IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

ASTELLAS US LLC, ASTELLAS PHARMA US, INC., and GILEAD SCIENCES, INC., Plaintiffs, v. HOSPIRA, INC., Defendant	C.A. No. 18-1675-CFC

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OPINION

May 19, 2022
Wilmington, Delaware

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COLM F. CONNOLLY
CHIEF JUDGE

This patent infringement case arises out of Defendant Hospira, Inc.'s submission of an Abbreviated New Drug Application (ANDA) to the U.S. Food and Drug Administration (FDA) for approval to market a generic version of Plaintiffs' Lexiscan® drug product. Lexiscan® is a pharmacological agent used in myocardial perfusion imaging (MPI), a type of nuclear stress test. MPI images a patient's heart before and after physical stress to determine the effect of stress on the flow of blood through the coronary arteries and the heart. To induce stress, patients typically exercise in a controlled fashion on a treadmill or stationary bike in the doctor's office during the MPI. When a medical condition prevents the patient from exercising, Lexiscan® can be injected into the patient to stimulate stress by widening the patient's blood vessels. The active ingredient (API) in Lexiscan® is regadenoson.

Plaintiffs have asserted three patents. They allege that Hospira's submission of its ANDA to the FDA constitutes infringement of claim 1 of U.S. Patent No. 8,106,183 (the #183 patent) and claim 6 of U.S. Patent No. RE47,301 (the #301 patent) pursuant to 35 U.S.C. § 271(e)(2)(A). And they seek a declaratory judgment that the manufacture of Hospira's regadenoson product after the FDA's approval of the ANDA would constitute direct and induced infringement of claims

1, 2, and 3 of U.S. Patent No. 8,524,883 (the #883 patent) under 35 U.S.C. § 271(a) and (b).

Hospira denies infringement and asserts in its defense that the asserted patents are invalid. It also filed counterclaims seeking declaratory judgments of noninfringement of the asserted patents.

I held a three-day bench trial, and, as required by Federal Rule of Civil Procedure 52(a)(1), I have set forth separately below my findings of fact and conclusions of law.

I. THE STATUTORY AND REGULATORY FRAMEWORK

The ANDA procedures out of which this case arise were established by FDA regulations promulgated pursuant to the Federal Food, Drug, and Cosmetic Act (FDCA), 21 U.S.C. § 301 et seq., and specifically by the so-called Hatch-Waxman Amendments to the FDCA. Justice Kagan provided in *Caraco Pharmaceutical Laboratories, Ltd. v. Novo Nordisk A/S*, 566 U.S. 399 (2012), this helpful summary of the provisions of the Amendments and the FDA regulations that bear on this case:

> The FDA regulates the manufacture, sale, and labeling of prescription drugs under a complex statutory scheme. To begin at the beginning: When a brand manufacturer wishes to market a novel drug, it must submit a new drug application (NDA) to the FDA for approval. The NDA must include, among other things, a statement of the drug's components, scientific data showing that the drug is safe and effective, and proposed labeling describing the

uses for which the drug may be marketed. The FDA may approve a brand-name drug for multiple methods of use—either to treat different conditions or to treat the same condition in different ways.

Once the FDA has approved a brand manufacturer's drug, another company may seek permission to market a generic version pursuant to legislation known as the Hatch-Waxman Amendments. Those amendments allow a generic competitor to file an abbreviated new drug application (ANDA) piggy-backing on the brand's NDA. Rather than providing independent evidence of safety and efficacy, the typical ANDA shows that the generic drug has the same active ingredients as, and is biologically equivalent to, the brand-name drug. As we have previously recognized, this process is designed to speed the introduction of low-cost generic drugs to market.

Because the FDA cannot authorize a generic drug that would infringe a patent, the timing of an ANDA's approval depends on the scope and duration of the patents covering the brand-name drug. Those patents come in different varieties. One type protects the drug compound itself. Another kind . . . gives the brand manufacturer exclusive rights over a particular method of using the drug. In some circumstances, a brand manufacturer may hold such a method-of-use patent even after its patent on the drug compound has expired.

To facilitate the approval of generic drugs as soon as patents allow, the Hatch-Waxman Amendments and FDA regulations direct brand manufacturers to file information about their patents. The statute mandates that a brand submit in its NDA the patent number and the expiration date of any patent which claims the drug for which the brand submitted the NDA or which claims a method of using such drug. And the regulations issued under that statute require that, once an NDA is approved, the brand provide a description of any method-of-use patent it holds. That description is known as a use code, and the brand

submits it on FDA Form 3542. . . . [T]he FDA does not attempt to verify the accuracy of the use codes that brand manufacturers supply. It simply publishes the codes, along with the corresponding patent numbers and expiration dates, in a fat, brightly hued volume called the Orange Book (less colorfully but more officially denominated Approved Drug Products With Therapeutic Equivalence Evaluations).

After consulting the Orange Book, a company filing an ANDA must assure the FDA that its proposed generic drug will not infringe the brand's patents. When no patents are listed in the Orange Book or all listed patents have expired (or will expire prior to the ANDA's approval), the generic manufacturer simply certifies to that effect. Otherwise, the applicant has two possible ways to obtain approval.

* * * *

[One of those ways] is to file a so-called paragraph IV certification, which states that a listed patent "is invalid or will not be infringed by the manufacture, use, or sale of the generic drug." 21 U.S.C. § 355(j)(2)(A)(vii)(IV). A generic manufacturer will typically take this path in either of two situations: if it wants to market the drug for all uses, rather than carving out those still allegedly under patent; or if it discovers, as described above, that any carve-out label it is willing to adopt cannot avoid the brand's use code. Filing a paragraph IV certification means provoking litigation. The patent statute treats such a filing as itself an act of infringement, which gives the brand an immediate right to sue [under 35 U.S.C. § 271(e)(2)(A)]. Assuming the brand does so, the FDA generally may not approve the ANDA until 30 months pass or the court finds the patent invalid or not infringed. Accordingly, the paragraph IV process is likely to keep the generic drug off the market for a lengthy period, but may eventually enable the generic company to market its drug for all approved uses.

566 U.S. at 404–08 (irrelevant citations and internal quotation marks omitted).

II. FINDINGS OF FACT

A. The Parties

1) Plaintiff Gilead Sciences, Inc. is a Delaware corporation with its principal place of business in California. D.I. 891-1 ¶ 4. Gilead owns the asserted patents. D.I. 891-1 ¶ 37.

2) Plaintiff Astellas US LLC, a Delaware limited liability company with its principal place of business in Illinois, is the exclusive licensee of the asserted patents. D.I. 891-1 ¶¶ 2, 38.

3) Plaintiff Astellas Pharma US, Inc., a Delaware corporation with its principal place of business in Illinois, is a sub-licensee of the asserted patents and a and a distributor of Lexiscan®. D.I. 891-1 ¶¶ 3, 39.

4) Hospira is a Delaware corporation with a principal place of business in Illinois. D.I. 891-1 ¶ 7.

B. Nonparty Curia

5) Curia Missouri, Inc. (formerly Euticals, Inc.) manufactures in Springfield, Missouri, the regadenoson used in Hospira's ANDA product. For ease of reference, I will refer to Euticals and Curia each as "Curia." D.I. 891-1 ¶¶ 71, 75–76.

C. The Asserted Patent Claims

6) The asserted patent claims all recite, or depend from independent claims that recite, a "monohydrate" or "crystalline monohydrate" form of regadenoson—i.e., "Form A regadenoson."

7) Claim 1 of the #183 patent reads: "A monohydrate of (1-{9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-aminopurin-2-yl}pyrazol-4-yl)-N-methylcarboxamide, which monohydrate is in a crystalline form." D.I. 891-1 ¶ 18.

8) Claim 6 of the #301 patent states:

> A pharmaceutical composition of an A2A-adenosine receptor agonist produced by a process comprising the following step:
>
> dissolving a crystalline monohydrate form of the compound (1-{9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-aminopurin-2-yl}pyrazol-4-yl)-N-methylcarboxamide that is substantially free of 2-hydrazinoadenosine in a pharmaceutically acceptable carrier.

D.I. 891-1 ¶ 25.

9) Claims 1–3 of the #883 patent recite methods of manufacturing Form A. They read:

> 1. A method of preparing a pharmaceutical composition comprising combining a monohydrate of the compound (1-{9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-aminopurin-2-

yl}pyrazol-4-yl)-N-methylcarboxamide with at least one pharmaceutically acceptable carrier.

2. The method of claim 1, wherein the pharmaceutically acceptable carrier comprises a buffered aqueous solution.

3. The method of claim 2, wherein the monohydrate is a crystalline monohydrate that is substantially free of 2-hydrazinoadenosine.

D.I. 891-1 ¶ 32.

10) The three asserted patents share a common written description. D.I. 891-1 ¶ 35.

D. The Parties' Witnesses

1. Plaintiffs' Witnesses

a. Fact Witnesses

11) Dr. Jeffrey A. Zablocki, a named inventor on the three asserted patents, is a medicinal chemist with a Ph.D. in organic chemistry from the University of Illinois at Urbana-Champaign. Dr. Zablocki worked for CV Therapeutics (CVT) from 1998 to 2009. While there, he helped lead the effort to develop the compound regadenoson. Tr. at 122:4–127:22 (Zablocki).

12) Dr. Elfatih Elzein also worked for CVT, where he was "the first to synthesize or identify the monohydrate of regadenoson." Tr. at 581:15–588:13 (Elzein). He is also a listed inventor for the three asserted patents. PTX-1.2; PTX-3.2; PTX-5.2.

13) Dr. Robert Seemayer is an executive director in chemical development and manufacturing at Gilead Sciences. He obtained a Ph.D. in organic chemistry from the University of Wuppertal in Germany before joining CVT in 2002 to assist its attempts "to scale up the manufacture[] of regadenoson monohydrate" and ensure that CVT could "achieve a robust, consistent manufacturing process." Tr. at 149:16–152:1 (Seemayer). He is also a named inventor for two of the asserted patents. PTX-3.2; PTX-5.2.

14) Dr. Daniel Smith is a professor at the Purdue University College of Pharmacy. He was shipped regadenoson samples from Curia's process that he then packaged, stored, and handed off to Dr. Eric J. Munson for testing. Tr. at 444:6–450:5 (Smith).

b. Expert Witnesses

15) Dr. Jeffrey A. Leppo is a retired clinical academic cardiologist who began practicing as a doctor in 1973. Tr. at 88:18–90:20 (Leppo).

16) Dr. Eric. J. Munson is a professor of pharmacy at Purdue University who specializes in the "characterization of pharmaceutical solids, using a variety of different analytical techniques," including "differential scanning calorimetry, thermogra[vi]metric analysis, but especially solid-state NMR spectroscopy, and powder X-ray diffraction." Tr. at 205:19–208:22 (Munson).

17) Dr. Allan S. Myerson is a professor of chemical engineering at the Massachusetts Institute of Technology (MIT) in Cambridge, Massachusetts. His research focuses on "crystallization, pharmaceutical manufacturing, and pharmaceutical dosing forms" and has resulted in 285 publications, around 75% of which focus on crystallization. Dr. Myerson has edited six books relating to crystallization. Tr. at 233:5–234:2 (Myerson).

18) Dr. Bernhard L. Trout has been a professor of chemical engineering at MIT for close to 25 years. He received his Ph.D. from the University of California at Berkeley, and the focus of his research is in "pharmaceutical formulation, development, [and] manufacturing technologies, including crystal forms and crystal structures." He is also "an expert in XRPD data and analysis." Tr. at 681:5–682:12 (Trout).

2. Hospira's Witnesses

a. Fact Witnesses

19) Dr. Andrew Knill works for Pfizer, which acquired Hospira Australia and Mayne Pharmaceuticals. Dr. Knill conducted synchrotron testing of Curia's regadenoson to investigate the possible presence of the monohydrate form, and he then prepared a report about the testing results in cooperation with a member of Pfizer's legal department, Katherine Legge. Tr. at 180:18–185:1 (Knill).

20) Balaji Paneerselvam is "the formulation and process development lead" for Hospira's regadenoson project. As such, he was involved in discussions between Curia and Hospira regarding the possible presence of infringing Form A regadenoson in Curia's manufacturing process. Tr. at 194:2–197:24 (Paneerselvam).

21) Emily Fearnow is Hospira's corporate representative and has been its senior manager of regulatory affairs since 2017. Fearnow oversaw Hospira's ANDA submission and its cooperation with Curia. Tr. at 189:1–193:11 (Fearnow).

22) Stephen Hancock has a B.S. in chemical engineering from the University of Missouri in Rolla and an MBA from Drury University. He works for Curia at its Springfield, Missouri, facility, where he serves as API project manager and "coordinate[s] projects in late stage development, developing the process, preparing drug master files, essentially commercializing late stage products." Since 2017, he has been the project manager directly responsible for Curia's regadenoson API, and prior to that point, he helped implement the technology transfer from Curia's research and development team in Italy to its Springfield location, along with scaling the technology up, validating the process, and starting API production. He continues to manage Curia's anhydrous regadenoson program, providing technical support, supporting customers and their requests for

information, supporting Curia's regulatory team, and preparing and reviewing Curia's filings with the FDA. Tr. at 369:8–372:6 (Hancock).

b. Expert Witnesses

23) Dr. Jonathan Steed is a professor of inorganic chemistry at Durham University in the United Kingdom and an expert in the field of solid state chemistry and crystallography. He obtained a B.S. and Ph.D. in chemistry from the University College London. His research includes the study of crystalline solids, X-ray crystallography, novel pharmaceutical solid forms, pharmaceutical hydrates, and crystal growth methodologies. Over his 30-year career in chemistry and crystallography, he has published over 350 peer-reviewed scientific articles relating to polymorphism, crystallization, and X-ray diffraction and coauthored two textbooks and eight book chapters. Dr. Steed also serves as editor-in-chief of the American Chemical Society journal "Crystal Growth and Design" and is a fellow of the Royal Society of Chemistry. He is a member of the American Chemical Society and the British Crystallographic Association. Dr. Steed is the recipient of numerous honors by the Royal Society of Chemistry, including most recently the Tilden Prize in 2021. Tr. at 452:4–454:23 (Steed).

24) Dr. John M. Galla received a B.S. in aerospace engineering from the University of Notre Dame and an M.D. from the University of Washington School of Medicine, whereupon he completed an internship and his residency at Duke

University. He is an expert in the field of cardiac stress testing. Tr. at 558:13–560:13 (Galla).

25) Dr. Trevor Laird is an expert in the field of process chemistry and pharmaceutical development. He received a B.S. in chemistry from the Imperial College in London and a Ph.D. in organic chemistry from London University, and he worked as a postdoctoral fellow at Sheffield University. Tr. at 588:14–591:12 (Laird).

E. The Artisan of Ordinary Skill

26) "A court construing a patent claim seeks to accord a claim the meaning it would have to a person of ordinary skill in the art at the time of the invention." *Innova/Pure Water, Inc. v. Safari Water Filtration Sys.*, 381 F.3d 1111, 1116 (Fed. Cir. 2004). The parties offered at trial competing but similar definitions of the artisan of ordinary skill to whom the asserted patents are directed. Both parties stated that their positions would not change if the Court were to adopt the other side's definition of a skilled artisan. *See* D.I. 891-1 ¶ 49. Accordingly, I will adopt Plaintiffs' proposal that an artisan of ordinary skill would have

> at least a bachelor's degree in chemistry, chemical engineering, pharmaceutical sciences, or a related discipline, along with several years of experience working in pharmaceutical development and/or solid state chemistry[] [and] would also have been part of a team which would have included synthetic organic chemists and

process chemists, formulation scientists, analytical scientists, and clinicians.

D.I. 891-1 ¶ 42.

F. Crystalline Forms and XRPD Testing

27) Solids are either amorphous or crystalline in form. The constituent atoms or molecules of an amorphous solid are randomly arranged. Tr. at 239:21–240:10 (Myerson). The constituent atoms or molecules of a crystalline solid are arranged in definite and repeating patterns. *Id.* at 467:23–468:15 (Steed). These repeating patterns, often referred to as "packing arrangements," vary. *Id.* When a compound has more than one crystalline form (because its constituent atoms or molecules can have more than one packing arrangement), it is said to exhibit polymorphism. Crystalline forms are sometimes referred to as polymorphs. *Id.* at 215:4–22 (Munson).

28) The crystalline forms of a pharmaceutical compound can exhibit markedly different physical properties and can affect the compound's stability, safety, and efficacy. In general, a pharmaceutical formulator prefers to use a crystalline form that is highly stable in order to reduce the likelihood that the compound will convert to a physical form that might be less safe or efficacious. Tr. at 130:18–131:11 (Zablocki).

29) Crystalline forms (i.e., polymorphs) that contain water are called hydrates. A monohydrate contains one molecule of water in the crystal lattice for

every molecule of the compound. Tr. at 136:24–137:1 (Zablocki); *id.* at 310:11–15 (Myerson); *id.* at 456:13–16 (Steed).

30) Anhydrous forms contain no water. Tr. at 373:6–22 (Hancock).

31) The parties identified at trial four methods used by scientists to analyze and identify crystalline forms: Fourier Transform Infrared Spectroscopy (FTIR), Differential Scanning Calorimetry (DSC), Thermogravimetric Analysis (TGA), and X-Ray Powder Diffraction (XRPD). *See, e.g.*, Tr. at 268:20–269:5, 311:21–312:14 (Myerson).

32) Both parties characterized XRPD as the "gold standard" for crystalline form identification. *See* D.I. 891-2 ¶ 22; *see also* D.I. 925 at 7 n.1.

33) XRPD testing is performed by shining a source of X-rays on a solid sample and detecting and measuring the X-rays that are diffracted from the sample. Tr. at 211:8–13 (Munson). The output of an XRPD test is called a diffractogram. *Id.* at 211:14–18 (Munson). Peaks in a diffractogram are identified at units called degrees 2-theta, and the standard error for these measurements is ± 0.2. *Id.* at 212:4–17, 225:1–12 (Munson); *id.* at 250:16–22, 254:17–19 (Myerson); *id.* at 464:23–465:6, 465:10–22 (Steed).

34) A special type of XRPD testing, using synchrotron radiation generated by a particle accelerator, can be performed at 16 research facilities in the United States. Synchrotron testing is more expensive and more sensitive than "standard"

or "regular" laboratory XRPD testing. The parties throughout the trial and in their briefing referred to laboratory or standard XRPD testing as simply "XRPD" and referred to synchrotron XRPD as "synchrotron." Tr. 299:5–17, 334:17–335:2 (Myerson); *id.* at 483:2–11, 531:21–532:5, 533:9–14, 536:15–18 (Steed).

35) The preparation and handling of a sample can affect the XRPD analysis of that sample. Tr. at 329:7–9 (Myerson).

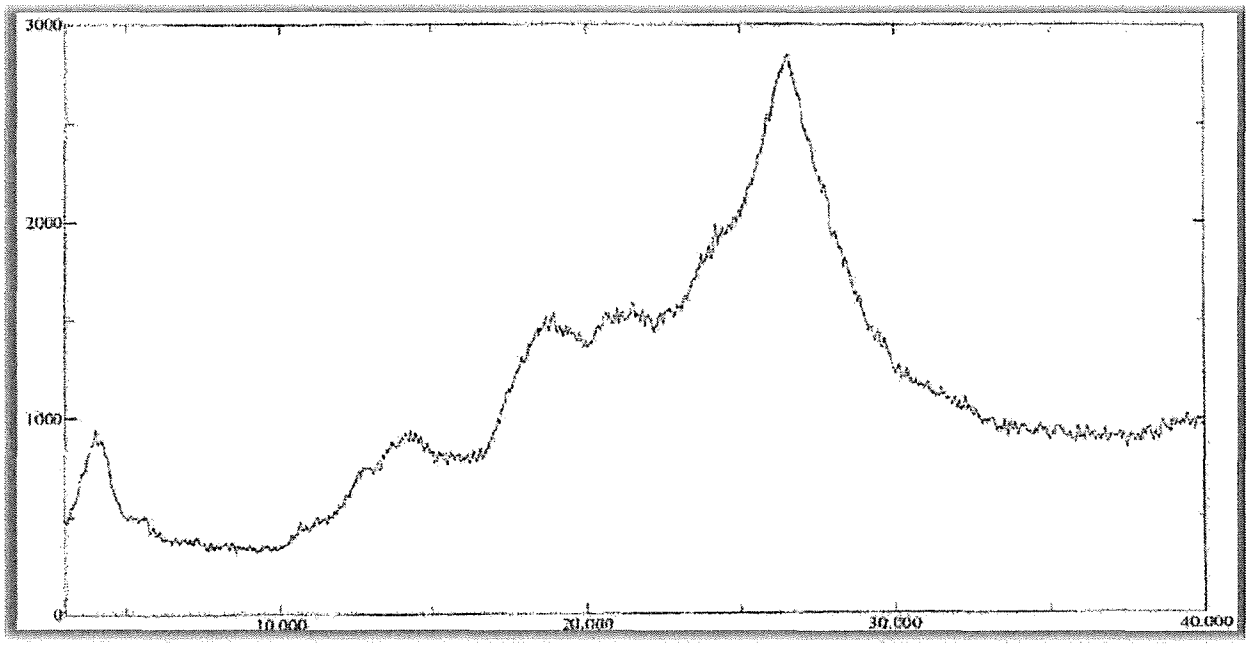
G. Regadenoson

36) Regadenoson is a compound with the chemical name (1-{9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-aminopurin-2-yl}pyrazol-4-yl)-N-methylcarboxamide. D.I. 891-1 ¶ 36.

37) Regadenoson can exist in various crystalline forms, each of which has different characteristics, including different XRPD patterns. Tr. at 215:4–22 (Munson).

38) "Crude" regadenoson is non-crystalline regadenoson that has an amorphous form, meaning that its molecules are randomly arranged and have no repeating internal structure. Crude regadenoson is not stable and has a tendency to convert to crystalline material. Tr. at 239:21–240:10, 243:5–9 (Myerson).

39) Crude regadenoson is amorphous, and its XRPD diffractogram shows no sharp peaks:



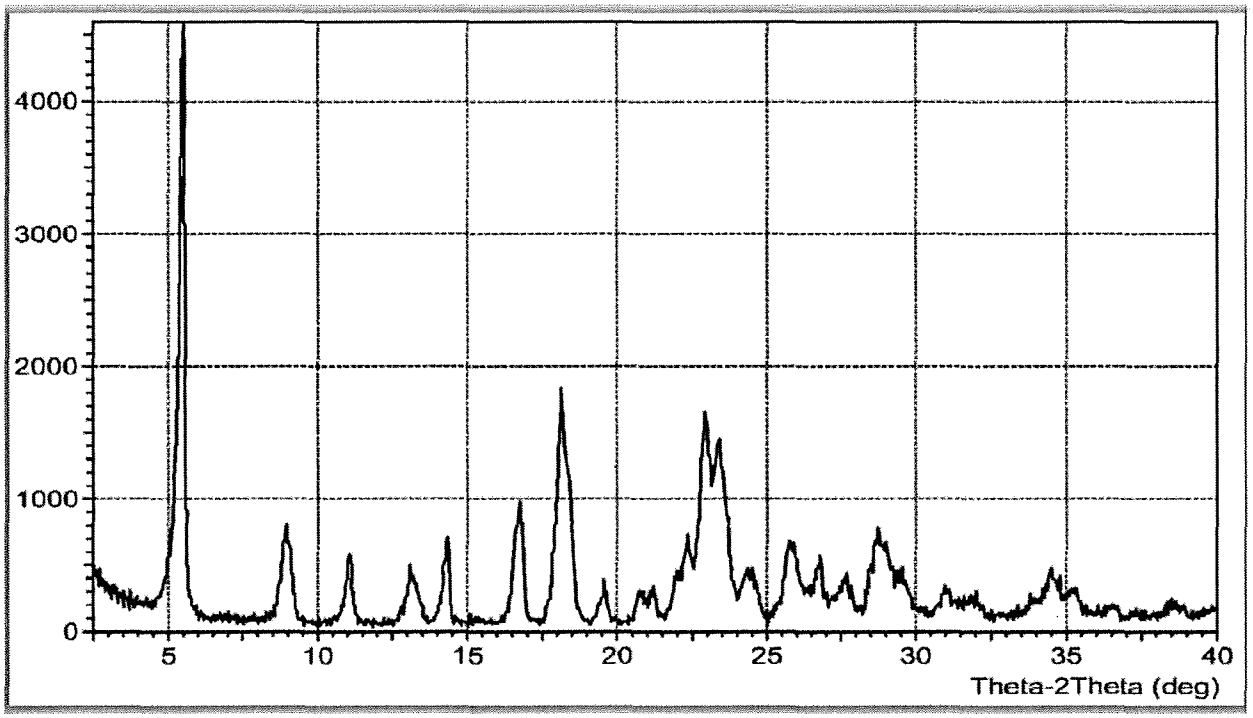
DTX-111.9.

1. Regadenoson Polymorphs

40) It is undisputed that eight crystalline forms of regadenoson have been identified to date: Form A, Form B, Form C, Form D, Form G, and two different forms that have each been designated by different artisans as Form E. Tr. at 139:1–5 (Zablocki); *id.* at 220:5–7, 226:11–17, 227:4–13, 227:20–25 (Munson); *id.* at 239:3–6 (Myerson); *id.* at 458:6–8, 464:7–8, 464:23–465:3, 465:12–22, 466:14–17 (Steed); PTX-273.5; *see* D.I. 914 ¶ 36; D.I. 914 at 11 n.3.

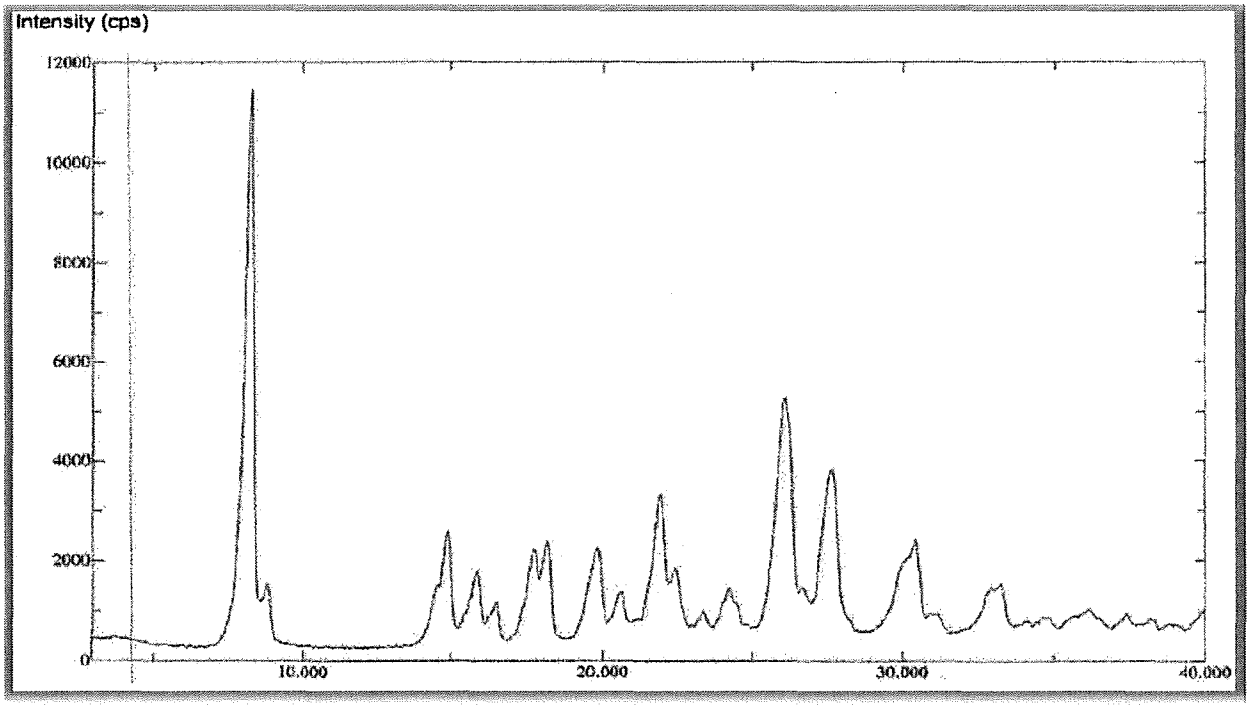
41) XRPD analysis of Form A regadenoson shows peaks near, among other points, 5.6, 9.1, 11.1, 13.1, 14.4, and 16.8° 2-theta. DTX-3.8; *see* Tr. at 253:23–254:2 (Myerson). It is undisputed that the most intense peak in Form A's XRPD diffractogram occurs at 5.6° 2-theta, as shown in Figure 3 of the #183 patent

depicted below. PTX-1.13 at 5:52–54, PTX-1.14 at 7:5–7; PTX-364 (raw data for the Form A diffractogram); Tr. at 218:6–10, 225:1–6 (Munson); *id.* at 512:23–25 (Steed).



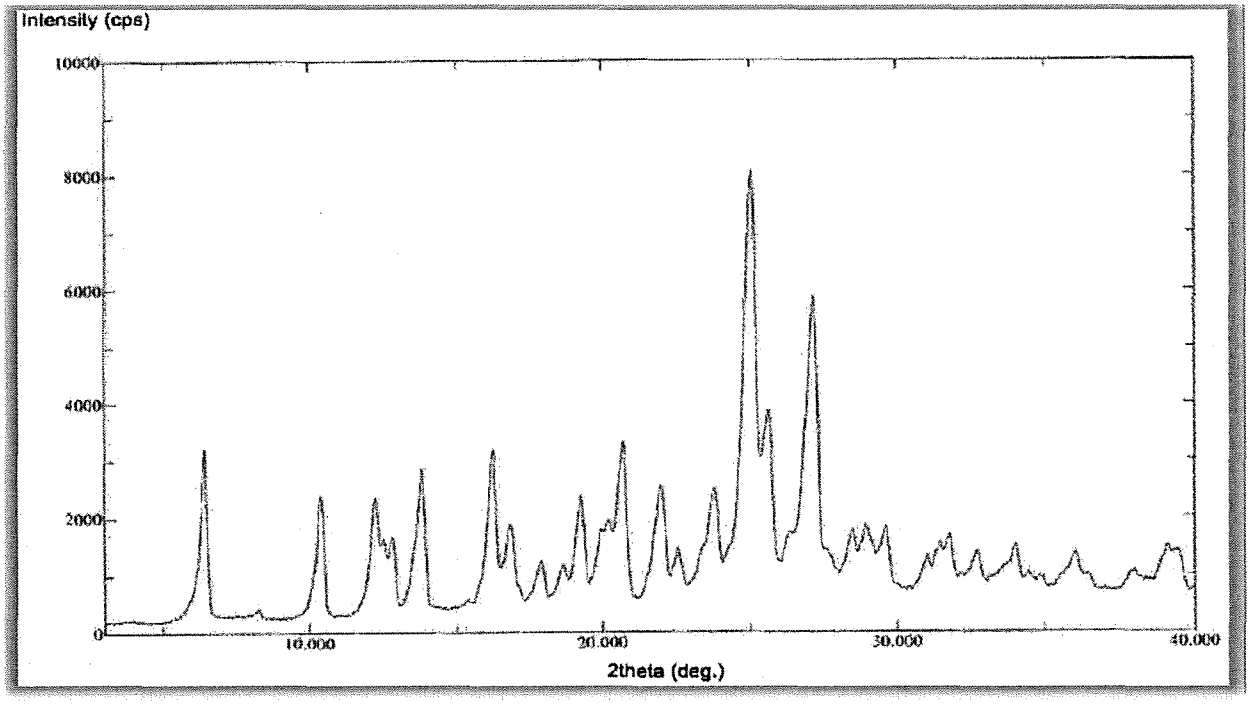
PTX-1.8, Fig. 3 (Form A); DTX-3.8.

42) Form G can be identified with the following XRPD diffraction pattern, having peaks near 8.24, 14.9, 17.7, 18.16, 19.84, 21.92, 26.16, 27.68, and 30.44° 2-theta, among others:



DTX-111.5; *see* DTX 111.20.

43) Form F is identified with the following XRPD diffraction pattern, having peaks near 6.42, 13.8, 16.24, 19.28, 20.2, 22, 23.38, 25.04, 25.6, and 27.18° 2-theta, among others:

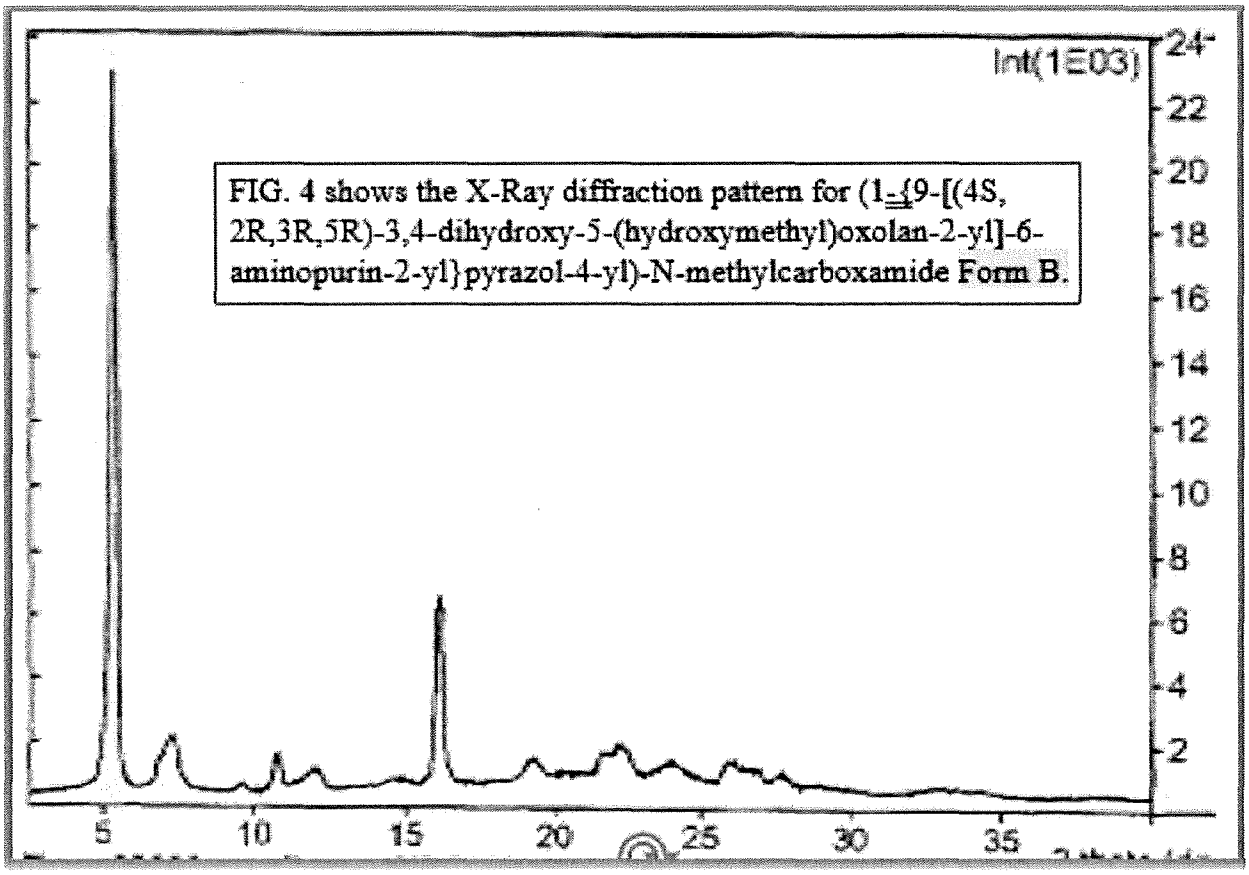


DTX-111.3; *see* DTX-111.17.

44) Neither crude, Form F, nor Form G regadenoson has a peak at 5.6° or 11.1° 2-theta. PTX-273.9, 11; Tr. at 459:7–14 (Steed).

45) There are, however, other known regadenoson polymorphs that have peaks that fall within the margin of experimental error of 5.6° 2-theta. Tr. at 463:11–15 (Steed).

46) For example, Dr. Steed testified that Form B, which is depicted in Figure 5 of the #883 patent, has "a peak that's in the vicinity of 5.6 within the plus or minus 0.2 degrees experimental error." Tr. at 464:7–10. Figure 5 supports that testimony:



DTX-3.1, 9, 13 (annotated).

47) Dr. Munson testified that Form B does not have a peak at 5.6° 2-theta, but instead at "a little bit lower than that[,] . . . a little closer to 5 degrees 2-theta." Tr. at 226:8–10. He did not, however, specify how close that peak is to 5° 2-theta as compared to 5.6° 2-theta; and thus, he did not rule out that this peak is at 5.4° 2-theta, which would put it within the 0.2° 2-theta margin of experimental error for the Form A peak at 5.6° 2-theta. *Id.* at 464:7–10 (Steed).

48) Dr. Munson testified that the asserted patents "say[] that the X-ray analysis of the [Form B] crystals was distinctly different from any other

polymorph." Tr. at 226:11–17. This is true but irrelevant. The pattern for Form B is distinct from other polymorphs. But that does not mean that every peak in Form B is different from every peak in every other regadenoson form.

49) Plaintiffs argue that a polymorph screening test conducted by Curia[1] in 2002 reported that Form B "contains a peak near 5.0, not at about 5.6." D.I. 914 ¶ 35. But the polymorph screen in question states only that "[t]he XRPD pattern for form B contains a peak near 5.0° 2-theta while there is no peak near this position in the XRPD pattern for Form C." PTX-55.23. No record evidence was adduced to establish what "near 5.0" means in the polymorph screen.

50) I therefore find based on Figure 5 of the #883 patent and Dr. Steed's testimony that Form B has a peak within the margin of error of Form A's characteristic peak at 5.6° 2-theta.

51) Form D regadenoson, disclosed in Figure 4 of U.S. Patent No. 8,859,522 (the #522 patent), also has a peak within the margin of error of 5.6° 2-theta. Tr. at 464:23–465:6 (Steed). In fact, as Dr. Steed testified, Forms A and D

[1] Technically, the polymorph screen had been completed by SSCI, which had been Curia's third-party testing partner for years, prior to its acquisition by Curia and its rebranding as "Curia Indiana." *See* Tr. at 346:14–17, 351:21–352:1 (Myerson); *id.* at 398:19–25 (Hancock). For ease of reference, I will refer to both SSCI and Curia Indiana simply as "Curia."

have several overlapping peaks. *Id.* at 521:18–522:14. Figure 4, depicted below, supports Dr. Steed's conclusion:

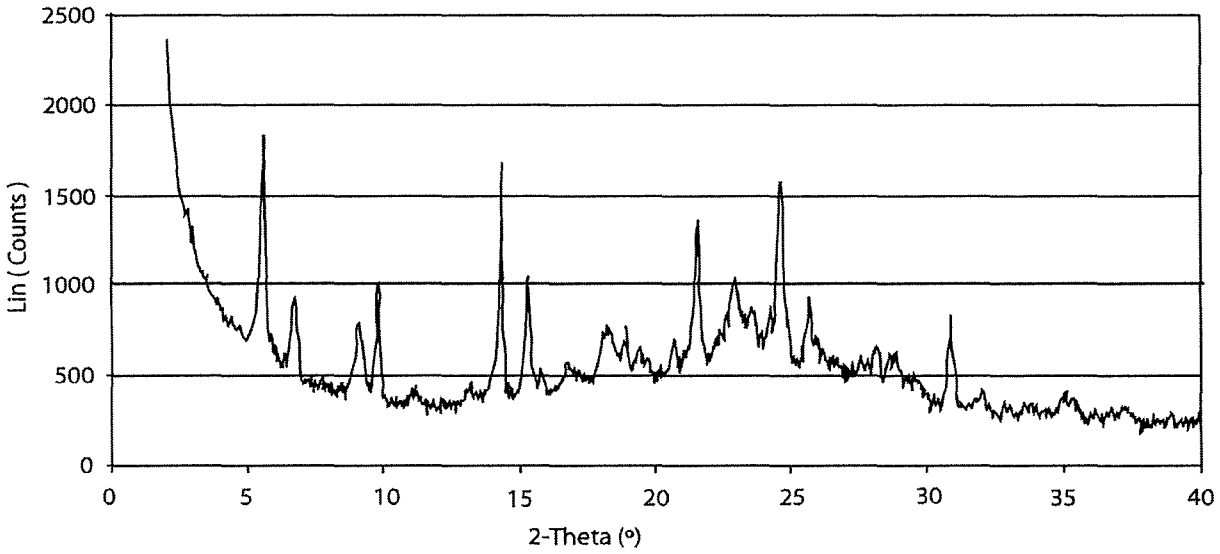


Figure 4

DTX-130.5.

52) Plaintiffs argue that Figure 4 "reflects a mixture of polymorphs that includes Form A." D.I. 914 ¶ 36. It is true that the #522 patent states that "[i]n [one] embodiment, the invention provides a composition comprising Form D of regadenoson and one or more other solid state forms of regadenoson, such as Form A, B[,] or C of regadenoson." DTX-130.9. But the patent explicitly states that "FIG. 4 is an [XRPD] pattern of Form D of regadenoson," that "[t]he [XRPD] pattern of the crystalline form (Form D) is provided in FIG. 4," and that "the crystalline form of regadenoson (Form D) is characterized by a[n] [XRPD] pattern substantially as shown in FIG. 4." *Id.* at 7, 9; *see* Tr. at 542:7–17 (Steed).

Accordingly, I reject Plaintiffs' argument that the presence of Form A accounts for the 5.6° 2-theta peak in Figure 4; and I find, based on Dr. Steed's credible testimony and Figure 4, that Form D has a peak at approximately 5.5° 2-theta, putting it within the margin of error of Form A's major peak. DTX-130.5; Tr. at 464:23–465:6.

53) The Form E regadenoson disclosed in U.S. Patent No. 9,441,006 (the #006 patent), DTX-114, also has a peak within the margin of experimental error of 5.6° 2-theta, namely 5.8° 2-theta. Dr. Steed, whom I found to be credible, testified that "[t]his particular polymorph E disclosed in the [#]006 patent is a polymorph that has a peak at 5.8 degrees. And that's[] listed in the claims of the patent, claim 1, and, of course that's within the 0.2 degrees error of 5.6 as well. . . . [T]he first peak that is indicated in the diffraction pattern [is] . . . 5.8 degrees." Tr. at 465:10–466:9; *see* DTX-114.1, 9.

54) Figure 1 of the #006 patent is depicted below:

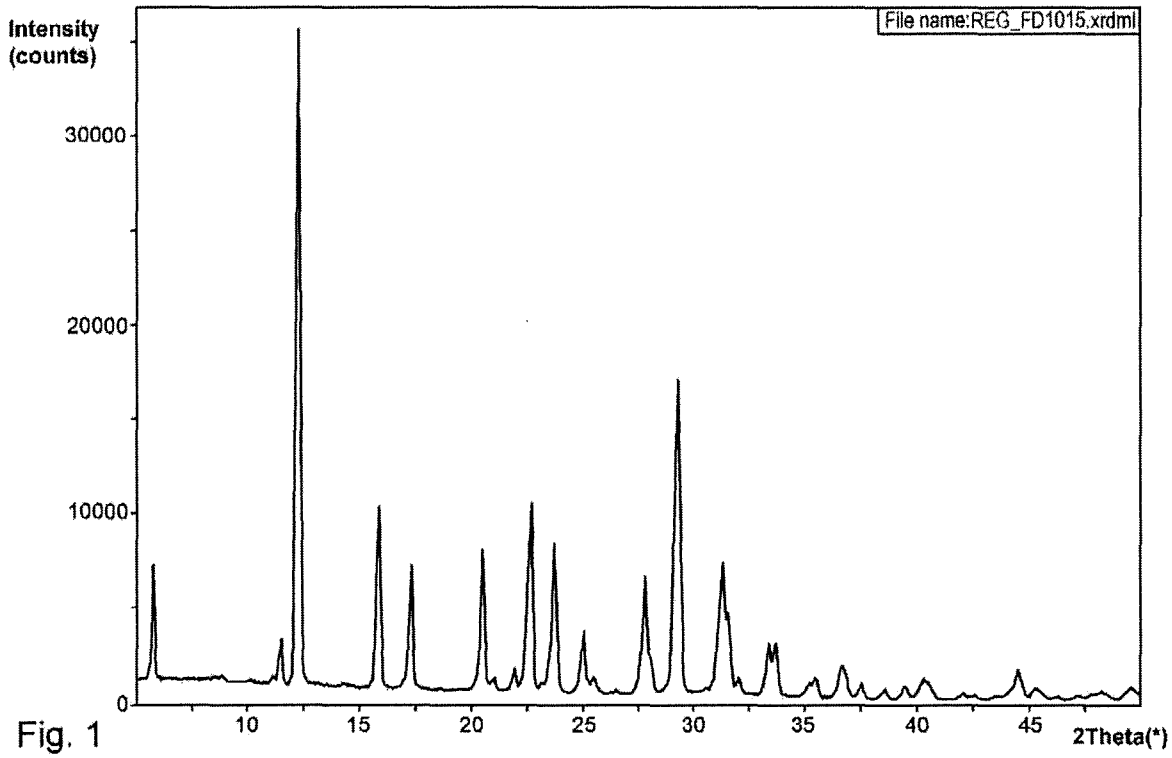


Fig. 1

DTX-114.3.

55) Plaintiffs assert that "Form E does not have a peak at about 5.6° 2-theta when converted to the same x-ray wavelength . . . used in the Patents-in-Suit to measure Form A," as "[t]he diffractogram and peak list for Form E were generated using a Cobalt anode wavelength," whereas "the Patents-in-Suit used a Copper anode to generate the Form A diffractogram, and Curia's patent application also used a Copper anode." D.I. 914 ¶ 37 (emphasis omitted). Plaintiffs' experts, however, did not offer any testimony about the #006 patent, nor does the term "copper anode" appear in any trial testimony—it was first used by Plaintiffs' counsel during closing argument. Tr. at 774:11–19. Even crediting Dr. Myerson's

testimony regarding the use of "Bragg's law" to convert from "the synchrotron wavelength" to "the wavelength used in laboratory diffractometers," Tr. at 304:2–15, and even though Dr. Steed agreed, "generally" or "[b]roadly" speaking, with Dr. Myerson's explanation of "polymorphism and different crystalline forms," *id.* at 457:6–14, there is no record evidence about whether a Cobalt anode XRPD diffractogram must be converted to be comparable to a Copper anode XRPD diffractogram. And in any event, I found Dr. Steed to be credible generally, and I deemed his testimony about Form E to be credible in particular. Accordingly, I find that the Form E regadenoson disclosed in the #006 patent has a peak within the experimental error of 5.6° 2-theta.

56) There may also be other, as yet undiscovered, crystalline forms of regadenoson. Tr. at 347:24–348:10, 359:11–20 (Myerson); *id.* at 489:17–24, 500:9–13 (Steed). And as Dr. Myerson admitted at trial, it is possible that an as yet undiscovered form of regadenoson will have a peak at 5.6° 2-theta. *Id.* at 347:24–348:10, 359:11–20.

2. Conversion of Crude and Anhydrous Crystalline Forms of Regadenoson to Form A

57) Form A is the only known monohydrate crystalline form of regadenoson and is the most stable of the known regadenoson crystalline forms. Tr. at 139:14–19 (Zablocki); *id.* at 177:18–22 (Seemayer); *id.* at 229:9–17 (Munson); *id.* at 343:9–17 (Myerson).

58) Crude, Form F, and Form G regadenoson are anhydrous. Tr. at 324:2–3 (Myerson); *id.* at 373:11–22 (Hancock).

59) It is undisputed that when crude and anhydrous crystalline forms of regadenoson are exposed to a sufficient amount of water, including water in the air (i.e., humidity) and in reagents, they will convert to Form A. Tr. at 271:5–13, 277:4–11, 277:18–281:7, 342:9–25, 358:19–23, 359:21–360:14, 360:22–367:2 (Myerson); *id.* at 467:23–469:5, 470:18–471:4, 504:10–18, 507:8–19 (Steed).

60) Neither side in this case adduced credible evidence to establish by a preponderance of the evidence what amount of water exposure is sufficient to convert crude and anhydrous crystalline forms of regadenoson into Form A.

61) Dr. Myerson testified at trial during his cross-examination in relevant part:

> Q. . . . And the concept underlining your theory is that Form A is the most stable polymorphic form in the presence of even small amounts of water, correct?
>
> A. Well, *if we're going to be precise, what that means is crude or Form F can convert to Form A in a particular -- something we call a water activity. And at a given water activity, Form A is more stable than amorphous or Form F.*
>
> Q. Your opinion is that the regadenoson monohydrate is the most stable form at room temperature in the presence of water, correct?
>
> A. Right. But I'm being precise because we're talking about *– we're not specifying how much water, but the way this works, remember – there's something called the water activity.* Okay.

> And *at a given water activity*, a Form A will be the most stable form in the presence of a given water activity and at room temperature.

Tr. at 343:2–17 (emphasis added).

62) On redirect examination, Dr. Myerson testified that "it's clear that Form F converts to Form A *at certain water activities*." Tr. at 359:25–360:1 (emphasis added).

63) Dr. Myerson never explained during his direct, cross-examination, or redirect testimony what "water activity" is. Nor did he offer an opinion about or describe the "given water activity" or "particular" water activity at which Form A is more stable than amorphous or Form F regadenoson such that conversion into Form A will occur.

64) After his redirect testimony was completed, I engaged in the following exchange with Dr. Myerson:

> THE COURT: . . . What is it about the quantity of water that would enable you to offer an opinion with a reasonable degree of scientific certainty that it's more likely than not [that Curia's crude regadenoson intermediate undergoes some conversion to Form A]; what is it about the quantity of water that leads you to that conclusion?
>
> THE WITNESS: I believe I did a rough calculation and there's about one water for every ten regadenoson present in that process, which is not a tiny amount of water. It's certainly enough water to cause some of the amorphous material to convert; not completely convert, but some of it to always convert or very likely convert.

THE COURT: Well, what if the water [in a sample of crude regadenoson] was one in every 20 of regadenoson present in [the] form – in the crude form; at that point what would the chances of – the likelihood of conversion to Form A be?

THE WITNESS: The likelihood of conversion would still be significant, just the amount of conversion would be less. Right. *The amount of conversion you can get is – how much Form A you can make is connected to how much water there is.*

THE COURT: That sounds to me like you're saying if there's any amount, even an infinitesimal, you know, small amount, you're saying there's still the likelihood of conversion over 50 percent[,] but the quantity could vary?

THE WITNESS: No. No. You get to a place. This is what I was talking about[,] and this is a little esoteric.

THE COURT: This is the water activity.

THE WITNESS: This is the water activity thing. *Below a certain water activity you're not going to get conversion.*

THE COURT: How is water activity measured?

THE WITNESS: *Water activity is related to the amount of water, but it's a thermodynamic quality that you can measure. It's a little complicated. You know, I don't want to start talking about thermodynamics.*

THE COURT: Let me stop you because you've already – even in your answer you just said it's related to the amount of water.

THE WITNESS: It's not exactly the amount of water.

THE COURT: What is it then – you know, I mean, I['ve] got to make a decision.

THE WITNESS: Yes.

THE COURT: I have to make a decision whether it's essentially more likely than not. And you're telling me, for every batch made using the [Form G] process that Curia uses, there's a better than 50 percent chance that the crude regadenoson is going to lead to the generation of Form A?

THE WITNESS: Yes.

THE COURT: That's what your opinion is?

THE WITNESS: That's what my opinion is.

THE COURT: Right. The burden's on you to persuade me, so – well, why is it that? Why is it better than 50 percent? Because yesterday you just said it was likely, you didn't say it was more than likely. So I'm trying to understand why.

THE WITNESS: No. It's – okay. *So it's the amount of water. And if we go to your hypothetical, there is an amount of water where it would not be likely.*

THE COURT: All right. So what's that? What's that amount of water?

THE WITNESS: *It's a lot less than, you know, one in –*

THE COURT: *One in ten?*

THE WITNESS: *One in ten.*

THE COURT: *What is it?*

THE WITNESS: *I don't know for sure[,] but I would say if it was one in 50, it would be unlikely. One in 100, certainly unlikely.*

THE COURT: *What could you point to that would give me comfort that you're not just pulling that out of the air right now, that one in ten is – gets you there, but one in 50 doesn't?*

THE WITNESS: What could I give you? *The only way you could have comfort there is looking at conversion studies and the fact – well, the only conversion studies we actually have seen relate to exposure to humid air, which is not exactly the same thing. But we do know that the amorphous material converts to Form A when it's exposed to humid air. And the amount of water in humid air, we can calculate what that number is and it's probably in that – you know, that one – the one to 20, you know, kind of range. You know, something like that.* So that would – that would be where we could quantify something. And you get to a humidity where it won't convert which is where it would be like one to 50. *There's actually some tests – there's actually a scientific test where you can actually measure this which I haven't seen enough data in this case for, but that's how you would quantify it.*

THE COURT: Now, you also testified yesterday that it was likely that the Form F would convert to Form A during the process. What's the percentage there?

THE WITNESS: In the Form F – yes. So the Form F – again it's, you know, *I would say more likely than not being in the current amount of water they use*[,] about 50 percent. *If they reduce the amount of water, of course it can – it would become less and less likely.*

THE COURT: What's the amount of water in the process then with respect to Form F?

> THE WITNESS: I think it's also – *it might be on the order of one in 20. In that – in this case I think I estimated it. It's just a quick estimate. I think that's right. The other issue with that part of the process is they seem to have trouble controlling their nitrogen blanket, and air has gotten into that process which includes humidity, which has led to conversion as well. I mean, that's kind of a control problem in their process. But when that happens, it certainly can convert. Also, another issue is when they let it sit a long time in the reactor between steps*, it's not like these things are done boom, boom, boom. *Sometimes the material sits for a long time before the next step, ten hours, 20 hours, 30 hours, you know, sometimes even a couple of days. And that can also cause a conversion or make the conversion more likely.*

Tr. at 362:17–367:4 (emphasis added).

65) Thus, according to Dr. Myerson, there is a level of water activity above which Form A will form, and there is a level of water activity below which Form A will not form. Dr. Myerson did not, however, identify what those levels are or explain how to identify those levels either in general or in the context of the manufacture, collection, or testing of regadenoson.

66) And according to Dr. Myerson, "there is an amount of water where it would not be likely" that crude or Form F regadenoson would convert into Form A. But when pressed to identify that amount, Dr. Myerson could only say that (1) "[i]t's a lot less than" the ratio of one water molecule for every ten regadenoson molecules, and (2) "the only way you could have comfort" in identifying that amount would be to look at "conversion studies" that examined amorphous

regadenoson's conversion upon "exposure to humid air." And even though Dr. Myerson testified that "there's actually a scientific test where you can actually measure . . . a humidity where [the crude regadenoson] won't convert" into Form A, neither Dr. Myerson nor any other witness at trial offered or discussed at trial the results of such a test.

67) I find therefore that Plaintiffs did not prove by a preponderance of the evidence what level of water activity or amount of water exposure is necessary to convert crude or anhydrous crystalline forms of regadenoson into Form A. Plaintiff proved only that some unspecified amount of water exposure—either by direct contact with water or by exposure to humidity in air—will cause crude and anhydrous crystalline regadenoson to convert to Form A regadenoson.

H. Astellas's NDA

68) In April 2008, the FDA approved Astellas Pharma US, Inc.'s NDA for Lexiscan®, a 0.4 mg/5 mL (0.08 mg/mL) intravenous solution of regadenoson. Astellas launched Lexiscan® two months later. D.I. 891-1 ¶¶ 52, 54–55, 57.

69) The Orange Book entry for Lexiscan® lists the #183 and #301 patents. D.I. 891-1 ¶ 61.

I. Hospira's ANDA

70) In April 2020, Hospira submitted ANDA No. 214349, seeking approval to market an intravenous solution of regadenoson Form G. D.I. 891-1 ¶ 69.

71) By letter dated June 16, 2020, Hospira notified Plaintiffs that Hospira submitted ANDA No. 214349 to the FDA under 21 U.S.C. § 355(j). D.I. 891-1 ¶ 81.

72) Hospira's ANDA No. 214349 contains certifications pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV) for the #183 patent and the #301 patent. D.I. 891-1 ¶ 82.

73) Hospira's Form G regadenoson is manufactured by Curia. D.I. 891-1 ¶ 71.

74) In May 2016, Curia filed a Drug Master File (DMF) with the FDA. D.I. 891-1 ¶ 76; Tr. at 405:3–8 (Hancock); PTX-1106.

75) A DMF provides confidential detailed information about the facilities, processes, and articles used in the manufacturing, processing, packaging, and storing of one or more human drugs. https://www.ecfr.gov/current/title-21/chapter-I/subchapter-D/part-314/subpart-G/section-314.420.

76) Hospira's ANDA incorporates Curia's DMF and its batch records for Form G regadenoson. D.I. 891-1 ¶¶ 71, 76.

77) Pursuant to a 2020 Quality Agreement, Curia must notify Hospira of its intent to amend its DMF, provide Hospira the opportunity to comment on the proposed changes, and get Hospira to agree in writing to any proposed new specifications. Tr. at 293:6–22 (Myerson); *id.* at 399:25–400:8 (Hancock); PTX-801J.

78) Curia's From G manufacturing process includes the following steps: (1) making a compound called 2-hydrazinoadenosine (2-HA); (2) reacting 2-HA to make an intermediate called pyrazole acetate; (3) converting pyrazole acetate into crude regadenoson using methylamine in ethanol; (4) converting crude regadenoson into Form F regadenoson by mixing it with ethanol; and (5) converting Form F into Curia's regadenoson Form G by heating it in ethanol. FGTX-101.3–7, 10; Tr. at 240:11–241:5 (Myerson); *id.* at 472:17–23 (Steed).

79) It is undisputed that Hospira and Curia do not want Form A to be used in or result from Curia's manufacture of Form G. Tr. at 342:3–5, 357:4–12 (Myerson). Hospira and Curia knew that Plaintiffs owned patents that covered Form A, and Hospira and Curia wanted to avoid infringement of those patents. PTX-838.8 (Hospira presentation noting "Regadenoson Monohydrate is covered by patent"); PTX-892.1; Tr. at 189:24–190:2 (Fearnow); *id.* at 294:14–17 (Myerson).

80) Plaintiffs allege that Curia disclosed in its original DMF "that Curia considered Form A as an impurity/intermediate in its process," D.I. 914 ¶ 98, but I find that the documents and deposition testimony Plaintiffs cite in support of that assertion are ambiguous and do not establish by a preponderance of the evidence that Curia disclosed in its DMF that it considered Form A to be an impurity or intermediate of its Form G manufacturing process. *See* PTX-51.392 (listing Form A in a table "of available *reference standards for* impurities and intermediates" and thus suggesting that Curia considered Form A to be a reference standard as opposed to an impurity or intermediate (emphasis added)); PTX-839.4 (listing Form A under heading "Impurity Descriptions" but not listing Form A under heading "Characterization of Potential Impurities"); *id.* at 4–11 (not listing Form A in tables of potential impurities); Tr. at 189:5–13, 191:11–15 (Fearnow).

81) Hospira and Curia nonetheless had reason to be concerned at the time Hospira filed its ANDA that Form A could result from the exposure of crude and Forms F and G regadenoson to water in Curia's manufacturing process. Curia had conducted and brought to Hospira's attention XRPD test results that suggested the presence of Form A in samples of crude and Forms F and G regadenoson taken from Curia's manufacturing process in 2016. As discussed more fully below, *see infra* Section II.L.2, whether the presence of Form A suggested by this testing resulted from the handling of the samples in connection with their testing or from

the manufacturing process itself is not clear today and was not clear at the time; but Hospira and Curia clearly had concerns about the test results at the time, and they had those concerns because they knew that Plaintiffs owned patents that covered Form A. PTX-838.8; PTX-892.1; Tr. at 189:24–190:2 (Fearnow); *id.* at 294:14–17 (Myerson).

1. 2021 Changes to Curia's DMF and Batch Records

82) As a result of those concerns, Curia amended its DMF in 2021 to "optimize[]" its manufacturing process to limit the presence of water in the process and to "tighten[]" its specifications for the identification of Form G by XRPD. PTX 1101O.1; Tr. at 382:14–389:9 (Hancock).[2]

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[2] The DMF was not changed from its original filed form in any way material to the parties' infringement dispute until Curia amended it in 2021. Plaintiffs assert that Curia made material changes in April 2018, when it dropped from its manufacturing process two in-process checks (IPCs) that used XRPD to test Curia's crude and Form F intermediates for the presence of Form A. D.I. 914 ¶¶ 61–62; *see* Tr. at 394:10–396:16, 402:8–408:20 (Hancock); FGTX-205.21; PTX-1101A. Plaintiffs say that Curia's dropping the IPC checks was "disingenuous[]" and "a tacit acknowledgement of [Curia's] infringement problem." D.I. 913 at 18–19. I disagree.

First, as Hancock credibly testified, Curia removed the IPCs after realizing (1) that exposure to airborne water during the removal, storage, shipping, and testing of samples of crude and Form F intermediates could be causing Form A conversion and rendering the tests unreliable, and (2) that it was not feasible to wait days or weeks for the results of XRPD testing—to confirm the absence of Form A—before continuing the process with those intermediates. Tr. at 395:3–397:22; *see id.* at 504:22–506:15 (Steed). As I discuss further below, Plaintiffs have not proven by a preponderance of the evidence that the Form A detected in samples from Curia's pre-2021 batches of crude, Form F, and Form G regadenoson were the product of

83) Specifically, Curia amended the "specifications" (section 3.2.S.4.1) and "stability" (section 3.2.S.7.2) sections of its DMF to explicitly require the identification of the final Form G product by an XRPD analysis in which the "[s]ample pattern conforms to the Regadenoson anhydrous Form G reference pattern, designated prominent peaks are present, *and no peaks are observed for other solid forms*." FGTX 328.2 (emphasis added); *see* FGTX 332.2; HTX 218.2. Curia's original XRPD specification had merely required an XRPD analysis that "include[d] the sixteen diffraction angles characteristic of Regadenoson anhydrous Form G," with "no additional peaks observed." FGTX-110.174, 221–222.

84) Curia also amended its corresponding analytical procedures relating to the XRPD testing. FGTX-329.45. Its validated test method now requires that the XRPD diffraction patterns show "all of the prominent peaks present in the sample pattern are present in the [Form G] reference pattern, all of the prominent peaks present in the [Form G] reference pattern are present in the sample pattern, *and no*

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intrinsic aspects of Curia's process as opposed to contamination or mishandling of the samples in connection with the testing. Thus, Hancock's explanation rings true.

Second, whether Curia tests its intermediates is not probative of the likelihood of conversion of those intermediates into Form A during Curia's manufacturing process. No doubt, *the results* of such tests could be probative of conversion; but Curia's decision to employ or not employ such tests is probative, at most, of Curia's (and Hospira's) knowledge and intent.

peaks are observed in the selected noise regions of the Form G pattern." *Id.* (emphasis added). These noise regions include the area at 5.6° 2-theta. *Id.*

85) As a result of these amendments, Curia's extant DMF specifications "rule[] out the observation of any other solid forms," including Form A regadenoson, in Curia's final product, measured both at the time of release, FGTX-328.2; HTX-218.2, and for the shelf life of the product, FGTX-332.2. And thus, "even if there's only one peak for any other solid form" found in a sample, that sample would fail the DMF's specifications. Tr. at 478:7–19 (Steed). Moreover, the analytical method used for the amended DMF and ANDA specifications requires that no peaks are observed in the ranges of 3–7° and 9.5–14° 2-theta. PTX-1101N.47–48. And although "identification methods typically do not assess low intensity peaks," Curia's current method expressly "require[s] evaluation of sample patterns for any peaks above the noise level in the two regions of interest." PTX-1101N.45. Therefore, any peak at or near 5.6° 2-theta of any intensity above noise would trigger a failed specification, and "the batch would be rejected and ultimately disposed of." Tr. at 388:16–22 (Hancock). Such a specification failure would also mean that Hospira "wouldn't be able to use that batch." *Id.* at 479:18–480:2 (Steed).

86) Hospira amended its ANDA in 2021 to incorporate the changes Curia made to its DMF. Specifically, on August 24, 2021, Hospira filed a "Gratuitous

Amendment" (i.e., unsolicited amendment) with the FDA that "provides for a change in the XRPD specification for the Regadenoson drug substance." PTX-801I.1; HTX-218.2; Tr. at 285:4–13 (Myerson). Hospira's XRPD specification for regadenoson is the same as Curia's XRPD specification for regadenoson. Tr. at 282:14–25, 285:4–11 (Myerson); *id.* at 382:22–383:7 (Hancock); PTX-1101M.2; HTX-218.2.

87) Curia also amended its batch records in 2021 to require Form F to be stored in an MSC weighing isolator before the Form G stage of the process. The MSC isolator is purged with nitrogen and, as a result, "free of water." FGTX-48.45, 58; FGTX-44.49–50; Tr. at 391:5–6 (Hancock); *id.* at 473:9–10 (Steed).

88) This addition of the MSC isolator provides an added layer of certainty that the Form F regadenoson will be protected from water and airborne humidity, thereby decreasing the likelihood that it (or the Form G generated further downstream in the process) will convert to Form A. Tr. at 391:2–8 (Hancock).

89) Plaintiffs did not adduce at trial evidence that the addition of the MSC isolator would not reduce the amount of airborne water exposure in the Form F and subsequent stages of Curia's manufacturing process. Plaintiffs argue that "Curia's introduction of the MSC isolator into its process fares no better [than Curia's original manufacturing process] as it does nothing to prevent the introduction of water *through the reagents* during the synthesis of the Curia API." D.I. 931 at 6

(emphasis added). But reagents are not the only potential source of water in the manufacturing process. Indeed, Dr. Myerson insisted at trial that "air has gotten into [Curia's original] process[,] *which includes humidity, which has led to conversion as well.*" Tr. at 365:13–366:23 (emphasis added). For that reason, I find that test results of samples taken from the Form F and Form G stages of Curia's manufacturing process before the process was amended to include an MSC isolator are not probative of whether Form A would be converted from Form F or Form G in Curia's current manufacturing process.

90) The 2021 batch records also require more than 20 additional in-process checks throughout the crude, Form F, and Form G stages to ensure that the water specification for the 200-proof ethanol reagent is below the specified level (1000 ppm) at all stages of the process and each time it is used. *See, e.g.*, FGTX-43–48; *see* Tr. at 390:18–391:1 (Hancock). Thus, ethanol is now sampled when it is brought into the manufacturing facility and is "tested for water content to verify that that ethanol is still meeting that specified water limit" at that time. Tr. at 390:19–391:1 (Hancock). This check differs from the pre-2021 process where the 200-proof ethanol was "tested . . . as [Curia] received it in the warehouse," sometimes "months potentially before use." *Id.* at 433:3–14 (Hancock). Curia did not, however, change the specification for the ethanol used in its process, and thus

the ethanol used both before and after the DMF and batch record amendments could contain up to 1000 ppm (0.1%) water. PTX-1101L.

91) Curia also tightened the water specification for its solvent methylamine (33% in ethanol), narrowing the upper limit from 1.0% water to 0.2%, but Curia represented that it had "historically met this [lower] limit." FGTX-324.

92) Accordingly, I find that the addition of the MSC isolator provided an "additional layer of certainty that [the Form F regadenoson] will be protected from water [and] from moisture." Tr. at 391:2–8 (Hancock). But I find that the changes to Curia's batch records and DMF did not necessarily provide an additional level of certainty that the *crude* regadenoson used in the manufacturing process would be better protected from water and moisture.

2. Whether Curia Will Follow Its 2021 DMF and Batch Record Amendments

93) Because Hospira's ANDA incorporates Curia's DMF, and Curia has no Form G "remaining that was manufactured according to the original pre-2021 process . . . available for sale to Hospira," Tr. at 400:9–12 (Hancock), going forward, the ANDA product that Hospira will market will be manufactured using Form G prepared by Curia according to Curia's amended process and in a manner consistent with Curia's extant XRPD specifications, batch records, and reagent

specifications, *id.* at 400:2–12 (Hancock); *see also id.* at 437:21–439:13 (Hancock) (Curia must follow its batch records).

94) Neither Plaintiffs nor Hospira sought to introduce at trial expert testimony about FDA procedures or regulations.

95) Hospira adduced credible record evidence to support its assertion that Curia is required by law to manufacture its Form G regadenoson in compliance with its extant DMF and batch records. *See* Tr. at 377:20–378:23, 389:10–390:15, 437:8–439:13 (Hancock).

96) Plaintiffs offered no credible evidence or legal authority to rebut that assertion. Plaintiffs never stated at trial or in their briefing that Curia and Hospira are *not* bound by Curia's extant DMF and batch records; nor did they ever *deny* Hospira's assertion that Hospira and Curia are bound by the 2021 batch records.

97) Instead, Plaintiffs intimate that Curia may be able to get away with not complying with its revised batch records. Plaintiffs state, for example, that the 2021 batch records "w[ere] not part of the 2021 DMF amendment, nor [were they] ever provided to [the] FDA because '[they] really didn't affect the key quality attributes that the FDA would typically review.'" D.I. 914 ¶ 79 (citing PTX-1101O.1; Tr. at 389:15–24, 431:3–6 (Hancock); *id.* at 476:20–477:1 (Steed)). Similarly, Dr. Myerson asserted at trial that "[t]here's [been] no optimization of Curia's process; they just changed specifications. An optimization o[r] change in

the process would require . . . a change letter to the FDA indicating how they changed their process and their batch records. There's no such filing that has been produced in this case." Tr. at 344:3–10. Plaintiffs also say that the 2021 changes must not have meaningfully affected Curia's process because "Hospira continues to rely on pre-2021 exhibit batches" that it had submitted to the FDA as "representative . . . of its ANDA product," without ever "supply[ing] new data" or "new exhibit batches in connection with" the optimized process. D.I. 931 at 2.

98) But none of these assertions, even if true, mean that Curia does not have to comply with the changes made in 2021 to its batch records. Moreover, Dr. Myerson's assertion that "[t]here's [been] no optimization of Curia's process; they just changed specifications" is demonstrably wrong. As discussed above, Curia changed its batch records in 2021 to add an MSC weighing isolator to reduce the exposure of Curia's intermediate Form F to airborne water. FGTX-48.45, 58; FGTX-44.49–50; Tr. at 391:5–6 (Hancock); *id.* at 473:9–10 (Steed). And as noted above, Dr. Myerson admitted that airborne humidity can convert crude and anhydrous crystalline forms of regadenoson to Form A, and he testified that because Curia's pre-2021 process had "trouble controlling [its] nitrogen blanket, . . . air has gotten into that process which includes humidity, which has led to conversion [of Form F to Form A] as well." Tr. at 366:18–23. Thus, the reduction by an MSC isolator of exposure to airborne water is not "just" a changed

specification, and it does contribute to the optimization of Curia's manufacturing process.

99) Plaintiffs also adduced no evidence at trial to show, and did not argue in their briefing, that Curia will not comply with its revised batch records.

100) Accordingly, I find that the Form G made by Curia that will be used in Hospira's ANDA product will meet the specifications of Curia's extant DMF and the requirements of its batch records revised as of 2021.

J. The Level of Water Activity and Amount of Water in Curia's DMF Manufacturing Process

101) As noted above, when I questioned Dr. Myerson after his redirect testimony, he testified that he "believe[d] [he] did a rough calculation and there's about one water for every ten regadenoson present in [Curia's manufacturing] process." Tr. at 362:17–25.

102) When I asked him, "What's the amount of water in the process then with respect to Form F?", he replied, "I think it's also – it might be on the order of one in 20. In that – in this case I think I estimated it. It's just a quick estimate. I think that's right." Tr. at 366:12–17.

103) Plaintiffs never offered at trial documents or testimony to support, confirm, or clarify Dr. Myerson's "rough calculation" and "quick estimate" of the relative amounts of water and regadenoson in Curia's manufacturing process.

104) Other than this "rough calculation" and "quick estimate," Dr. Myerson never provided at trial any quantitative estimate of the level of water activity or amount of water present in Curia's manufacturing process.

105) Dr. Myerson testified only that there are "finite amounts of water present" in the process. Tr. at 342:12–13; *see also id.* at 267:1–3 ("Well, there's quite a bit of methylamine [in the process]. And even with a small percentage of water, that's going to be a finite amount of water."); *id.* at 268:3–5 ("[T]here's a lot of ethanol in the process[,]" and "a lot of ethanol means a finite amount of water.").

106) I find that Dr. Myerson's "rough calculation" and "quick estimate" of the relative amounts of water and regadenoson in Curia's process are exactly what he said—"rough" and "quick"—and therefore of little probative value. Accordingly, I find that Plaintiffs failed to prove by a preponderance of the evidence the level of water activity in Curia's manufacturing process; and I find that Plaintiffs failed to prove by a preponderance of the evidence the amount of water present in Curia's manufacturing process.

107) I find more credible than Dr. Myerson's testimony was the testimony of Dr. Steed that "the trace" and "residual amounts of water" in Curia's process are "far, far less than [the required] concentration" to convert the crude and anhydrous

crystalline forms of regadenoson into Form A and "can't be enough to induce the crystallization of Form A." Tr. at 510:3–7, 11–13.

K. Whether Form A Has Been Found in or Is Likely to Be Found in Hospira's ANDA Product or During the Manufacture of That Product

108) Curia manufactured a Form G regadenoson batch in May 2021 using its optimized processes. Tr. at 392:12–14 (Hancock); *see* FGTX-43; FGTX-44.

109) Curia obtained samples of the crude, Form F, and Form G regadenoson from the May 2021 batch. Tr. at 398:4–11 (Hancock). Curia followed "supplemental instructions with very specific procedures" when it collected and handled the samples. *Id.* at 398:8–11 (Hancock). These instructions required that the sample containers used to ship the sample to the XRPD testing site be "filled in the glove box under a nitrogen atmosphere, sealed, and then . . . not . . . opened again until [they were] received at the testing laboratory and they were ready to conduct the analysis." *Id.* at 398:12–18 (Hancock). The handling of these samples was "very different than [Curia's] . . . informal handling with no procedures in place in earlier batches" made before the 2021 optimizations. *Id.* at 398:17–18 (Hancock).

110) Curia provided Plaintiffs with samples of the crude, Form F, and Form G regadenoson from the May 2021 batch. FGTX-30; Tr. at 347:2–4 (Myerson).

111) Plaintiffs offered at trial no testing evidence for the crude and Form G regadenoson obtained from the May 2021 batch samples it was provided. Tr. at 324:25–325:18, 347:5–8 (Myerson).

112) Hospira, by contrast, offered at trial evidence of XRPD testing conducted by Curia of the crude, Form F, and Form G samples from the May 2021 batch. That testing showed that Form A was not present in the crude, Form F, and Form G regadenoson. FGTX-42; FGTX-44; Tr. at 333:13–17, 346:18–21 (Myerson); *id.* at 481:3–9, 498:4–17, 499:11–15 (Steed).

113) Plaintiffs offered no evidence to suggest that Curia's testing of the May 2021 samples was deficient in any respect, other than to suggest that Form A, even if undetected, might still be present below the limit of detection of the XRPD testing. Tr. at 332:6–334:7 (Myerson).

114) Plaintiffs did not adduce at trial evidence of synchrotron testing of the 2021 batch samples, even though "synchrotron tests yield the lowest potential limit of detection for Form A regadenoson" and therefore "would have provided the best evidence for [them] to prove that Form A exists in Curia's API, but [that] it's not observed in standard XRPD testing." Tr. at 334:3–7, 334:17–335:2 (Myerson). Nor did Plaintiffs employ any other alternatives that would have enabled them to prove the presence of Form A in Curia's Form G in trace amounts (e.g., "a longer scan XRPD test to lower the limit of detection"). *Id.* at 334:8–16 (Myerson).

115) Curia's XRPD testing of the Form G regadenoson obtained from the 2021 batch shows no Form A peaks. FGTX-42.7. The pattern from that testing shows that the "largest peak of Form A at 5.6 is completely absent . . . [a]nd there are no other peaks of Form A. . . . [F]or example, the 11.1 peak is absent as well." Tr. at 481:3–9 (Steed). Dr. Myerson agreed that he had "not seen anything on . . . th[e] most recent Form G batch which showed any Form A peaks." *Id.* at 333:13–17.

116) Because the "peak at 5.6 is the most prominent peak," if it is absent from a pattern, "that tells you that Form A can't be there." Tr. at 460:8–10 (Steed).

117) Curia's XRPD testing of the crude regadenoson obtained from the 2021 batch also showed no Form A peaks. FGTX-42.9; Tr. at 498:4–10 (Steed).

118) Curia's XRPD testing of the Form F regadenoson obtained from the 2021 batch was conducted six days after the sample was removed from the manufacturing process. FGTX-42.8; FGTX-44.30–33; Tr. at 499:19–20 (Steed). This testing showed no Form A peaks. FGTX-42.8; Tr. at 499:11–15 (Steed). Notably, there is no peak located at or near 5.6° 2-theta. FGTX-42.8; Tr. at 499:11–15 (Steed). Again, the absence of a peak at 5.6° 2-theta is sufficient to prove the absence of Form A. Tr. at 460:8–10 (Steed).

119) Plaintiffs also offered at trial testing evidence for Form F obtained from the May 2021 batch. That evidence was based on XRPD analysis performed by Dr. Munson. Tr. at 347:2–19 (Myerson); *see id.* at 428:21–429:17 (Hancock).

120) Dr. Munson testified that his XRPD analysis showed that the Form F contained Form A based on a peak at 5.74° 2-theta, which is within ± 0.2° 2-theta of Form A's 5.6° 2-theta peak. Tr. at 217:7–12, 224:16–25; PTX-1175A.1; PTX-126.2–13 (Curia patent showing no peak at about 5.6° 2-theta for Form F).

121) Dr. Munson's testing results, however, have less probative value than Curia's testing results because the samples tested by Dr. Munson were exposed to atmospheric water outside of the manufacturing process that could account for the presence of Form A in the samples.

122) Curia removed the samples of the Form F intermediate from the 2021 batch on June 18, 2021. FGTX-44.30–33. Curia sent the samples to Dr. Smith at Plaintiffs' request. FGTX-30.2.

123) Dr. Smith testified that he "[f]ound" the Form F samples in his mailroom on June 29, 2021. FGTX-30.1. Dr. Smith testified that no one "provide[d] [him] any storage instructions," and he had no "knowledge at that time about the properties of Form F." Tr. at 445:1–16.

124) On August 24, 2021—nearly two months after receiving the Form F samples—Dr. Smith opened the samples "in a glove bag under an argon

atmosphere" having a relative humidity of 23%. FGTX-30.5; Tr. at 445:21–447:4 (Smith). At this time, "[t]wo 200mg samples were weighed out under argon [and] then transferred to previously labeled glass screw cap vials," which "were capped . . . [and] removed" from the glovebox. FGTX-30.5. Once the vials were sealed, "the head space [in the vial] would match the argon atmosphere that was in the glove bag," which had "23 percent relative humidity." Tr. at 447:16–20 (Smith). Dr. Smith confirmed that "[m]ost of the vial space" was "head space," meaning that most of the vial was filled with argon having 23% relative humidity. *Id.* at 447:12–20.

125) Seventeen days later, on September 10, 2021, Dr. Smith placed one of the 200mg samples of Form F back "in a glove bag under an argon atmosphere," again with 23% relative humidity. FGTX-30.6; Tr. at 448:8–17 (Smith). The sample was divided into two 100mg samples, and the "vials were capped" and "removed from the glove bag." FGTX-30.6. "[M]ost of the vial volume" was "head space," which "would be the same as the argon atmosphere." Tr. at 449:5–14 (Smith).

126) When Dr. Munson finally conducted his XRPD testing—"90 days after [the sample] was taken out of Curia's process"—he again "exposed Curia's Form F sample to moisture for more than an hour." Tr. at 229:5–24 (Munson).

127) It is unclear from the record evidence whether using argon as opposed to nitrogen makes a difference, as both gasses can provide an inert atmosphere. Tr. at 446:9–12 (Smith).

128) No record evidence was adduced, however, to contradict or even call into question the testimony of Hancock and Dr. Steed that the use of nitrogen in Curia's process renders the Form F "free of any air or humidity and water." Tr. 380:20–22 (Hancock). At best, Plaintiffs assert that "[t]here is nothing in the trial record to support Hospira's assertion that the nitrogen atmosphere is 'free of water,' as the certificates of analysis for the nitrogen for the regadenoson process do not measure water content." D.I. 931 at 11 n.5 (citation omitted). Plaintiffs, however, offered *no evidence* to show whether there is water in that atmosphere or what that water content would be.

129) Dr. Steed testified credibly that Curia's handling and testing of the 2021 Form F sample employed "precautions taken to make certain that no moisture got into that sample," Tr. 502:5–6, whereas the "non-rigorous handling at the testing stage" by Drs. Smith and Munson allowed for the "ingress of moisture" and exposed the two small samples of Form F to a relatively large amount of atmospheric air with 23% humidity, such that the testing samples Dr. Munson relied on "are not representative" of the Form F used in Curia's current manufacturing process, *id.* at 503:9–504:6, 504:10–18.

130) Dr. Munson's testing also did not show any Form A peak other than a peak within the margin of error of Form A's 5.6° 2-theta peak. Form A, for example, has a peak at 11.1° 2-theta, Tr. at 253:23–254:2 (Myerson), but no such peak appeared in Dr. Munson's test results for the Form F samples he tested, *id.* at 347:12–23 (Myerson).

131) For these reasons, I find that Dr. Munson's testing results do not establish by a preponderance of the evidence that the Form F intermediate in Curia's manufacturing process contains Form A or is likely to contain Form A.

132) Based on that finding, as well as (1) Plaintiffs' failure to adduce evidence of any testing that showed the presence of Form A in the May 2021 crude and Form G regadenoson samples provided to Plaintiffs, and (2) Curia's XRPD test results for the crude, Form F, and Form G samples taken from the May 2021 batch, I find that Plaintiffs have not proven by a preponderance of the evidence that Curia's Form G product or its manufacture contains or will likely contain or produce Form A regadenoson. It follows that Plaintiffs have also failed to prove by a preponderance of the evidence that Hospira's ANDA product will likely contain Form A.

L. Testing of the API Product and Intermediates Obtained from Curia's Manufacturing Process Before the 2021 DMF and Batch Record Amendments

133) Plaintiffs allege that the results of certain polymorph tests of samples taken from Curia's manufacturing process before the process was amended in 2021 ("the pre-2021 test results") show that Curia's amended manufacturing process will result in the formation of Form A.

134) Prior to 2021, Curia manufactured eleven batches of API. One of the batches (US15600292) "failed a purity specification and was reprocessed to become batch no. US15600856." D.I. 926 at 30 n.1. Of the remaining ten batches, three were submitted to the FDA in support of Hospira's ANDA (its "ANDA exhibit batches"), US18600671, US18600308, and US18600250. HTX-19.1; FGTX-366. The remaining seven batches are US15600290, US15600291, US15600293, US15600856, US16600386, US16600476, and US19600219. FGTX-366; FGTX-200; FGTX-269; FGTX-93.1, 5; FGTX-159; FGTX-150; HTX-150. Following the parties' lead, I will refer to these batches by their last three numbers.

135) The pre-2021 test results relied on by Plaintiffs were for: (1) a sample of crude regadenoson taken from batch 476 in 2016, D.I. 914 ¶¶ 53–54; Tr. at 258:24–259:11, 261:4–24 (Myerson); PTX-1122; PTX-1124; (2) a sample of Form F regadenoson taken from batch 386 in 2016, D.I. 914 ¶¶ 55–58; Tr. at 414:8–

415:18 (Hancock); PTX-1113; PTX-1116; (3) a sample of Form F regadenoson taken from batch 308 in 2018, D.I. 914 ¶ 59; Tr. at 416:17–417:10 (Hancock); PTX-1134; (4) a sample of Form F regadenoson taken from batch 290 in 2016, *see* D.I. 914 ¶ 60 (mistakenly referencing "Form F batch 15600291"); Tr. at 243:19–244:16 (Myerson) ("They have a batch, 15600291, of pure Form F which is the powder diffractogram at the bottom, and then they have Form F contaminated with a low level of Form A at the powder diffraction pattern [of batch 290] above that."); PTX-77.2 (referencing the "[l]ow level . . . of Form A in Form F" for "US15600290"); *id.* at 1 ("No evidence for the presence of Form A was detected in the validation batches listed in the following table[,] [including] US15600291 . . . ."); and (5) two samples of Form G regadenoson taken from batch 856, one in late 2015/early 2016 and one in 2020, D.I. 914 ¶¶ 64–65; Tr. at 279:2–281:7, 302:2–304:18 (Myerson); PTX-78; PTX-87; PTX-879; PTX-1214. In all cases, the samples were removed from Curia's manufacturing facility in Missouri and transported to a testing facility in either Indiana or Italy. Tr. at 369:12–19, 395:21–396:16, 397:7–22, 398:4–25, 407:12–16, 415:9–416:5 (Hancock); *id.* at 497:10–25 (Steed).

136) As explained below, I find that the pre-2021 test results do not prove by a preponderance of the evidence that Curia's Form G regadenoson or its manufacture will likely contain Form A. For that reason, Plaintiffs have failed to

prove by a preponderance of the evidence that Hospira's ANDA product or its manufacture will likely contain or produce Form A regadenoson.

1. A Single XRPD Peak Is Insufficient to Identify Form A

137) As an initial matter, all the pre-2021 testing results cited by Plaintiffs are based solely on the identification of a single XRPD peak at around 5.6° 2-theta. I find, however, that a single XRPD peak is insufficient to identify Form A by a preponderance of the evidence since, as noted above, four known forms of regadenoson—Forms A, B, D, and E—have a peak within the margin of error of 5.6° 2-theta, and as yet undiscovered forms of regadenoson could also have a peak within the margin of error of 5.6° 2-theta . As Dr. Steed testified, a detected peak at 5.6° 2-theta "could arise from some Form A, [or] it could arise from any other form that has a peak in that region[,] . . . [or] [i]t could be an unknown [polymorph]." Tr. at 489:20–24, 492:3–6.

138) Plaintiffs cite statements made by Hospira and Curia employees suggesting that the peak at 5.6° 2-theta is "characteristic" of Form A. D.I. 914 ¶¶ 25–29. It is undisputed, however, that Form A's most prominent peak occurs at 5.6° 2-theta and that Form G does not have such a peak. Accordingly, it makes sense that the employees who reviewed the test results would conclude that the tests showed that Form A could be present in the tested Form G samples.

139) That the employees recognized the significance of the 5.6° 2-theta peak, and that Form A *might* be present if the peak is detected, does not constitute an admission that Form A *must* be present so long as that one peak is detected. *See* Tr. at 460:8–10 (Steed) (a single, diagnostic peak's presence is insufficient to identify Form A, but that peak's absence is sufficient to conclude that Form A is absent).

140) Moreover, no evidence was introduced that the Hospira and Curia employees making statements about the 5.6° 2-theta peak were qualified to analyze XRPD patterns. Instead, the evidence showed the opposite. *See, e.g.*, Tr. at 183:3–5 (Knill) ("Q. Do you consider yourself an expert in the area of X-ray diffraction? A. No."); *id.* at 194:11–13 (Paneerselvam) ("Q. Have you ever run an X-ray powder diffraction experiment? A. No.").

141) Several of the statements in question were also made in the context of spiking studies. *See, e.g.*, PTX-1262 (a spiking study conducted by Curia). The parties agree that reliance on a single peak may be appropriate in spiking studies because those studies involve "quantifying how much [of a purposefully added polymorph] is there," such that the scientist "already know[s] what the materials are." Tr. at 460:12–18 (Steed); *see, e.g.*, D.I. 914 ¶ 26; D.I. 926 ¶ 122. Under such circumstances, a single "diagnostic" or "characteristic" peak may be sufficient for the identification of polymorphs. But those circumstances do not exist here, since

Form A is not added purposefully to the tested sample, and the whole point of the testing is to determine *whether* Form A is present in the tested sample.

2. Likely Contamination of Pre-2021 Testing Samples

142) I also find that Plaintiffs did not establish by a preponderance of the evidence that the Form A detected in the pre-2021 testing cited by Plaintiffs was formed during or by Curia's manufacturing process, as opposed to being formed because of exposure to water when the samples were collected, transported to the testing facilities, and tested.

143) In other words, even assuming for argument's sake that the single 5.6° 2-theta peaks observed in the pre-2021 testing samples relied on by Plaintiffs showed the presence of Form A in the samples, Plaintiffs failed to prove that Curia's manufacturing process—and not water exposure during the collection, transportation, storage, and testing of the samples—created the identified Form A.

144) Plaintiffs cite Curia's 2013 "process protocols" as evidence that Curia's pre-2021 testing did not expose the samples to water. D.I. 914 ¶¶ 45, 50–51, 63. Those protocols stated that when crude or Form F regadenoson is "exposed to moisture, it changes its crystal form by hydration and it becomes A form (patent infringing)." PTX-1106.10. The protocols further stated that "samples (accurately protected by moisture) must be analyzed by XR[P]D in 2–3 days in order to get data to confirm not patent infringing." *Id.* And the protocols instructed employees

to "[k]eep [the] sample[s] protected from moisture" when testing for the presence of Form A at both the crude and Form F stages. *Id.* at 11–12.

145) The protocols, however, did not provide specific guidance or directions. They did not identify or even suggest what steps to take or equipment to use to "accurately protect[]" the samples from moisture.

146) Plaintiffs also produced no evidence to suggest or confirm that any of the pre-2021 tests were in fact conducted within 2–3 days of when the tested samples were removed from Curia's manufacturing process. And the record evidence shows that testing occurred many days and even years after the samples were taken, thus greatly expanding the amount of time during which the samples could have been exposed to humidity (and, as a result, converted to Form A). *See, e.g.*, PTX-1113.5 (XRPD testing on the 386 batch from "21-Jul-2016"); PTX-1116.2 ("The Crude, amorphous Regadenoson [from the 386 batch] was held in the FD250 from June 30 to July 13 due to the chemist being on vacation," during which time "some air, containing atmospheric moisture," entered and caused "the formation of some monohydrate when analyzed by XRPD."); PTX-77.1–2 (noting that XRPD for batch 290 "was obtained ~4 weeks after the sample was taken"); *cf.* HTX-150 (September 2020 synchrotron testing on several Form G API batches, including batch 856, that had been manufactured as early as 2015).

147) The evidence adduced at trial suggested that no precautions were taken to protect Curia's pre-2021 crude and Form F samples from moisture during the sampling, handling, shipping, or testing steps. Tr. at 394:25–395:5 (Hancock); *id.* at 504:23–505:18 (Steed).

148) The "samples were collected, transferred to other containers, packaged, shipped off to an offsite laboratory[,] and results could [take] several days or weeks to get back." Tr. at 395:14–18 (Hancock).

149) On the shipping transit forms that accompanied the samples during transportation to the testing sites, Curia either did not specify any special conditions to be used to limit the samples' exposure to water or checked the form's box for "ambient conditions." FGTX-232.

150) Around the time the testing was conducted, Curia concluded that exposure to water after the removal of the samples from the manufacturing process could account for the presence of Form A in the tested samples. Curia's Principal Scientist, Jim Aldred, for example, wrote in a report on a test of the 476 batch in 2016 that "the XRPD result shows that it is present as Form A." PTX-1124.1; Tr. at 261:25–264:11 (Myerson); *id.* at 411:12–412:4 (Hancock). And he identified two possibilities for conversion of crude regadenoson into Form A in the 476 batch: "(1) the sample of amorphous Regadenoson absorbed water and converted to Form A before it was analyzed by [Curia's facility in Indiana], or (2) water

entered the reaction through one of the reagents, methylamine or ethanol." PTX-1124.1; Tr. at 411:5–412:4, 412:22–413:13 (Hancock).

151) Dr. Myerson effectively conceded at trial that the pre-2021 testing exposed the tested samples to air (and thus humidity):

> Q. And the XRPD testing that was done by [Curia in Indiana] was not done in an airtight system, right?
>
> A. I'd have to look at the test spec. I think that's right, but I'd have to look at the test protocol[,] which I don't recall.
>
> Q. So you wouldn't think that XRPD testing on Curia's crude regadenoson was done in an airtight system, right, you wouldn't think that's what happened?
>
> A. Unless I saw something – yeah, and I think what – you mean in an inert atmosphere is what you're actually asking me, to be precise. But you're asking me if they're doing their XRPD test in an inert atmosphere in an environmental chamber, and I don't think I've seen anything that tells me they did that.
>
> Q. Right. [Curia's] XRPD testing was not done in an environmental chamber that controls for humidity, right?
>
> A. That's correct. I should say, as far as I know, that's correct. I'd have to see their protocol.

Tr. 356:6–22. As noted above, Curia's protocol did not specify that the XRPD testing or the collection and transportation of the samples to the testing site had to be performed in an inert atmosphere or environmental chamber that controlled the amount of humidity to which the sample was exposed.

3. The Pre-2021 Form F and Form G Test Results Are Inapposite

152) With the exception of the 476 batch test results, all the pre-2021 test results were for samples of Form F and Form G obtained from Curia's manufacturing process. But as noted above, Plaintiffs did not adduce at trial evidence that the addition of the MSC isolator would not reduce the amount of exposure to airborne water during the Form F and subsequent stages of Curia's manufacturing process.

153) This failure of proof is especially striking in light of Dr. Myerson's testimony that Curia's "trouble controlling [its] nitrogen blanket" had resulted in "air . . . g[etting] into [its] process[,] which includes humidity," and that this circumstance "ha[d] led to conversion as well." Tr. at 366:18–23; *see id.* ("[W]hen that happens, [Form F] certainly can convert."); *see also* PTX-1116.2 ("The Crude, amorphous Regadenoson was held in the FD250 from June 30 to July 13 due to the chemist being on vacation. The batch was to be held in the FD250 at room temperature under nitrogen. A nitrogen valve was inadvertently left in the CLOSED position and with a slow leak on the FD250, the nitrogen pressure was eventually replaced with some air, containing atmospheric moisture, leading to the formation of some monohydrate when analyzed by XRPD. The Form F had already been converted to Form G by the time the XRPD result was received from [Curia].").

154) For that reason, I found above that the samples taken from the Form F and Form G stages of Curia's manufacturing process before that process was amended are not probative of whether Form A would be converted from Form F or Form G in Curia's current manufacturing process. This finding is an additional reason why the pre-2021 tests of the Form F and Form G samples do not prove by a preponderance of the evidence that the Form F used in Curia's current manufacturing process and the Form G made by that process will convert to Form A.

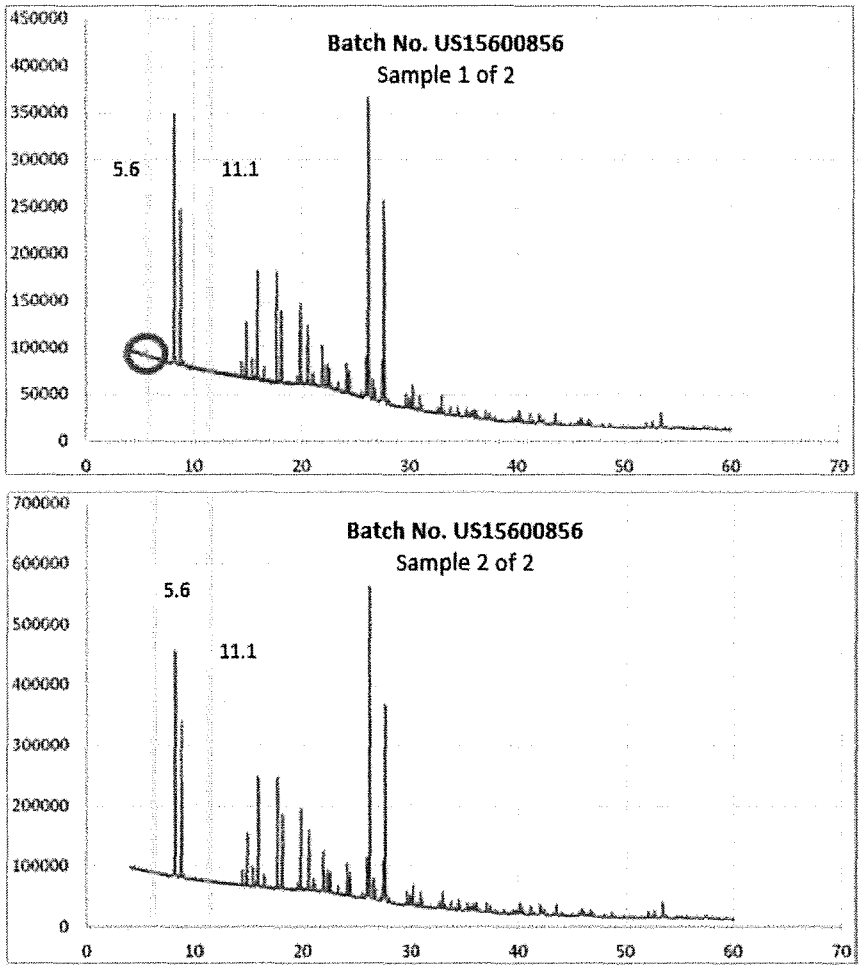
4. Testing on the Form G API from the 856 Batch

155) Plaintiffs rely solely on tests on two samples from the 856 batch to show that Curia's Form G API will more likely than not contain Form A. Tr. at 325:11–18 (Myerson) ("Q. In your opinion, . . . those two tests on . . . the 856 batch[] showed one Form A peak at [5.6° 2-theta], correct? A. Correct. Q. You didn't rely on any other testing to support your opinion[,] . . . correct? A. Correct.").

156) Form A peaks were detected in two out of five tests conducted on the 856 batch. PTX-78.1; PTX-879.2; PTX-1214; PTX-87.8; Tr. at 280:18–281:7, 302:2–304:18, 325:3–14 (Myerson).

157) Dr. Knill ran synchrotron tests on two samples from the 856 batch. HTX-150.8. Testing on the first sample showed a small peak at about 5.6° 2-theta.

Tr. at 304:2–18 (Myerson); PTX-879.2. But "[w]hen Dr. Knill tested the second sample from the 856 batch, no Form A peaks were detected," Tr. at 329:3–6 (Myerson), as seen in the following diffraction patterns:



HTX-150.8 (annotated).

158) Dr. Myerson "rel[ied] solely on [a] signal at 5.6 2[-]Theta" from testing on that first sample to support his opinion that the Form G sample from the 856 batch contained Form A. Tr. at 328:20–24 (Myerson).

159) The remaining three tests were accelerated stability tests performed by Curia in Indiana. The first test showed a single XRPD peak at about 5.6° 2-theta. Tr. at 279:2–280:7, 329:15–17 (Myerson); PTX-1214. When the samples from the 856 batch were tested one month and then again two months after the first test, "no peak was detected between five and six 2-Theta." Tr. at 330:11–14 (Myerson).

160) Based on these inconsistent test results, both Dr. Knill and Dr. Steed concluded that the testing does not prove that Form A crystals exist in the examined Form G API from the 856 batch. PTX-844.9; Tr. at 187:5–15 (Knill); *id.* at 491:3–14 (Steed). Dr. Steed reasoned that the "mismatch or . . . contradiction between two measurements of the same material" from the 856 batch must indicate that whatever is giving rise to the peak at 5.6° 2-theta is not "intrinsic to the 856 batch" but instead "must arise from the point where sample one was separated from sample two." *Id.* at 490:15–20. Therefore, "something happened, and we don't know what . . . is giving rise to that peak," that is, some handling or experimental error occurred, even if the precise nature of that error is unknown. *Id.* at 490:20–22 (Steed).

161) Plaintiffs argue that it is "erroneous[] [to] suggest[] that two different samples from the same batch should both show a peak for Form A," and they have offered an alternative explanation for the "contradiction" in testing on the 856 batch. D.I. 913 at 26. Referencing Dr. Steed's testimony that "you might get a

situation in which some particles that are near the surface, that have touched water, have transformed from G to A, whereas . . . other Gs that, perhaps, are beneath the surface have not been touched by the water so haven't transformed," Tr. at 470:25–471:4, Plaintiffs note "that conversion of Form G to Form A may not be uniform across [an] entire sample," D.I. 913 at 26–27. Thus, according to Plaintiffs, any inconsistency in Curia's stability tests or Dr. Knill's synchrotron tests on samples from the 856 batch reflects "sampling error," i.e., the samples in which a Form A peak was detected were taken from regions of the batch where conversion had occurred (or where enough localized water was present for conversion to occur thereafter), whereas the samples in which a Form A peak was not detected were taken from regions where there had been neither conversion nor sufficient amounts of water to cause conversion over time. D.I. 913 at 27.

162) I agree with Plaintiffs that the three tests that failed to detect Form A peaks *could* have been false negatives (because they were taken from regions where conversion had not yet occurred in the 856 batch). But it is also the case that the two tests that detected a Form A peak *could* have been false positives (because they were exposed to atmospheric moisture after being removed from the batch). Plaintiffs, however, bear the burden of proof here. And while Dr. Steed and Hancock credibly testified as to the lax handling of samples prior to 2021, making mishandling more likely the culprit for any Form A conversion, Plaintiffs

adduced no affirmative evidence regarding the likelihood of sampling error. Instead, they simply say that two tests showed a Form A peak, conversion *may* not be uniform, and sampling error *may* occur, and they then conclude that the three samples without a peak at 5.6° 2-theta were "likely due to sampling error." D.I. 913 at 27. That sampling error can occur does not mean that sampling error (as opposed to mishandling) caused the Form A conversion, especially since Hospira adduced credible evidence—and Dr. Myerson conceded—that regadenoson samples taken prior to 2021 were not subject to any specialized handling conditions.

163) In sum, I find that the test results for the 856 batch samples do not establish by a preponderance of the evidence that Curia's Form G API will likely convert to or contain Form A. On the contrary, I find Dr. Steed's testimony to be logical and credible. And based on that testimony and the inconsistent results from the 856 tests, I find that, even were a single peak sufficient to identify Form A, any Form A in the two positive 856 samples likely resulted from airborne water exposure during their sampling, storage, transport, and/or testing. And, in any event, I find these tests results are less probative than the test results conducted by Curia of the 2021 batches that showed no Form A in Curia's crude, Form F, and Form G regadenoson.

III. LEGAL STANDARDS

A. Direct Infringement

Analyzing infringement involves two steps. The first step is to construe disputed patent terms consistently with how they would be understood by an artisan of ordinary skill. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1313 (Fed. Cir. 2005) (en banc). The second step is to determine whether the accused products or methods infringe the patent by comparing those products or methods to the construed claims. *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 976 (Fed. Cir. 1995) (en banc), *aff'd*, 517 U.S. 370 (1996). The first step in the infringement analysis is a question of law; the second is a question of fact. *Glaxo, Inc. v. Novopharm, Ltd.*, 110 F.3d 1562, 1565 (Fed. Cir. 1997). A patentee bears the burden of proving infringement by a preponderance of the evidence. *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 758 (Fed. Cir. 1984).

As noted above, § 271(e)(2)(A) of the Patent Act defines the filing of an ANDA with a paragraph IV certification as an act of infringement. That definition "create[s] case or controversy jurisdiction to enable a court to promptly resolve any dispute concerning infringement and validity" of patents listed in the Orange Book. *Glaxo*, 110 F.3d at 1569. "Notwithstanding this defined act of infringement, a district court's inquiry in a suit brought under § 271(e)(2) is the same as it is in any other infringement suit, *viz.*, whether the patent in question is 'invalid or *will not be*

infringed by the manufacture, use, or sale of the drug for which the [ANDA] is submitted.'" *Id.* (italics and alteration in original) (underline added) (quoting 21 U.S.C. § 355(j)(2)(A)(vii)(IV)). Thus, "the ultimate infringement question is determined by traditional patent law principles and, if a product that an ANDA applicant is asking the FDA to approve for sale falls within the scope of an issued patent, a judgment of infringement must necessarily ensue." *Sunovion Pharms., Inc. v. Teva Pharms. USA, Inc.*, 731 F.3d 1271, 1278 (Fed. Cir. 2013). By the same token, if the product that an ANDA applicant is asking the FDA to approve falls outside the scope of an asserted patent, a judgment of noninfringement must follow. In short, "[w]hat [the ANDA applicant] has asked the FDA to approve as a regulatory matter is the subject matter that determines whether infringement will occur." *Id.*

The infringement analysis in an ANDA case is most straightforward when the ANDA's specification directly addresses the elements of the asserted claims that are at issue. "Because drug manufacturers are bound by strict statutory provisions to sell only those products that comport with the ANDA's description of the drug, an ANDA specification defining a proposed generic drug in a manner that directly addresses the issue of infringement will control the infringement inquiry." *Abbott Lab'ys v. TorPharm, Inc.*, 300 F.3d 1367, 1373 (Fed. Cir. 2002).

As the Federal Circuit explained in *Bayer AG v. Elan Pharmaceutical Research Corp.*, 212 F.3d 1241 (Fed. Cir. 2000):

> [i]f any of the statements in [the ANDA's] specification are false, [the ANDA filer] is subject to civil penalties and the withdrawal of the approval of its drug. Additionally, if [the ANDA filer] introduces a drug into interstate commerce without complying with the approval requirements of 21 U.S.C. § 355, it is subject to various additional penalties, including an injunction, criminal sanctions, seizure of the unapproved drug, and debarment of its corporation and individual officials from submitting or assisting in the submission of an ANDA in the future. [The ANDA filer] also would be subject to criminal prosecution for making false statements to the FDA under 18 U.S.C. § 1001, conspiring to defraud the United States under 18 U.S.C. § 371, and obstructing proceedings before a federal agency under 18 U.S.C. § 1501. If [the ANDA filer] changes its ANDA, it must file the changes with the FDA, and if the changes are to the drug's specification, [the ANDA filer] must obtain approval for the changes before they can be made.

Id. at 1249–50 (citations omitted). Because of these statutory and regulatory requirements and the consequences that flow from failing to abide by them, courts "cannot assume that [an ANDA filer] will not act in full compliance with its representations to the FDA." *In re Brimonidine Pat. Litig.*, 643 F.3d 1366, 1378 (Fed. Cir. 2011).

This principle that an ANDA filer is bound by the representations and specifications in its ANDA is central to the infringement inquiry. And if an ANDA specification describes a product that either necessarily infringes an

asserted patent or necessarily does not infringe the patent, the specification dictates the outcome of the infringement analysis. *See Ferring B.V. v. Watson Lab'ys, Inc-Fla.*, 764 F.3d 1401, 1408 (Fed. Cir. 2014) ("In some cases, the ANDA specification directly resolves the infringement question because it defines a proposed generic product in a manner that either meets the limitations of an asserted patent claim or is outside the scope of such a claim."); *Elan*, 212 F.3d at 1249 (finding that an ANDA specification that clearly defined a noninfringing product "mandate[d] a finding of no literal infringement").

When the ANDA specification does not answer the question of infringement, "[t]he relevant inquiry is whether the patentee has proven by a preponderance of the evidence that the alleged infringer will likely market an infringing product." *Glaxo*, 110 F.3d at 1570. In such cases, "[w]hat is likely to be sold, or, preferably, what will be sold, will ultimately determine whether infringement exists." *Id.*

While § 271(e)(2) provides the federal courts with jurisdiction to entertain infringement claims directed to drugs or to methods of using drugs, it does not provide jurisdiction to hear infringement claims directed to methods for making drugs. *See* 35 U.S.C. § 271(e)(2) (defining infringement as the submission of an application to the FDA "for a drug claimed in a patent or the use of which is claimed in a patent"). Accordingly, Plaintiffs' claims that Hospira infringes claims

1–3 of the #883 patent are necessarily based on the Declaratory Judgment Act, 28 U.S.C. § 2201, and the relevant direct infringement inquiry is whether the manufacturing process used to make Hospira's ANDA product will infringe the asserted claims.

B. Induced Infringement

"Whoever actively induces infringement of a patent shall be liable as an infringer." 35 U.S.C. § 271(b). A finding of inducement requires establishing an underlying act of direct infringement, the defendant's knowledge of or willful blindness with respect to the direct infringement, and that the defendant's specific intent was to encourage the acts that constituted direct infringement. *See DSU Med. Corp. v. JMS Co.*, 471 F.3d 1293, 1303, 1306 (Fed. Cir. 2006) (en banc in relevant part).

IV. CONCLUSIONS OF LAW

A. Claim 1 of the #183 Patent

Plaintiffs argue that Hospira induces Curia's infringement of claim 1 of the #183 patent because "Form A will be made at the crude and Form F stages" of Curia's manufacturing process. D.I. 913 at 10–11. But as explained above, I have already found as a factual matter that Plaintiffs failed to establish by a preponderance of the evidence that the crude or Form F regadenoson in Curia's manufacturing process contains or likely will contain Form A. And since Plaintiffs failed to prove direct infringement by Curia of claim 1 of the #183 patent, their

induced infringement claim necessarily fails. *See Epcon Gas Sys., Inc. v. Bauer Compressors, Inc.*, 279 F.3d 1022, 1033 (Fed. Cir. 2002). ("[T]here can be no inducement of infringement without direct infringement by some party.").

B. Claim 6 of the #301 Patent and Claims 1–3 of the #883 Patent

Plaintiffs argue that Hospira directly infringes claim 6 of the #301 patent because "the only claim element Hospira disputes is whether it 'dissolves a crystalline monohydrate form of [regadenoson]' during manufacturing of its ANDA product" and "Plaintiffs have demonstrated that Curia's [Form G] API will contain Form A, which is a crystalline monohydrate form of regadenoson." D.I. 913 at 30 (alteration in original). Plaintiffs similarly argue that Hospira directly infringes claims 1–3 of the #883 patent because "the only claim element Hospira disputes is whether Curia's [Form G] API contains a 'monohydrate' or 'crystalline monohydrate' of regadenoson" and "Plaintiffs have demonstrated that Curia's [Form G] API will contain Form A regadenoson[.]" D.I. 913 at 31.

As an initial matter, Hospira does in fact dispute another claim element of these asserted claims—namely, the claims' requirement that the monohydrate be "substantially free" of 2-HA. D.I. 925 at 31–32. Hospira argued at trial that claim 6 of the #301 patent and claim 3 of the #883 patent are invalid as indefinite because "substantially free" of 2-HA is a "qualitative" and "subjective" term, the precise contours of which "would be unknown until a drug filer [has] engaged in a

'back and forth' with [the] FDA," such that it would not "know until [it] get[s] approved by the FDA whether [its] product is substantially free." D.I. 915 at 7–9. Plaintiffs asserted in the pretrial order that "substantially free" should be construed as incorporating and based upon regulatory guidance that "provides for 10 ppm levels" of 2-HA. D.I. 891-2 ¶¶ 495, 499. But it adduced no evidence at trial to establish what the ppm level of 2-HA in Curia's Form G is, let alone that it is less than 10 ppm. Plaintiffs argue nonetheless that they met their burden to establish infringement of this limitation based on (1) Dr. Myerson's unrebutted trial testimony that 2-HA levels measured in Curia's manufacturing process are below the limit of detection, and (2) the fact that the FDA has granted Hospira tentative approval to market its ANDA product. D.I. 931 at 15 (citing Tr. at 287:14–288:13, 307:12–15 (Myerson)).

I need not, however, and therefore do not decide today whether Plaintiffs proved that Hospira's ANDA product is "substantially free" of 2-HA because, as explained above, I have found as a factual matter that Plaintiffs failed to meet their burden to show by a preponderance of the evidence that Form A will be present in or produced by Curia's manufacturing process. That finding precludes a finding of infringement of the asserted claims of the #301 and #883 patents.

As discussed above, I have already found that Plaintiffs did not prove that Form A will be present in Hospira's ANDA product for two independent reasons.

First, Curia's amended DMF, which is incorporated into Hospira's amended ANDA, requires that the Form G be identified with an XRPD analysis that (1) shows a pattern that conforms to the Form G reference pattern *and* (2) shows that "no peaks are observed for other solid forms." *See supra* ¶¶ 82–86. Thus, both the extant DMF and the extant ANDA rule out the observation of any other solid forms, including Form A. Plaintiffs complain that this change "does not rule out the presence of Form A" because the XRPD test called for in the ANDA amendment "is an identification, not [a] limit of detection[,] test" and thus it may fail to "observe[]" Form A that is present. D.I. 913 at 6. Plaintiffs also fault Hospira and Curia for "not us[ing] synchrotron testing as part of their [Form G] API specifications." D.I. 913 at 6.

Plaintiffs, however, never pointed to any authority that requires either a "limit of detection test" or synchrotron testing to identify a crystalline form for FDA purposes. Moreover, Plaintiffs themselves called XRPD analysis "the gold standard" for crystalline form identification, D.I. 891-2 ¶ 22; the asserted patents rely on XRPD testing when characterizing Form A, D.I. 891-2 ¶ 24; Tr. at 463:4–6 (Steed); DTX-3.13–14; Plaintiffs cited and relied extensively at trial on XRPD testing to prove their case; and, tellingly, Plaintiffs used XRPD, *not* synchrotron testing, in the only testing they offered at trial that they had conducted themselves, D.I. 891-2 ¶¶ 274, 355; Tr. at 334:3–335:2, 347:12–19 (Myerson). Nothing

prevented Plaintiffs from using synchrotron testing to determine whether the Form G produced in Curia's May 2021 batch contained Form A. Plaintiffs either conducted synchrotron testing and got results they did not like, or they chose to forego the very testing they now fault Hospira and Curia for failing to incorporate into their ANDA and DMF specifications.

Plaintiffs' failure to adduce evidence of synchrotron testing at trial to back up their arguments regarding Form A being present in the Form G API in trace amounts is consistent with a second, independent finding of fact that is dispositive of Plaintiffs' infringement claims. Putting aside Hospira's amendment to the Form G specification, for the reasons explained above, I found that Plaintiffs failed to show by a preponderance of the evidence that Curia's Form G will likely contain Form A regadenoson. A judgment of noninfringement of the asserted claims of the #301 and #883 patents necessarily follows from that finding.

C. Plaintiffs' Principal Argument Is Unavailing

The thrust of Plaintiffs' infringement theory is that crude and Forms F and G regadenoson have "a propensity" to convert to Form A when exposed to water, and that water is introduced into Curia's DMF manufacturing process through at least two reagents (methylamine and ethanol) and/or humidity. D.I. 913 at 1–5, 10–12, 14–19. This "propensity," however, as Dr. Myerson explained at trial, and as I have found as a matter of fact based in part on his testimony, exists only if the

crude and Forms F and G regadenoson are exposed to *a sufficient* level of "water activity" and a *sufficient* amount of water. And, as I have already found as a factual matter, Plaintiffs failed to prove by a preponderance of the evidence both (1) what level of water activity and amount of water are necessary to convert crude and Forms F and G regadenoson into Form A and (2) the level of water activity and amount of water in Curia's manufacturing process. That failure of proof necessitates a finding of noninfringement.

V. CONCLUSION

For the reasons discussed above, I find that Hospira does not infringe claim 1 of the #183 patent, claim 6 of the #301 patent, or claims 1–3 of the #883 patent. In light of that finding, I need not and do not address Hospira's affirmative defenses of invalidity.

The Court will issue an Order directing the parties to submit a proposed order by which the Court may enter final judgments consistent with this Opinion.