formulation provide

efficacy over the course of eight hours on the first day of treatment, nor does it contain language that requires efficacy without the aid of residual amphetamine from previous administrations. Trial Ex. 2 at 13:42-45; Trial Tr. Day 3 at 109:17-110:24. Moreover, the recognized practice of dose titration contemplates that the first administration of the product may not provide an optimal effect, and that efficacy may be achieved after administering a higher dosage until "optimal response is obtained, suggesting the first day of administration is negligible." Trial Ex. 138 at 3; Trial Tr. Day 3 at 43:22-44:11, 85:13-23; Trial Tr. Day 4 at 30:23-31:20, 32:7-12. There is nothing in the '148 Patent to suggest that the "effective level of amphetamine" must be achieved on the first day of administration. See Trial Ex. 2 at 21:12; Trial Tr. Day 3 at 109:17-110:24.

Pharmacokinetic data from Abhai's bioequivalence studies, which tracks the concentration of the drug in the plasma over time, also demonstrates that Abhai's ANDA Product satisfies the "effective level" limitation. The mean plasma concentration versus time curves from all three of Abhai's bioequivalence studies show that the ANDA Product's plasma profile matches the plasma profile of Adderall XR. Trial Tr. Day 3 at 55:9-56:19; Trial Exs. 68 at 47-48; 69 at 48-49; 70 at 46-47.

Pharmacokinetic data from clinical studies of Adderall XR show that once ingested, Adderall XR has a rapid onset effect and continues to reduce ADHD symptoms for at least four hours after the maximum concentration is reached. Trial Tr. Day 3 at 59:25-60:18, 63:1-16. Pharmacokinetic data from Abhai's biostudies show that after ingestion, its ANDA Product will produce a maximum concentration at four hours, and in many instances a maximum concentration at eight hours after ingestion. Trial Tr. Day 3 at 59:25-60:18, 63:1-16. Because Abhai's ANDA Product, like Adderall XR, will have a rapid onset of effect that continues for 4–6 plus hours after the maximum concentration is reached, the mean maximum concentration values from Abhai's ANDA studies indicate that Abhai's ANDA Product will reduce ADHD symptoms for the course of at least 8 hours and in many instances up to 12 plus hours. Trial Tr. Day 3 at 63:17–64:10.

For all these reasons, Abhai's ANDA Product meets the "effective level" limitation of the '148 Patent.

Abhai's ANDA Product meets the "peak plasma concentration" limitation in Claims 1, 11, and 13 of the '148 Patent. Each of the asserted claims requires that Abhai's ANDA Product results in a "peak plasma concentration of amphetamine base salts reached after release of said delayed enteric release dosage form" that "exceeds the peak plasma concentration previously

reached after release of said immediate release dosage form." Trial Ex. 2 at 13:46–50, 14:41–45. Specifically, the claim, known as the "additive effect," states that:

> the levels of drug in blood plasma of the pharmaceutically active amphetamine salts will reach a peak fairly rapidly after about 2 hours, and after about 4 hours a second pulse dose is released, wherein a second fairly rapid additive increase of plasma drug levels occurs which slowly decreases over the course of the next 12 hours.

Trial Ex. 2 at 10:21-26.

After administration, the amphetamine in the immediate release dosage form will release, dissolve, and begin to be absorbed into the blood plasma, until the concentration of amphetamine in the plasma reaches a "peak plasma concentration" "after release of the immediate release dosage form." Maggio Opening ¶¶ 118-19. The delayed enteric release dosage form then enters the small intestines where it releases another burst of amphetamine, which dissolves and is then absorbed into the plasma. Id.; Trial Tr. Day 1 117:17-21. Dr. Maggio[5] used two

[5] John Maggio, Ph.D. ("Dr. Maggio") was the Floor van Maanen Professor of Pharmacology and Experimental Therapeutics in the Department of Pharmacology and Cell Biophysics at the University of Cincinnati College Of Medicine, and an Instructor of Neurology at Harvard Medical School in Boston. Maggio Expert Report ¶ 4. He passed away before the conclusion of the trial. Dr. Maggio's major topic of research included organic chemistry, biologically active peptides and their receptors, tachykinins and tachykinin receptors, central nervous system and other amyloidosis, pharmacology, neurological and inflammatory diseases, Alzheimer's disease photoaffinity labeling, pharmacokinetics, pharmacodynamics, and general pharmacology.

pharmacokinetic analyses on Abhai's ANDA Product to test this claim: (1) superposition principle, illustrating the additive concept; and (2) percent absorption analysis, using the Wagner-Nelson method. Maggio Opening ¶¶ 51–68, 124–34.

Using the superposition principle, Dr. Maggio compared the plasma concentration versus time curves plotted after administration of Abhai's ANDA Product, which contained both immediate release and delayed enteric release dosage forms, to a plasma concentration versus time curve from a formulation containing only an immediate release dosage form of the same mixed amphetamine salts used in Abhai's ANDA Product. Trial Exs. 75 at 30–55; 201 at 43-44; Maggio Opening ¶¶ 129–34. Dr. Maggio found that the peak plasma concentration reached after the release of the delayed enteric release dosage form, around five to six hours, exceeded the peak plasma concentration reached after the release of the immediate release dosage form. Maggio Opening ¶¶ 129–34. This analysis suggests that the plasma concentration versus time curve for Abhai's ANDA Product continues to rise further than the peak plasma concentration from the immediate release only dosage form. Maggio Opening ¶ 133.

Id. ¶ 8. As a professor, Dr. Maggio taught on a range of topics in general pharmacology, including absorption, distribution, metabolism and elimination of drugs, and drug delivery. Id. ¶ 9.

Dr. Maggio then used the Wagner-Nelson method to analyze the percent of drug absorbed over time, and correlated the percent drug absorbed to plasma concentration over time and release of the two dosage forms in Abhai's ANDA Product. Maggio Opening ¶¶ 51-68, 120, 135. Dr. Maggio found that when 50% of the drug has been absorbed, the plasma concentration on the plasma profile reached the highest or peak plasma concentration after release of the immediate release dosage form. Maggio Opening ¶¶ 60, 64, 67; 57–58, 120. The plasma concentration continues to rise to a second peak plasma concentration, indicating that the peak plasma concentration after release of the delayed enteric release dosage form exceeds the peak plasma concentration after release of the immediate release dosage form. Id. This analysis indicates that the concentration of amphetamine in the plasma continues to increase after release of the drug from the IR dosage form, and the increase is caused by the remaining 50% of the amphetamine in the DR release dosage form, as required by the claims of the '148 Patent.

There are three possible plasma concentration versus time curves -- Figures 1, 7, and 8 -- that come within the claim specifications. Trial Ex. 2. Each of these figures illustrates possible plasma concentration versus time curves that one would see from administering a pharmaceutical formulation containing an IR and a DR dosage form. Trial Ex. 2 at 6:39–42, 6:64–7:4.

A formulation that contains the IR and DR forms of amphetamine will exhibit the additive concept. Id.

"FIG 1 illustrates a . . . target plasma profile of the drug delivery system of the present invention. The profile reflects an immediate-release component followed by a delayed-release component." Trial Ex. 2 at 6:39-42. Figures 7 and 8 are "plot[s] of a profile of plasma amphetamine concentration after administration of a composite capsule containing the immediate release pellets and delayed release pellets." Trial Ex. 2 at 6:64–7:4. Individual plasma concentration versus time curves in "FIGS. 7 and 8 show the typical profiles of plasma amphetamine concentration after administration of a composite capsule containing the immediate-release pellets and delayed-release pellets." Trial Ex. 2 at 12:40–43. These "general plasma profiles are similar to the desired target plasma level profile shown in FIG. 1." Trial Ex. 2 at 12:47–48. The claims encompass all three figures of the plasma concentration versus time curves depicted in the patent. Maggio Opening ¶ 90. Abhai is incorrect when it defines the "peak plasma concentration" as "the point where the plasma concentration reaches a high-point before declining." Bergstrom Decl. ¶ 36. Abhai claims that this definition requires a declining concentration after reaching a high-point in the plasma concentration. Bergstrom Dep. 109:14-109:22. Such an assertion is not based on anything

included in the patent. Id. Rather, the claim requires a decrease in plasma concentration after the peak plasma concentration reached after release of the drugs from the delayed enteric release dosage form. Trial Ex. 2 at 10:21-26 (". . . wherein a second fairly rapid additive increase of plasma drug levels occurs which slowly decreases over the course of the next 12 hours."). Figures 7 and 8 are also pertinent to the claim because the numerical values of the area under the curve and the maximum concentration ranges found in the claim "are taken directly from Figures 7 and 8." Trial Ex. 179 at 281.

Even if the Court were to interpret the peak plasma concentration limitation as Abhai suggests, its ANDA product meets the limitation. See Trial Ex. 201. Abhai suggests that when interpreting the term in the claim "a human patient" as "human patient population," and looking to the plasma concentration versus time curves from the mean data in Abhai's ANDA studies, its product does not meet the "peak plasma concentration" limitation. Abhai is incorrect. The term "a human patient" means one or more human patients. See Maggio Rebuttal Claim Construction Dec. ¶ 53. The claim does not require a look at the mean data, but rather an examination of individual data. Trial Ex. 2 at Fig. 7, 8. The captions for Figures 7 and 8 state that the plasma concentration versus time

curves come from two individuals. Id. This is consistent with the FDA's requirement that drug applications provide individual subject graphs and individual subject plasma concentrations, and not only the mean data. Trial Ex. 135 at 25.

Abhai's ANDA Product meets the AUC limitation in Claim 1, 11 and 13 of the '148 Patent. The AUC limitation in Claim 1 states that "said pharmaceutical formulation, when containing about a total dose of 20 mg, will produce in a human individual a plasma concentration versus time curve (ng/ml versus hours) having an area under the curve (AUC) of about 467 to about 714 ng hr/ml." Trial Ex. 2 at 13:51-55. The Court construed this term to mean "a plasma concentration versus time curve (ng/ml versus hours) having an area under the curve (AUC) of about 467 to about 714 ng hr/ml." Markman Hearing Tr. At 23-24, 34.

"[A] human individual" limitation as used in the claim means "one or more humans." See Maggio Rebuttal Claim Construction Dec. ¶ 44, 45; 01 Communique Lab., Inc. v. LogMeIn, Inc., 687 F.3d 1292, 1297 (Fed Cir. 2012). "[A] human individual" does not mean "human patient population" as Abhai claims. Furthermore, the claim requires an examination of individual data rather than looking only at the mean AUC. Trial Ex. 2 at Figs. 7, 8; Maggio Opening ¶¶ 102, 104, 107.

As used in the claim, the term "about" "has its usual meaning in the field, e.g. roughly ± 20%, for example as used by

FDA in its determinations of bioequivalency." Trial Ex. 179 at 269. According to the FDA:

> Numerically, [± 20%] [] is expressed as a limit of test-product average/reference-product average of 80% for the first statistical test and a limit of reference-product average/test-product average of 80% for the second statistical test. By convention, all data is expressed as a ratio of the average response (AUC and Cmax) for test/reference, so the limit expressed in the second statistical test is 125% (reciprocal of 80%).

Trial Ex. 64 at 7; see also Maggio Opening ¶¶ 80-81.

Dr. Maggio calculated the range around each number in Claim 1 using the FDA method described above. Maggio Opening ¶ 81. Dr. Maggio found that eighty percent of 467, the low end of the numerical AUC range in Claim 1, is 373.6 and 125% of 467 is 583.75, meaning that 80–125% of 467 is 373.6 to 583.75 ng hr/ml. Maggio Opening ¶ 81, 144. He also found that eighty percent of 714, the high end of the numerical AUC range in Claim 1, is 571.2, and 125% of 714 is 892.5, meaning that 80–125% of 714 is 571.2 to 892.5 ng hr/ml. Maggio Opening ¶ 81, 144. Therefore, the AUC range contemplated by Claim 1 is 373.6 to 892.5 ng hr/ml, meaning that Abhai's ANDA Product meets the AUC limitation if the ANDA Product produces in a human individual a plasma concentration versus time curve having an AUC of 373.6 to 892.5 ng hr/ml. Maggio Opening ¶ 81.

AUC_{0-48} is the proper time period for calculating AUC in the patent. Bergstrom Dep. 74:21-75:3. AUC is the area under the

plasma concentration versus time curve. One way to calculate AUC is from time zero to time "t" ("AUC_{0-t}"), where "t" is a specific time point and the time of the last measured concentration. Maggio Opening ¶ 28(a), 74. AUC can also be calculated from time zero to infinity ("$AUC_{0-\infty}$") by taking AUC_{0-t} and then extrapolating from time "t" to time infinity. Id. Based on Claim 1 of the '148 Patent and the prosecution history, AUC_{0-t} is the proper method of calculation. Maggio Opening ¶¶ 75-78; Bergstrom Dep. 74:21-75:3. In this case, the AUC_{0-t} for the '148 Patent is 48 hours because it is the last recorded time point in Figures 7 and 8, and the prosecution history states that the AUC values in Claim 1 were "taken directly from Figs. 7 and 8. Id.; Trial Exs. 2 at Figs. 7 and 8; 179 at 281.

It follows that Abhai's ANDA Product meets the AUC Limitation if, when administered to one or more individuals, it results in a plasma concentration versus time curve having an AUC_{0-48} of about 373.6 to 892.5 ng hr/ml. Based on Abhai's three ANDA Studies, its product meets the AUC Limitation. The number of subjects with an AUC_{0-48} that met the AUC Claim for the group of people who fasted prior to dosing was 21/28 (75%) + mean AUC. Maggio Opening ¶ 144; Trial Ex. 201 at 6065. For the group that was fed prior to dosing, 36/38 (94.7%) + mean AUC met the limitation. Id. For the group that had the contents of the product sprinkled in their meal, 26/28 (92.9%) + mean AUC met

the limitation. Id. Even under Abhai's interpretation of the limitation, narrowing the AUC range and requiring the use of $AUC_{0-\infty}$, a substantial number of individuals met the AUC limitation. See Maggio Opening ¶¶ 143-46, 150-53, 196-97. Therefore, Abhai's ANDA Product meets the AUC limitation in Claim 1, 11, and 13 of the '148 Patent.

Abhai's ANDA Product meets the "maximum concentration of about 22.5 to about 40 ng/ml" limitation in Claim 11 as it depends from Claim 2 through Claim 10. Claim 2 requires "[a] formulation of Claim 1 wherein said plasma concentration curve has a maximum concentration of about 22.5 to about 40 ng/ml for about a total dose of 20 mg." Trial Ex. 2 at 13:56-58. Claim 2 provides a range of maximum concentration values, in which each end point is modified by the word "about," meaning ± 20%, as explained above. Trial Exs. 2 at 13:56-58; 64 at 7; Maggio Opening ¶¶ 83-84. Using the FDA 80-125% bioequivalence standard, the range contemplated by Claim 2 is 18-50 ng/ml, meaning that Abhai's ANDA Product meets the concentration maximum limitation if it produces a concentration maximum of 18-50 ng/ml in an individual. Maggio Opening ¶ 84 & n.36. Additionally, because Claim 2 depends from Claim 1, Claim 2 is met only when an individual meets both the AUC limitation of Claim 1 and the concentration limitation in Claim 2. Trial Ex. 2 at 13:56-58.

Abhai's ANDA studies report concentration maximum for each individual subject, as well as separate concentration maximum values for d- and l- amphetamine. Maggio Opening ¶ 157-61; Trial Ex. 201. Dr. Maggio determined the concentration maximum values by examining the summed plasma concentration data for d- and l- amphetamine, to determine the maximum concentration of total amphetamine that appeared in each individual's plasma. Maggio Opening ¶¶ 158-61; Trial Ex. 201. In the three studies described above, 75%, 94.7%, and 85.7% of subjects met both the AUC and concentration max limitations. See Maggio Opening ¶¶ 163-64, 198; Trial Ex. 201. Even under Abhai's interpretation of the claim, the concentration limitation is met. See Maggio Opening ¶¶ 162-70, 198; Trial Ex. 201. Therefore, the maximum concentration limitation in Claim 11 is met as it depends from Claim 2.

Abhai's ANDA Product also meets the maximum concentration limitation in Claim 11 as it depends form Claim 7 through Claim 10. Claim 7 requires "[a] formulation of claim 2 wherein maximum concentration is about 40 ng/ml." Trial Ex. 2 at 14:4-5. As in Claim 2, the maximum concentration value is also modified by "about," defined as ± 20%. Trial Exs. 179 at 281; 64 at 7; Maggio Opening ¶¶ 83-84, 183-84; Trial Ex. 2 at 14:4-5. Dr. Maggio once again calculated the claimed maximum concentration range using the FDA's 80-125% bioequivalence

standard. Maggio Opening ¶ 183. The maximum concentration contemplated by Claim 7 is 32-50 ng/ml. Maggio Opening ¶ 183. Claim 7 is met when an individual meets both the AUC limitation of Claim 2 and the concentration maximum limitation in Claim 7. Trial Ex. 2 at 14:4-5, 13:56-58, 13:51-55. Based on Abhai's three studies described above, a total of 60 individuals out of 94, or 63.8%, demonstrated a plasma concentration versus time curve that meets both the AUC and the maximum concentration limitations when the AUC is calculated from time zero to 48. Maggio Opening ¶¶ 186-92, 200; Trial Ex. 201. Even when the AUC was calculated from time zero to infinity, as suggested by Abhai, 56 individuals out of 96, or 58.3%, meet both the AUC and the concentration limitations. Id.

Each of Abhai's dosage strengths meet the Pharmacokinetic Claim Limitations in the asserted claims of the '148 Patent. Absorption and elimination of amphetamine in Abhai's ANDA Product doses exhibit first-order kinetics (otherwise known as first-order or dose proportional pharmacokinetics). Maggio Opening ¶¶ 29, 31, 40; Trial Exs. 56 at 5; 55 at 4. Given the dose-proportional pharmacokinetics, the AUC and maximum concentration are linearly proportional to the dose administered. Maggio Opening ¶¶ 29, 31, 40; Trial Ex. 55 at 4. This suggests that if an individual were to double the dose, it would also double the AUC and maximum concentration. Id.

Moreover, the analyses discussed above relating to the pharmacokinetic elements ("peak plasma concentration," "AUC," and "maximum concentration") will also apply to all dosage strengths even though Abhai performed its ANDA Studies on the 30 mg dosage strength. Maggio Opening ¶¶ 203, 204. Therefore, the pharmacokinetic elements are met for all five dosage strengths of Abhai's ANDA Product.

Therefore, it follows that Abhai's ANDA Product meets the maximum concentration limitations of Claim 11 as it depends from Claims 2 and 7.

C. Abhai's ANDA Product Meets the "Coating Thickness" Limitation in Claims 11 and 13 of the '148 Patent'

Claim 11, as it depends from Claim 10, and Claim 13, as it depends from Claim 12 of the '148 Patent, require that the delayed enteric release dosage have a coating thickness of at least 25 μm. Trial Ex. 2 at 14:17-18, 46-47. Dr. Luk received samples of Abhai's ANDA Product in controlled shipping conditions on August 9, 2016. Trial Tr. Day 1 at 43:16-18; Trial Ex. 193. He performed a two-step coating thickness analysis on the samples. Id. First, Dr. Luk used Raman microscopy to identify the layers in Abhai's ANDA Product. Trial Tr. Day 1 at 36:21-37:6; Trial Ex. 195. Second, he used optical microscopy to measure the thickness of the enteric coating. Id.

Optical microscopy is a technique used in the pharmaceutical industry to capture images at high magnification to determine coating thickness. Trial Tr. Day 1 at 37:4-17; Trial Ex. 42.

Raman microscopy, also known as spectroscopy, is used to provide chemical information about compounds. Trial Tr. Day 1 at 37:19-38:1; Trial Ex. 43. In the pharmaceutical industry, it is used to analyze the properties and microstructure of complex materials, such as pharmaceutical tablets. Trial Ex. 43-44. A Raman microscope takes light that has undergone Raman scattering and produces a Raman spectrum from that scattered light. Trial Tr. Day 1 at 37:19–38:1; Trial Ex. 43-44. When light shines on the sample compound, it interacts with that compound and Raman scattered light results. Trial Tr. Day 1 at 37:19–38:1; 38:20–39:8; Trial Ex. 43-44. The Raman scattered light carries a specific chemical signature for that compound, is reflected back to the microscope, and is then directed towards a spectrometer. Id. Raman measurements can be used as a compendial ID (identification) test and for structural elucidation because the Raman spectrum is specific for a given compound. Id. The output of a Raman spectrometer is a plot of intensity against frequency, appearing as a series of peaks, referred to as a spectrum. Trial Tr. Day 1 at 37:19–38:1; Trial Exs. 43, 44,

194. The spectrum can then be compared against spectra obtained from reference spectra to confirm chemical identity. Id.

Dr. Luk used Raman microscopy to confirm the identity of the seal coat, DR polymer layer, otherwise known as the enteric coat, and the mixed amphetamine drug layer for each dosage strength of Abhai's ANDA Product. Trial Tr. Day 1 at 47:2-9, 47:21-48:9, 48:10–49:3, 49:10–14, 49:19-50:8, 50:12-18; Trial Exs. 27, 28, 29, 45, 48, 121, 194, 195, 200. Dr. Luk also confirmed the correlation of the optical features associated with each layer to the reference spectrum in each of the samples that he analyzed. Trial Tr. Day 1 at 50:15–18; Trial Ex. 194.

To measure the coating thickness of the samples of Abhai's ANDA Product, Dr. Luk selected two pellets from each dosage strength of Abhai's ANDA Product and bisected each pellet using a microtome, cutting sequentially thin slices (less than 1 µm for each slice) until the middle of the pellet was reached. Trial Tr. Day 1 at 42:20–43:2, 51:4–7; Trial Exs. 195, 196. Dr. Luk then performed optical microscopy on each of the pellets at low magnification to give an overall view of a cross-sectioned pellet and at high magnification to give a more detailed view of the coatings that Abhai applied to the sugar sphere core. Trial Tr. Day 1 at 51:14–52:4; Trial Exs. 195, 200. Dr. Luk was able to identify the enteric coat, the seal coat, the drug layer, and

the sugar sphere core. Trial Tr. Day 1 at 51:21-52:4; Trial Ex. 196 at 39.

Dr. Luk then used the measure function on the Olympus microscope control software, Cell-F, to measure the coating thickness. Trial Tr. Day 1 at 52:10–13; Trial Ex. 42; Trial Ex. 197. The coating thickness was determined as the shortest distance from a given point at the seal layer and the enteric coat, by using the circle function where the center of a circle is located on a point at the seal layer–enteric coat interface and is increased until the circle touches any part of the exterior interface of the enteric coat. Trial Tr. Day 1 at 53:1–54:3; Trial Exs. 42, 197. The perimeter of the circle forms a tangent to the exterior of the enteric coat, and the radius of the circle represents the shortest distance between the boundaries of the enteric coat. Id. Dr. Luk took at least 100 measurements for each pellet. Trial Tr. Day 1 at 54:4-9; Trial Ex. 196-198. He found the average enteric coating thickness for Abhai's ANDA Product to be 38.04 µm, with a standard deviation of 2.13 µm. Trial Ex. 198 at 156; Trial Tr. Day 1 at 55:20-2. The minimum measurement on any bead was 25.9 µm, and the majority of the measurements were substantially greater than 25 µm. Trial Ex. 198.

Abhai's ANDA Product thus infringes the '148 Patent because it meets the coating thickness limitation in claims 11 and 13.

IV. ABHAI'S LITIGATION MISCONDUCT AND SANCTIONS

In the midst of trial in April, Abhai revealed that an essential factual matter -- its stability dissolution testing data -- was incorrect. Def.'s Mem. Supp. Mot. Amend Pretrial Mem. It proffered its corrected data, which it admitted it had failed to supplement in place of the incorrect data it had originally provided during discovery. Id. Such litigation misconduct warrants sanctions.[6]

Abhai conducted stability dissolution testing on its ANDA Product at different times after manufacture in order to submit this data to the FDA. Trial Exs. 130 at 43, 46, 50, 54, 57, 60, 64, 67; 240. Abhai provided this original data to Shire during the discovery process. Pls.' Rep. Supp. Mot. Compel, Ex. HH at Req. No. 10, ECF No. 226. The data showed that the highest release of the DR Beads after one hour at pH 6.0 for the 10, 20, and 30 mg strengths occurred at a shelf life of 24 months ("24 month"). Trial Ex. 206. The highest release of the DR beads after one hour at pH 6.0 for the 15 and 25 mg strengths occurred at a shelf life of 18 months ("18 month"). Id.

[6] The Court gave Abhai every opportunity to counter the imputation of misconduct, going so far as to name the witnesses under Abhai's control from whom it wished to hear. Abhai called none of them to testify. Thus, the Court "may infer that the testimony of [these witnesses] is unfavorable to [Abhai]." Grajales-Romero v. American Airlines, Inc., 194 F.3d 288, 298 n. 10 (1st Cir. 1999). The Court has drawn such adverse inferences in the recital which follows.

On April 4, 2017, with two days of trial remaining, Abhai declared that its 24 month stability data for the 10, 20, and 30 mg dosage strength, and its 18 month stability data for the 15 and 25 mg dosage strength, were incorrect. Def.'s Mem. Supp. Mot. Amend Pretrial Mem. Abhai also revealed that it had retested those specific shelf lives and dosage strengths back in November 2016. Id.; Joint Status Rep. at 4. The new data demonstrated that there was a much slower release of the DR beads within the first hour of exposure to pH 6.0 than had first been discovered. Id.

How did this happen? On October 14, 2016, Shire deposed Dr. Namburi as Abhai's Rule 30(b)(6) witness. Namburi 2016 Dep. at 6.8. There, Dr. Namburi confirmed that Abhai's dissolution data were accurate and that the measure of dissolution was taken at appropriate times, meaning 1 hour after the sample was exposed to a buffer medium (3 hours after the start of the entire test). Namburi 2016 Dep. at 210:13-21. He further explained that "as long as the dissolution does meet to the specifications," there was no cause for concern that the 24 month samples showed a faster rate of release than samples tested at earlier dates. Namburi 2016 Dep. at 214:12–215:6.

As Dr. Namburi later testified, he emerged from the deposition "confused and concerned" about the accuracy of his testimony given on October 14, 2016, focused as it was on the

importance of the dissolution data. Namburi 2017 Dep. at 105:16-20.

On October 15, 2016, Dr. Namburi e-mailed Nimish Patel (Quality Control Manager), Thomas Saboe (Associate Director of Quality Control), Ashvin Panchal (Director of Quality), Dhanvant Amin (Technical Reviewer), and Murty Vepuri ("Vepuri").[7] Trial Ex. 247 at 4. Dr. Namburi asked these individuals to "verify all recent test results" of Abhai's stability data. Trial Ex. 247 at 4.

On Monday, October 17, 2016, Abhai opened an internal investigation to determine whether its second dissolution measurements had been taken after exposure to the buffer medium for three hours instead of one hour. Trial Ex. 220 at 1. That afternoon, Thomas Saboe and Dr. Namburi concluded that the 24 month dissolution data for Abhai's 30 mg strength was incorrect because the second dissolution measurement had been taken after four hours of exposure to the buffer medium. Trial Ex. 247. At some point prior to October 21, 2016, investigators found that testing for all five dosage strengths – the 24 month data for the 10, 20, and 30 mg, and the 18 month data for the 15 and 25 mg -- were affected by the error in testing. Trial Ex. 220 at 3-4.

[7] Vepuri is a consultant and an advisor to KVK, and part of the company's upper management.

On October 17, 2016, KVK's investigation review board met and determined that the error in the stability dissolution data was a result of ambiguities in KVK's method of analysis. Trial Exs. 220 at 18-27; 222 at 3. It concluded that the samples needed to be retested using a clarified test procedure. Id.

On October 25, 2016, KVK revised its dissolution testing protocols and clarified the time points for sampling. Trial Ex. 220 at 4, 18-27. KVK then proceeded to retest the 24 month and 18 month batch of Abhai's ANDA Product. Trial Ex. 225 at 14. The retesting for the 18 month and the 24 month batches was conducted on samples that were 7-9 months old because KVK only manufactured a single batch of each strength of Abhai's ANDA Product for testing. Trial Ex. 240.

On November 9, 2016, Shire requested production of all versions of KVK's methods of analysis, including dissolution testing protocols. Trial Tr. Day 7 at 124:3-7. On November 23, 2016, Abhai produced all of KVK's methods of analysis and dissolution protocols, **except** for the revisions made on October 25, 2016. Compare Trial Ex. 337 with Trial Ex. 220 at 18-27.

On December 6, 2016, Anthony Tabasso ("Tabasso")[8] was informed of the October 25 revisions to the dissolution testing

[8] Tabasso is the President and CEO of KVK and Managing Member of Abhai.

and methods of analysis. Trial Ex. 340; Trial Tr. Day 7 at 129:19-131:19.

On November 17, 2016, Dr. Namburi signed an errata report for his 30(b)(6) deposition but did **not** correct his statements regarding Abhai's stability testing on the 18- and 24- month ANDA Products. Proposed Trial Ex. 412. At this time, Dr. Namburi was aware that there were errors with the data and that Abhai had retested the 18- and 24-month Products using KVK's revised dissolution testing and methods of analysis. Namburi 2017 Dep. 140:6-141:17; Trial Tr. Day 7 at 129:9-14. Abhai also failed to supplement any of its prior discovery production with the revised methods of analysis or any other documents relating to the errors in its stability testing. Abhai also failed to notify the FDA of the errors in its testing.

Importantly, neither Vepuri nor Dr. Namburi notified Abhai's attorneys of the errors in the dissolution data, despite their awareness of the error and the ongoing litigation.

There matters rested during the run up to trial. Not surprisingly, Shire's experts, unfortunately, had already relied on the incorrect data produced by Abhai. From March 27 into March 28, 2017, Dr. Burgess, Abhai's expert, testified about Abhai's dissolution testing of its ANDA Product. Unbeknownst to Dr. Burgess, however, her testimony was based on the old (and now discredited) dissolution data. Trial Tr. Day 1 at 106:7-

127:4, Day 2 at 5:3-124:20. At the time of Dr. Burgess's testimony, Vepuri, Dr. Namburi, Dr. Late, and Panchal had determined that Abhai's 24 month stability data did not show a faster release than other time points as the older data had previously stated. Trial Tr. Day 7 at 68:4-69:18. At this point, Tabasso, though aware of the retesting, was not yet aware of the material discrepancies in the results.

On Thursday, March 30, 2017, the Court shared its "musings" about the strength of Shire's case, specifically stating that it was contemplating interpreting the "essentially all" dissolution claim element as something more than 75 percent but less than 100 percent. Trial Tr. Day 4 at 62:20-67:3.

On Friday, March 31, KVK created an "Escalation to Management Form" to inform Tabasso of certain issues. Trial Ex. 234. The form stated that "On 3-31-17 it was identified that the 24 month data was revised in 11/2016 and not reported to Regulatory." Trial Ex. 234 at 2. Later that same day, Abhai finally informed its counsel of the errors in its data.

On Monday, April 3, 2017, Abhai informed Shire of the errors in its data. Def.'s Mem. Supp. Mot. Amend Pretrial Mem. 5. Abhai also submitted a "stability update" to the FDA that same day, providing them with 36 month stability data for the 10, 20, and 30 mg dosage strength and 24 month stability data for the 15 and 25 mg dosage strength. Trial Ex. 238. Abhai

also indicated to the FDA that the "[d]issolution test results at incorrect time point (3 hours in phosphate buffer, pH 6.0) [for the 18- and 24- month products,] [were] replaced with re-analyzed and corrected time point (1 hour in phosphate buffer, pH 6.0) dissolution test results (16-LIR-054)." Trial Ex. 240 at 6.

On April 4, 2017, Abhai filed a Motion to Amend Pretrial Memorandum where it admitted to errors in its dissolution testing and that further dissolution retesting was conducted to update the 18 and 24-month data. Def.'s Mem. Supp. Mot. Amend Pretrial Mem.

The conduct of Abhai and KVK reflects an appalling lack of awareness of a litigant's responsibility to our justice system -- in Dr. Namburi's case conduct laced with mendacity as well. It is worth remembering that Vepuri and Dr. Namburi are not bit players here. Vepuri is the owner of KVK. Both he and Dr. Namburi are members of KVK's management team. Def.'s Opp'n Pls.' Mot. Compel at 1; Rees Dep. 51:18-52:6, 107:19-110:20. Dr. Namburi was an integral member of Abhai's litigation team. See Trial Tr. Day 7 at 49:20-24, 50:4-12, 115:23-116:8, 117:10-25, 119:9-21; Trial Exs. 336, 338. He reviewed all expert reports and provided his views on the strength of Abhai's case to Tabasso. Trial Ex. 338. Vepuri also participated deeply in the litigation, and was a party to over 150 privileged

communications discussing the strategy for the case. Trial Ex. 336, 338. The FDA would be well advised to take notice of this pervasive corporate unwillingness to play by the rules. See United States v. Aegerion Pharmaceuticals, Inc., Criminal Action No. 17-10288-WGY, 2017 WL 5586728 (D. Mass. Nov. 20, 2017). The Clerk is therefore directed to send a certified copy of this opinion to the General Counsel of the FDA. Sanctions are amply warranted here.

Unfortunately Shire, which otherwise presented a clear, cogent, and compelling case, asks for far too much.

Shire claims that, due to Abhai's litigation misconduct, it is entitled to an order holding that Abhai's ANDA Product meets the release elements of the patents-in-suit. Pls.' Post-Trial Brief at 34, ECF No. 333. Basing existential reality on litigation conduct does not commend itself to this Court. Here, such a sanction would be supererogatory. Abhai's ANDA Product infringes the '096 and '148 Patents for the reasons explained above. See supra Sections III.A, B, and C.

Shire also claims that Abhai engaged in an array of other litigation misconduct, including: (i) not issuing a litigation hold notice concerning the law suit; (ii) not instructing their employees to preserve documents relating to the case; (iii) omitting the names of KVK employees with substantial involvement in the development of Abhai's ANDA Product; (iv) stating that

certain documents did not exist when in fact they did; (v) failing to supplement any of its prior production at the end of the original fact discovery period; and (vi) failing to cooperate with the Court's instruction to provide Shire with "full discovery" of its knowledge of the errors in its stability data. See Trial Tr. Day 7 at 133:2-12; Late Dep. 160:14–19; O'Loughlin Dep. 77:17–78:9; Leo Dep. 172:6–15; Pls.' Mot. Compel Disc. Ex. A at 3; Pls.' Mot. Compel Disc. Ex. WW at 7-8; Pls.' Mot. Compel Disc. Ex. ZZ; Pls.' Mot. Compel Disc. Ex. BB at 4; Trial Ex. 250, 334.

Based upon this array of reported misconduct, Shire comes up with a whopping $2,750,000.00 claim for attorneys' fees.

Let's step back and take a deep breath.

Abhai should be sanctioned for its litigation misconduct. Abhai elected to withhold its dissolution errors from Shire. Vepuri and Dr. Namburi were both aware of the errors in Abhai's stability and dissolution data as far back as October 2016. Trial Ex. 247; Vepuri Dep. 282:5-10, 282:14-20, 285:8-287:17. Dr. Namburi was questioned at length about the data during his deposition and therefore was aware that the accuracy of this data was of great importance to Shire and the overall litigation. See, e.g., Namburi 2016 Dep. at 22:4-18, 210:13-215:6. Both Vepuri and Dr. Namburi were included in dozens of privileged communications related to the litigation of this

case, as well as the stability and dissolution data. Trial Tr. Day 7 at 49:20–24, 50:4–12, 106:18–20, 117:10–25, 119:9–21, 123:20-124:2; Trial Exs. 336, 338; Vepuri Dep. at 170:17–172:7, 202:8–19, 209:9–12, 209:15–210:5, 218:14–219:3. They were also involved in the discovery process and were aware of Shire's request for stability and dissolution data. Id. Abhai had in fact produced the original stability and dissolution data as requested in discovery, albeit with errors, and this data should have been supplemented once the errors were discovered. See Fed. R. Civ. Pro. 26(e).

> [A] party that disregards its [discovery] obligations may create a reasonable suspicion that further investigation is warranted, and thereby imposes costs on its adversary that would never have been incurred had the party complied with its obligations in the first instance. In that situation, the offended adversary's counsel is not being rewarded for its success in the litigation; rather, the adversary is simply being compensated for costs it should not have had to bear.

Klipsch Group, Inc. v. ePRO E-Commerce Ltd., 880 F.3d 620, 634 (2d Cir. 2018).

Recently while serving as a visiting judge in the Middle District of Florida, I have been privileged to sit on a panel with three other truly distinguished district court judges limning the contours of the law of sanctions in a most complex array of related cases. I can do no better than to quote that opinion in outlining the extent of this Court's authority here.

The formulation for determining the appropriate sanction varies somewhat depending on which authority the Court invokes to impose sanctions. However, some common themes govern the calculation of monetary sanctions, regardless of whether they are imposed under Rule 11 sua sponte, § 1927, or the Court's inherent power. First, a district court has broad discretion under all three authorities to determine the type and amount of a sanction. Peer, 606 F.3d at 1316 (under their inherent authority "district courts have broad discretion to determine whether to impose sanctions and the nature or amount of those sanctions."); Amlong, 500 F.3d at 1237–38 (abuse of discretion standard applies to a court's decision about sanctions under § 1927 and its inherent authority, which "recognizes the range of possible conclusions the trial judge may reach.")); Riccard, 307 F.3d at 1295 ("Although the sanctions most commonly imposed [under Rule 11] are costs and attorney's fees, the selection of the type of sanction to be imposed lies with the district court's sound exercise of discretion.").

Second, where, as here, the sanction is not to compensate the opposing party but the Court itself, the Court may, in its discretion, design a monetary sanction so that it compensates the public for the waste of judicial resources caused by an attorney's misconduct. E.g., Eisenberg v. Univ. of New Mexico, 936 F.2d 1131, 1136–37 (10th Cir. 1991) (affirming district court's imposition of $250 Rule 11 sanction related "to excess court time expended in deciding the [frivolous] issue."); Magnus Electronics, Inc. v. Masco Corp. of Indiana, 871 F.2d 626, 634 (7th Cir. 1989) ("A district judge, once the grounds for sanctions [under Rule 11] have been established, may impose various costs and expenses upon the attorney. The district judge is free to fine an attorney for the court's time, but that fine must be based on court costs and paid to the clerk's office.") (citing with approval Robinson v. Moses, 644 F.Supp. 975, 982 (N.D. Ind. 1986) (imposing $3,600 sanction on litigant, representing the value of six hours of the judge's time at $600 per hour, to account "for the waste of judicial resources this suit has caused."), and Nixon v. Rose, 631 F.Supp. 794, 797 (N.D. Ind. 1985) (imposing $2,000 sanction, payable to the court, to account for the "significant expenditure of judicial

resources in order to deal with the absolutely groundless and frivolous claims asserted in this case.")). With respect to 28 U.S.C. § 1927, "the dollar amount of the sanction must bear a financial nexus to the excess proceedings, i.e., the sanction may not exceed the 'costs, expenses, and attorneys' fees reasonably incurred because of such conduct.'" Amlong, 500 F.3d at 1239 (quoting Peterson, 124 F.3d at 1396). And in imposing sanctions under the Court's inherent power, "a district court is well within its discretion to 'fashion[] a sanction which is a direct response to the harm that the bad faith conduct of the attorney causes.'" Peer v. Lewis (Peer II), 571 Fed.Appx. 840, 845 (11th Cir. 2014), cert. denied, --- U.S. ----, 135 S.Ct. 1176, 191 L.Ed.2d 133 (2015) (quoting Barnes, 158 F.3d at 1215). Therefore, a sanction that reimburses the public for the diversion of judicial resources caused by frivolous, bad faith litigation falls within the scope of the three applicable authorities -- Rule 11, § 1927, and the judiciary's inherent power.

[I]f a court seeks to impose a sanction that is compensatory rather than punitive, there must be a causal link between the amount of the sanction and the litigant's misbehavior. Goodyear Tire & Rubber Co. v. Haeger, --- U.S. ----, 137 S.Ct. 1178, 1186, 197 L.Ed.2d 585 (2017) (causal link required for compensatory sanction under a court's inherent authority);[9] id. at 1186 n.5 (noting the need for a causal link for sanctions under Rule 11 and 28 U.S.C. § 1927). "That kind of causal connection...is appropriately framed as a but-for test": the sanction must be based on the costs that would not have been incurred but for the misconduct. Id. at 1187 (citing Fox v. Vice, 563 U.S. 826, 836, 131 S.Ct. 2205, 180 L.Ed.2d 45 (2011); Paroline v. United States, --- U.S. ----, 134 S.Ct. 1710, 1722, 188 L.Ed.2d 714 (2014)). "This but-for causation standard generally demands that a district court assess and allocate specific litigation expenses," but it does not require district courts to "'become green-eyeshade accountants.'" Id. (quoting Fox, 563 U.S. at 838, 131 S.Ct. 2205). "The essential goal" in fashioning a compensatory sanction

[9] Due to the Supreme Court's caution in Goodyear, this Court eschews any cost estimate that includes building costs, fully distributed costs, or total resource costs.

is "to do rough justice, not to achieve auditing perfection." Fox, 563 U.S. at 838, 131 S.Ct. 2205. Therefore, a district court "may take into account [its] overall sense of a suit, and may use estimates in calculating and allocating" costs. Goodyear, 137 S.Ct. at 1187. In "exceptional cases," the but-for standard even allows a court to shift all of the costs "from either the start or some midpoint of a suit, in one fell swoop." Id.

> Chambers v. NASCO offers one illustration. There, we approved such an award because literally everything the defendant did—"his entire course of conduct" throughout, and indeed preceding, the litigation—was "part of a sordid scheme" to defeat a valid claim. 501 U.S. at 51, 57, 111 S.Ct. 2123 (brackets omitted). Thus, the district court could reasonably conclude that all legal expenses in the suit "were caused...solely by [his] fraudulent and brazenly unethical efforts." Id., at 58, 111 S.Ct. 2123. Or to flip the example: If a plaintiff initiates a case in complete bad faith, so that every cost of defense is attributable only to sanctioned behavior, the court may again make a blanket award.

Id. at 1187–88 (emphasis added). Thus, under the "but-for" test, the Court can impose the entire cost of a lawsuit if the suit was a sham from the beginning.

There are good reasons for tying the monetary sanction to the costs that an attorney or litigant imposes on the Court. "The judicial system of dispute resolution is not cost free and those who abuse it through misconduct impose direct costs on the law abiding taxpayers who support it." Specialized Plating, Inc. v. Federal Envtl. Serv., Inc., 975 F.Supp. 397, 398 (D. Mass. 1997) (basing $5,250 sanction on the waste of three hours of the court's time). "[T]he crowded dockets of the federal courts cannot tolerate the burden posed by factually baseless suits that drain judicial resources. This court will sanction those cases, like this one, that are so meritless they can only waste the court's resources." Robinson, 644 F.Supp. at 983. Indeed, one of the purposes of Rule 11 sanctions is to "discourage dilatory or abusive tactics and help to streamline the litigation process by lessening frivolous claims or defenses." Fed. R. Civ. P. 11, Adv. Cmt. Note, 1983

> Amend. Frivolous litigation diverts the time and attention of judges and their chambers away from meritorious lawsuits, leaving the public and other litigants to pay for misbehaving lawyers' malfeasance, mainly in the form of longer delays. And, as the familiar maxim goes, "justice delayed is justice denied." Of course, the Court cannot restore lost time to those parties whose cases were delayed while the Court sorted through the mess . . . . But the Court can restore the public fisc and deter similar abuses of the court system by requiring [counsel] to reimburse the taxpayer for the waste of judicial resources.

In re Engle Cases, No. 3:09-cv-10000-J-WGY-JBT, 2017 WL 4675652, at *63-64 (M.D. Fla. 2017).

A. Attorneys' Fees and Costs

Accordingly, Shire, within thirty days of the date of this order, may submit a revised claim for attorneys' fees and costs **limited** to (a) recovering for the time wasted dealing with Abhai's inaccurate stability and dissolution data, (b) discovering the litigation misconduct discussed immediately above, and (c) dealing with Abhai's revised stability and dissolution data. Abhai may have fifteen days thereafter to respond. The Court will award appropriate monetary sanctions.

B. The Drain on Judicial Resources

Abhai's litigation misconduct is not simply a private matter of adjusting the legal fees to be borne by Shire. It has a direct impact on the citizens of the United States. Two trial days were taken up wrestling with Abhai's (knowingly incorrect) stability and dissolution data and an additional three days were

necessary to unwind the incorrect data and address the corrected version. The necessity of a sanctions analysis has occupied an additional writing day. Thus, Abhai's misconduct has occasioned over a full week of court time. "The judge's time is the most expensive resource in the courthouse." Judith Resnik, Managerial Judges, 96 Harv. L. Rev. 374, 423 (1982). Five precious trial days were essentially wasted. This is especially disheartening now that the average active federal district judge tries fewer than 3.4 civil trials and 2.8 criminal trials in an entire **year**. America's Most Productive Federal District Courts, FY 2017.[10] Such wastage is not confined to the instant case. It has a ripple effect. As is true in any well managed trial session, other cases were ready to go and other litigants were seeking resolution by trial. Some of these cases were jury cases. Abhai's misconduct caused these cases to be displaced, and delayed (and in some cases denied) American citizens' rights under the Seventh Amendment to adjudicate them.[11]

> Inspired by Judith Resnik, Managerial Judges, 96 Harv. L. Rev. 374, 423 n. 188 (1982), I determined,

[10] Sadly, the number of cases actually tried by the average active federal district court judge has fallen steadily over the past decade. See id. 2006-2017; Jordan M. Singer & William G. Young, Bench Presence 2014: An Updated Look at Federal District Court Productivity, 48 New. Eng. L. Rev. 565, 566-68 (2014).

[11] It must be remembered that these are the **minimum** reliable cost estimates. Fully amortizing the cost of court buildings could raise these estimates markedly. Indeed, the fully distributed or total resource costs of a daily district court session are much higher.

while a Justice of the Massachusetts Superior Court, that in those rare instances when it is appropriate to impose monetary sanctions, simply ordering a transfer of money between litigants is wholly inadequate. The judicial system of dispute resolution is not cost free and those who abuse it through misconduct impose direct costs on the law abiding taxpayers who support it. Professor Resnik's article taught me that those costs can be calculated with a fair degree of accuracy. Thereafter, in every instance where I have imposed a monetary sanction, I have sought to make whole the judicial system itself.

I set forth the methodology I use and the underlying assumptions in Chappee v. Commonwealth, 659 F.Supp. 1220, 1226–1228 nn. 9–10 (D. Mass. 1987), rev'd on other grounds, 843 F.2d 25 (1st Cir. 1988).

. . .

It is possible to place a per day monetary cost to the taxpayer on this process of adjudication -- the core "product," if you will, of the judicial branch of government. For example, it has been estimated that in 1982 the costs, including salaries, support staff, and other resources of each federal district judge, came to $752,000 annually. J. Resnik, Managerial Judges, 96 Harv. L. Rev. 374, 423 n. 188 (1982) (citing J. Kakalik & A. Robyn, Costs of the Civil Justice System: Court Expenditures for Processing Tort Cases 64 (1982)).[12] If 230 court days are devoted to actual adjudication (365–day year less 104 weekend days, 10

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[12] Since its publication, a number of courts and academics have looked to this study as authoritative on the public cost of litigation, e.g., J. Resnik, Managerial Judges, 96 Harv. L. Rev. 374, 423 n.188 (1982); A. Levin & D. Colliers, Containing the Cost of Litigation, 37 Rutgers L. Rev. 219, 219–22 (1985), including in the context of imposing sanctions, Nogess v. Poydras Center, LLC, Civil Action No. 16-15227, 2017 WL 396307, at *14 (E.D. La. Jan. 30, 2017) (collecting cases using figures from the Rand Study to calculate sanctions). Adjusting for inflation in 2017 dollars, this amounts to an average cost to the public of $6,983.42 for each tobacco lawsuit. This data provides a basis for assessing the value of judicial resources wasted by frivolous litigation.

In re Engle Cases, 2017 WL 4675652, at *64.

> holidays, 20 vacation days, and 1 sick day) the per day cost to the taxpayer of adjudication in the federal district court comes to $3,270.
>
> . . .
>
> Updated figures break down to an average of $9,795 per trial day for civil cases and $47,950 per trial day for criminal cases. FY 1994 Total Resource Costs, Economy Subcommittee Office, Administrative Office of the U.S. Courts. "Total Resource Costs" are the entire FY 1994 Judiciary Budget (including the costs of the Courts of Appeals, Bankruptcy Courts, pre-trial services, probation officers, defenders of indigent criminals, and the like) divided by the number of daily district court sessions. Indeed, the actual "door opening" costs to process an average case amount to $4,300. Leonidas Ralph Mecham, Director of the Administrative Office, Memorandum to All Judges, Nov. 12, 1996 at 2.

Specialized Plating, Inc. v. Federal Environmental Services, Inc., 975 F.Supp. 397, 398-99, 401 (D. Mass. 1997).

Using figures now nearly a decade old (2009), it was reliably estimated that it would cost $175,872,000 to add 174 federal district court judges and necessary support staff to the judiciary. Stephen B. Burbank, S. Jay Plager, and Gregory Ablavsky, Leaving the Bench, 1970-2009: The Choices Federal Judges Make, What Influences Those Choices, and Their Consequences, 161 U. Pa. L. Rev. 1, 96-97 (2012). This works out to a per judge cost of $1,010,769 and a per judge working

day cost of $4,395.[13] A conservative yet measurable estimate of the per judge and support staff work day cost to the American tax payers in FY 2017 is $5,000 per day.

Pursuant to the authority discussed above, and finding that Abhai has recklessly squandered five days during which this Court could better have devoted itself to teaching American jurors and attending to litigants prepared to follow the straightforward rules of civil procedure, this Court sanctions Abhai in the amount of $30,000.00. Abhai shall forwith pay such sum to the Clerk, United States District Court for the District of Massachusetts.

V. CONCLUSION

For these reasons, the Court finds and rules that Abhai's ANDA Product infringes Claim 1 of the '096 Patent and Claims 1, 11 (as it depends from Claims 1, 2, and 7), and 13 of the '148 Patent.

Abhai never developed a viable evidentiary attack on the validity of either of Shire's patents and the Court necessarily finds in Shire's favor on Abhai's counterclaims.

These findings and rulings dispose of the claims before the Court. Judgment shall enter for Shire.

SO ORDERED.

[13] Assuming the same conservative 230 working days estimate used in Chappee.

/s/ William G. Young
WILLIAM G. YOUNG
DISTRICT JUDGE