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

| | | |
|---|---|---|
| NEXUS PHARMACEUTICALS, LLC,<br><br>Plaintiff,<br><br>v.<br><br>EXELA PHARMA SCIENCES, LLC,<br><br>Defendant. | ) | C.A. No. 22-1233-GBW<br><br>**Jury Trial Demanded** |

**SECOND AMENDED COMPLAINT**

Plaintiff Nexus Pharmaceuticals, LLC ("Nexus" or "Plaintiff"), by its undersigned attorneys, for its Second Amended Complaint against Exela Pharma Sciences, LLC ("Exela" or "Defendant"), alleges as follows:

**NATURE OF THE ACTION**

1. This is a civil action for patent infringement arising under the patent laws of the United States, Title 35 of the United States Code, and for a declaratory judgment of patent infringement under 28 U.S.C. §§ 2201 and 2202 and the patent laws of the United States, Title 35, United States Code, that arises out of Defendant's manufacturing, using, offering for sale, and selling an ephedrine sulfate 25 mg/5 mL (5 mg/mL) solution in a 5 mL prefilled syringe under the brand name AKOVAZ that infringes claims of Nexus's U.S. Patent Nos. 11,426,369 ("the '369 patent") and 11,464,752 ("the '752 patent") (collectively, "the patents-in-suit").

**PARTIES**

2. Nexus is a limited liability corporation organized and existing under the laws of the State of Illinois, having its principal place of business at 400 Knightsbridge Parkway, Lincolnshire, Illinois. Nexus is a continuing entity recently registered and stands entirely in the place of Nexus Pharmaceuticals, Inc., and it is for all practical purposes related to this litigation a renaming of the

same ongoing concern. By operation of Illinois law, all assets and operations of Nexus Pharmaceuticals, Inc. have now converted and merged into Nexus Pharmaceuticals, LLC. Nexus is in the administrative process of updating filings and documentation to reflect the name change, but Nexus already owns all the assets and operations of Nexus Pharmaceuticals, Inc.

3. Nexus is the holder of New Drug Application ("NDA") No. 213407 for EMERPHED®, (ephedrine sulfate) 50mg/10mL (5mg/mL) IV solution. EMERPHED® was the first FDA-approved "ready to use" ephedrine formulation with a 5 mg/mL concentration.

4. Nexus applied for and obtained patents related to its inventions for the ready to use 5 mg/mL concentration, including the patent-in-suit. Nexus is the owner and assignee of the patent-in-suit.

5. Exela is a corporation organized and existing under the laws of the State of Delaware, having a principal place of business at 1245 Blowing Rock Blvd, Lenoir, NC 28645.

6. Exela is and purports to be a pharmaceutical manufacturer and seller that specializes in "the development and manufacturing of generic and proprietary sterile injectable products with high barriers to market entry, via an Abbreviated New Drug Approval or 505(b)(2) regulatory pathway."[1]

## JURISDICTION AND VENUE

7. This Court has subject matter jurisdiction pursuant to 28 U.S.C. §§ 1331, 1338(a), 2201, and 2202.

8. Personal jurisdiction and venue are proper in this Court under 28 U.S.C. §§ 1391 and 1400(b), at least because Exela is incorporated in Delaware. Exela is a company organized

[1] Corporate Overview, https://www.exelapharma.com/overview/ (last visited April 5, 2023).

and existing under the laws of the State of Delaware, is registered to do business in this State, and has appointed a registered agent to accept service.

9. On information and belief, Exela has manufactured and will manufacture a prefilled syringe product pursuant to its sNDA No. 208289/S-006 and has and will continue to offer for sale and sell its infringing prefilled syringe product in the United States, including in Delaware.

10. Exela consented to jurisdiction and venue in this District, and confirmed the same to counsel for Plaintiff and by way of agreement between the parties.

**BACKGROUND**

11. Nexus's EMERPHED® is sold and marketed under New Drug Application No. 213407, which was approved by the FDA in April 2020.

12. Ephedrine, the active ingredient in EMERPHED®, is an alpha- and beta-adrenergic agonist and a norepinephrine-releasing agent. EMERPHED® is indicated for the treatment of clinically important hypotension occurring in the setting of anesthesia.

13. Nexus's '369 patent, entitled "Compositions comprising Ephedrine or an ephedrine salt and methods of making and using same" was duly and legally issued on August 30, 2022. Exhibit A.

14. The '369 patent claims are directed to shelf-stable, ready to use ephedrine sulfate compositions.

15. The '369 patent was filed on December 20, 2021, as a continuation of earlier applications filed on July 21, 2021 and May 16, 2020. All of the applications, including the application resulting in the '369 patent, claim priority based on a provisional patent application filed on May 16, 2019.

16. The '369 patent is valid and duly issued, and will not expire until at least May 16, 2040.

17. Nexus's '752 patent, entitled "Compositions comprising Ephedrine or an ephedrine salt and methods of making and using same" was duly and legally issued on October 11, 2022. Exhibit B.

18. The '752 patent claims are directed to pharmaceutical products including packaged syringes containing shelf-stable, sterilized ready-to-use ephedrine compositions.

19. The '752 patent was filed on July 21, 2021, as a continuation of an earlier application filed on May 16, 2020. All of the applications, including the application resulting in the '752 patent, claim priority based on a provisional patent application filed on May 16, 2019.

20. The '752 patent is valid and duly issued, and will not expire until at least May 16, 2040.

21. Based on FDA records available publicly, the first product associated with NDA No. 208289 for an ephedrine sulfate injection product to be marketed under the trade name AKOVAZ was originally approved by the FDA on or about April 29, 2016. But that product was not approved by the FDA for a ready-to-use concentration. In addition, that product was not approved by the FDA in a pre-filled syringe. Instead, the product described in NDA No. 208289 at the time of approval was a highly concentrated version of ephedrine sulfate and required manipulation steps including dilution prior to administration before it could be administered to patients.

22. According to SEC filings, Exela acquired NDA No. 208289 for AKOVAZ on or about June 30, 2020.

23. Before June 30, 2020, Nexus had already filed a provisional application and full utility application that led to both asserted patents in this litigation, which include claims on a

ready-to-use ephedrine sulfate concentration and/or for a pre-filled syringe with a ready-to-use concentration of ephedrine sulfate.

24. Before Nexus's invention, there had been a long felt but unmet need for health professionals to be able to administer formulations that were in ready-to-use concentrations, without requiring dilution and other steps that are associated with safety and efficacy issues. After all, the old Akovaz product (concentrated in a vial) itself had been on the market for many years but was only available in high concentrations that required dilution and other steps before administration. The old Akovaz product was not in a ready-to-use concentration and was not available in a syringe.

25. At some time after June 30, 2020, Exela sought and obtained approval from FDA for a pre-filled syringe with a ready-to-use ephedrine sulfate formulation. Exela filed a supplemental New Drug Application sNDA No. 208289/S-006 on or about November 10, 2020, seeking FDA approval to market a shelf stable, ready to use prefilled syringe (PFS) composition of ephedrine sulfate with a 5 mg/mL concentration that requires no dilution prior to administration ("Exela's Akovaz PFS Product").

26. Exela now has FDA approval for the Akovaz PFS Product, which means it meets certain requirements set by FDA, including for product safety and efficacy. On information and belief, Exela's Akovaz PFS Product is the same as the invention disclosed in Nexus's asserted patent specifications and including the earlier-filed related patent applications.

27. Exela recognizes the benefits and advantages associated with a ready-to-use formulation as compared to one requiring dilution. Exela itself touted these benefits for another of its products in its portfolio, Nipride RTU, which it boasted was "the ONLY ready-to-use sodium nitroprusside available" with "no need to mix in the hospital."

28. Exela's ready-to-use Akovaz PFS Product is not the same as the original concentrated formulation sold in vials under the Akovaz name.

29. According to FDA records publicly available, Exela is the present holder of sNDA No. 208289/S-006, regarding the Akovaz PFS Product.

30. An sNDA is a supplemental New Drug Application, whereby Exela can reference an earlier approved product and add to it with new information about a different product or version in the supplement. Exela maintains a copy of the sNDA and any updates thereto.

31. The sNDA for Akovaz PFS Product is a non-public set of confidential communications between Exela and the FDA. The sNDA is not publicly available, and Nexus does not have access to the sNDA. Exela has not publicly disclosed its manufacturing processes.

32. Exela's complete internal manufacturing processes and product specifications for Akovaz PFS Product are non-public and confidential to Exela. Exela has not publicly disclosed its manufacturing processes.

33. Because of the confidential nature of the sNDA and the Exela internal information, Exela possesses additional supporting information that will further prove patent infringement, and these allegations for purposes of the complaint are based on publicly-available information that tends to show the Akovaz PFS Product infringes and provides facts supporting an inference of infringement. The additional supporting information is peculiarly within Exela's knowledge and control.

34. When the FDA approved the Akovaz PFS Product, the FDA also approved an associated Prescribing Information document, or package insert, commonly referred to as a product label. The product label is publicly available, and includes information about the Akovaz PFS Product description, formulation, and usage so that healthcare professionals know about the

product and how to use it. The label is attached as Exhibit C and incorporated by reference. The product label provides information tending to show that Exela's Akovaz PFS Product more likely than not infringes the asserted patents and providing facts supporting an inference of infringement.

35. After the FDA approved the Akovaz PFS Product, the FDA created an Approval Package summarizing the basis of approval. The FDA published online a redacted version of some of the materials in the Approval Package. The Approval Package provides additional information tending to show that Exela's Akovaz PFS Product more likely than not infringes the asserted patents and providing facts supporting an inference of infringement.

36. FDA standards are stringent for injectable products like the Akovaz PFS Product. Unlike other commercial products, there is reason to believe based on Nexus's experience with the FDA that the FDA standards will require high levels of stability and sterility. As Nexus's patent claims refer to variables like pH control and sterility and potency, which would aid in obtaining FDA approval, there is a substantial likelihood that Exela's Akovaz PFS Product also meets the claimed criteria.

37. Nexus applied for and obtained its own FDA approval for a PFS ephedrine product consistent with Nexus's own patent, and on that additional basis and consistent with its experience, the Nexus invention would help others in order to obtain FDA approval.

38. By letters dated February 1, 2022, May 1, 2022, and July 25, 2022 ("the Nexus Letters"), Nexus notified Exela regarding then-pending applications and the continuing nature of additional applications filed by Nexus relating to ephedrine formulations in containers including prefilled syringes and methods related thereto, and inviting Exela to continue monitoring Nexus's patents for applicability to Exela's prefilled syringe product.

39. Exela responded to the February 1 Nexus letter but did not respond to the May 1 or July 25 letters sent by Nexus. Nexus reached out again after the U.S. Patent and Trademark Office issued a Notice of Allowance, saying that a pending application would soon issue to become the '369 approved patent and invited the parties to discuss. Nexus and Exela did have an initial discussion but did not come to terms about any Nexus patent. Nexus's prior letters also identified the application that since resulted in the '752 patent, and Nexus reported to Exela's counsel on October 14, 2022 that the new patent will be issuing.

40. Despite all of these communications, Exela has not withdrawn or stopped selling its Akovaz PFS Product.

41. The Akovaz PFS Product is a shelf-stable, ready-to-use ephedrine sulfate composition that meets each and every limitation of at least one claim of the '369 patent, either literally or under the doctrine of equivalents.

42. The Akovaz PFS Product is a pharmaceutical product including a packaged syringe containing shelf-stable, sterilized ready to use ephedrine compositions that meets each and every limitation of at least one claim of the '752 patent, either literally or under the doctrine of equivalents.

43. The FDA-approved label for the Akovaz PFS Product states that "Akovaz injection, 5 mg/mL in a prefilled syringe, is a premixed formulation. Do not dilute prior to use."

44. The FDA-approved label for the Akovaz PFS Product states that the instructions for use include a "visual inspection" of each syringe, "remove tip cap and tamper evident seal by twisting off," "depress plunger rod to deliver medication," and "discard into appropriate receptacle." The instructions further state to "not re-sterilize the syringe" and confirm that "this product is for single dose only."

45. The FDA-approved label for the Akovaz PFS Product in the "How Supplied" section reports that individual vials are available with the strength of "25 mg/ 5mL (5 mg/mL) of ephedrine sulfate" and in "5 mL single-dose prefilled syringe."

46. The FDA-approved label for the Akovaz PFS Product reports that "The single-dose 5 mL prefilled syringe is intended for use in one patient during one surgical procedure."

47. The FDA-approved packaging for the Akovaz PFS Product states that the product "may contain Sodium Hydroxide, NF and/or Glacial Acetic Acid, USP as needed for pH adjustment, pH 4.5-6.5." Exhibit C, at 11.

48. Exela is continuing to market its product despite notice of infringement. Exela's infringing product threatens Nexus's existing and new customers, market share, price erosion, and distribution channels because of Exela's attempts to increase product marketing.

49. Exela's acts of infringement of the patent-in-suit were and are willful. Exela was on notice of Nexus's patent family and the fact that the patent-in-suit would issue and continued its infringing actions. Such acts have caused and will continue to cause substantial damages and irreparable harm to Nexus.

**COUNT I – INFRINGEMENT OF**
**U.S. PATENT NO. 11,426,369 UNDER 35 U.S.C. § 271(a), (b), (c), and § 154(d)**

50. Nexus repeats and re-alleges each of the foregoing paragraphs as if fully set forth herein.

51. Nexus is the assignee and owner of all right, title, and interest in the '369 patent and Nexus has the legal right to enforce the patent, sue for infringement, and seek equitable relief and damages.

52. The '369 patent is valid, enforceable, and was duly issued in compliance with Title 35 of the United States Code.

53. Claim 1 of the ’369 patent, reproduced below, recites a method of making a shelf-stable, ready-to-use ephedrine sulfate composition:

> 1. A method of making a shelf-stable, ready-to-use ephedrine composition, the method comprising:
>
> combining ephedrine sulfate, sodium chloride or dextrose, and water to form a batch solution comprising an initial ephedrine sulfate level of 5 mg/mL, 9mg/mL sodium chloride or 5% dextrose, and no preservative;
>
> optionally contacting the batch solution with an acid or a base to obtain an initial pH level of the solution of 4.5 to 7;
>
> filtering the batch solution through a membrane filter to obtain a filtered batch solution;
>
> sanitizing one or more containers;
>
> placing not more than 20 mL of the filtered batch solution into one of the one or more sanitized containers to obtain one or more filled containers;
>
> sealing each filled container to obtain sealed containers including a shelf-stable, ready-to-use ephedrine sulfate composition in the sealed containers that is within 0.5 pH units of the initial pH level during storage at 25°C and 60% relative humidity for at least 12 months or during storage at 40°C and 75% relative humidity for at least 6 months.

54. The Akovaz PFS Product embodies every limitation of at least claim 1 of the ’369 patent, literally or under the doctrine of equivalents, as set forth below. Each heading below provides a claim term and associated sufficient basis for showing infringement of each claim term. It is fully expected that discovery will provide additional factual support and details.

> **A method of making a shelf-stable, ready-to-use ephedrine composition, the method comprising:**
>
> **combining ephedrine sulfate, sodium chloride or dextrose, and water to form a batch solution comprising an initial ephedrine sulfate level of 5 mg/mL, 9mg/mL sodium chloride or 5% dextrose, and no preservative;**

55. The Akovaz PFS Product FDA-approved product label identifies the composition and use of the Akovaz PFS Product.

56. According to the FDA, the Akovaz PFS Product label was updated in March or April 2021, and that label contains additional details about the infringing Akovaz PFS Product.

57. According to the Akovaz PFS Product label, each mL of the Akovaz PFS product "contains 5 mg ephedrine sulfate" and "9 mg Sodium Chloride, USP" and "in Water for Injection." Exhibit C at Section 11. The label makes no mention of using any preservative. *See id.* As pharmaceutical products are expected to disclose on the label the ingredients contained in the product, and no preservative is listed, on information and belief Akovaz PFS Product does not include a preservative.

58. Pharmaceutical manufacturing is commonly if not always accomplished by creating large batches of solutions combining ingredients, and then providing a conveyor belt approach to fill individual vials from those large batches. It is not always known unless and until someone invents a formulation whether or not it will work for its intended purpose. But now that Nexus has demonstrated through its invention that its claimed formulation can be made, on information and belief, Exela uses this same general manufacturing process to make Akovaz PFS Product.

59. To appear in the vial with the components in the claim and just as reported on the Akovaz PFS Product label, and on information and belief, Exela on information and belief takes the step as required by the patent for combining ephedrine sulfate, sodium chloride, and water to form a batch solution. Just as Nexus invented, FDA-approved products use commercial manufacturing scale processes, because their facilities and procedures have been reviewed for large-scale applications. On information and belief, Exela's FDA-approved product is very likely manufactured to make vials containing 5 mg/mL ephedrine sulfate and 9 mg/mL of sodium chloride by first making a batch solution with those concentrations, and then dispensing the batch into individual vials. Otherwise, they would have to manually prepare formulations in each

individual syringe one at a time, which is inefficient and costly for an FDA-approved manufactured process.

**optionally contacting the batch solution with an acid or a base to obtain an initial pH level of the solution of 4.5 to 7;**

60. This claim limitation references an "optional[]" step so is not required to show infringement. Exela reports, however, that it does use this step.

61. The FDA-approved packaging for the Akovaz PFS Product states that the product "may contain Sodium Hydroxide, NF and/or Glacial Acetic Acid, USP as needed for pH adjustment, pH 4.5-6.5." Exhibit C, at page 11.

62. A formulation's pH is the representation of how acidic or basic it is, commonly on a scale from 0 to 14, with 7.0 representing a neutral pH and lower values representing more acidic formulations and higher values representing more basic formulations. A pH can be adjusted by adding acid to reduce pH or by adding base to increase pH.

63. The Akovaz PFS Product label provides that the pH range for the PFS product in particular is 4.5 to 6.5. Exhibit C at Section 11.

64. Upon information and belief, to substantiate this claimed pH range, Exela had to test and demonstrate to FDA that it reached the 4.5-6.6 pH, consistent with claim 1 of the '369 patent. Based on Nexus's experience with FDA and industry knowledge, it is common as far as Nexus is aware for an FDA filing reciting a particular pH range to include specifications for achieving that pH, which allow for the optional use of acid or base in order to meet the pH range that will be shown on the label. The FDA then uses such information to assess product safety and efficacy. Upon information and belief, therefore, Exela includes in its Akovaz PFS Product specification the target pH range and allows optionally adding acid and/or base as needed to obtain the desired pH within the patent's claimed range.

**filtering the batch solution through a membrane filter to obtain a filtered batch solution;**

65. Nexus invented a suitable formulation for FDA approval, including to help components within the product vials to meet stringent FDA specifications by using filtering of the batch solution and before dispersing into a vial.

66. As Nexus reported in its patent, the batch solution was "filtered through Opticap® XL4 Durapore® non-fiber releasing membrane filter membranes" before dispersing into containers. Exhibit A at 17:59-18:2. This filtering step helps to remove impurities and other particles from the batch solution before it is dispersed into vials or syringes. To the best of Nexus's knowledge, the filtering step is an essential part of manufacturing in order to achieve the stringent FDA specifications for individual containers. Nexus is not currently aware of methods to achieve the FDA specifications and obtain FDA approval without filtering or an equivalent step to filtering.

67. Upon information and belief and given that the Akovaz PFS Product is approved by the FDA including to meet stringent FDA standards regarding impurities and other contaminants within individual syringes, Exela filters its Akovaz PFS Product to obtain a filtered batch solution or performs an equivalent sterilization step.

68. In the alternative, and at a minimum, Exela's product meets this filtering claim limitation under the doctrine of equivalents. The Exela product label confirms that the Akovaz PFS Product meets stringent FDA criteria regarding potency, impurity controls, and pH, which must be done by a carefully controlled system in place with large scale manufacturing to fill individual syringes in a manufacturing facility. To do so and maintain the entire 24-month shelf life, Exela would have to demonstrate to FDA that it has taken appropriate manufacturing steps, which would include some degree of confirmation regarding minimizing particulate matter in the syringe, since these are injectable intravenous products and one should not as a general matter for

safety purposes inject solid particles intravenously into patients. For this reason, the Akovaz PFS Product label tells health professionals to "[i]nspect parenteral drug products visually for particulate matter and discoloration prior to administration, whenever solution and container permit." Exhibit C at Section 2.1. Thus, if the filtering is not done precisely as claimed, the FDA approval based on the stringent standards of FDA review support the inference that Exela at least uses an equivalent approach that would be insubstantially different from the claimed step and would be well within the doctrine of equivalents for the filtering step.

**sanitizing one or more containers;**

69. Nexus invented a suitable formulation for FDA approval, including to sanitize individual containers—whether vials or syringes—to achieve a safe and effective product that can be reliably used in the industry.

70. Obtaining FDA approval requires establishing to FDA that individual unit containers are sanitized, because otherwise the individual vials or syringes would be placed in the stream of commerce and their contents administered to patients without appropriate sanitization controls. FDA thus requires sanitization specifications, which in turn require sanitizing steps in the protocol to provide the individual containers, which is also consistent with Nexus's invention.

71. Upon information and belief and given that the Akovaz PFS Product is approved by the FDA including to meet stringent FDA standards regarding impurities and other contaminants within individual syringes, Exela sanitizes the syringe containers it uses for its Akovaz PFS Product.

**placing not more than 20 mL of the filtered batch solution into one of the one or more sanitized containers to obtain one or more filled containers;**

72. In general for FDA-approved manufacturing processes, when manufacturing from a batch solution into individual containers, each individual container is filled in an assembly-line

type manner using specific conditions. One is a volume fill level in order to ensure consistency across individual containers in a batch. On information and belief, Exela uses this same general approach.

73. The approved labeling for the Akovaz PFS Product provides that it is a "5 mL single-dose prefilled syringe." Exhibit C at Dosage Forms and Strengths. As 5 mL is less than 20 mL, and each syringe contains 5 mL in the syringe, Exela places not more than 20 mL of the filtered batch into the syringe containers.

**sealing each filled container to obtain sealed containers including a shelf-stable, ready-to-use ephedrine sulfate composition in the sealed containers that is within 0.5 pH units of the initial pH level during storage at 25°C and 60% relative humidity for at least 12 months or during storage at 40°C and 75% relative humidity for at least 6 months.**

74. Exela reports on its Akovaz PFS Product label that the individual units are sealed with a "tamper evident seal." Exhibit C at Section 2.4. In addition, Exela sells individual syringes, which meets stringent FDA criteria for safety and efficacy as to each individual unit, so that they are sealed in order to ensure consistency. As Exela instructs on its Akovaz PFS Product label, "The single-dose 5 mL prefilled syringe is intended for use in one patient during one surgical procedure." Exhibit C at Section 16. These facts confirm that each individual syringe container is individually sealed. For at least these reasons, Exela meets the "sealing" step for each individual syringe container.

75. The composition inside the syringe must meet stringent criteria to maintain a pH as specified on the product label itself. The Akovaz PFS Product label provides that the pH range of the syringe product must be between 4.5 to 6.5. Exhibit C at Section 11. The product shelf life is believed to be 24 months, based on the FDA Review Approval Package for the Akovaz PFS Product, which reports that Exela documented sufficient "in-process controls in the manufacturing process to ensure quality assurance, adequate sterility assurance, and adequate stability data to

support the proposed shelf-life of 24 months." Nexus is not aware of ways to maintain this shelf life duration without maintaining pH within the tight specifications as required by the claims.

76. To obtain FDA approval, maintaining pH within a tight range is important to show to FDA that the pH level is consistent and stable. The pH is a controlled specification because drug stability, in general, depends on pH. The pH-stability relationship is especially true for ephedrine sulfate. As Nexus explained in its patent, "[e]phedrine sulfate compositions are known to be susceptible to light, pH changes, and humidity." Exhibit A at 1:63-2:2. In other words, if pH is allowed to stray, then the product will lose ephedrine sulfate potency over time, as the drug will become unstable and turn into something other than ephedrine sulfate. The FDA requires stringent controls and tests to make sure product potency is maintained, and for a drug like ephedrine sulfate that is pH-sensitive, that in turn means monitoring pH for purposes of product stability. On information and belief, therefore, Exela's FDA approval on the ephedrine sulfate syringe product means that the pH of the product is maintained throughout the shelf life. Otherwise the pH will vary over time, and in turn will affect the product stability.

77. Companies routinely submit two types of stability testing to the FDA. Stability testing means evaluating a product's properties—including potency—over time. One type of stability testing is real-time, meaning leaving the product at room temperature with standard humidity (and the standard or common approach to test this condition is 25 degrees Celsius and 60% relative humidity). The other type of stability testing is accelerated, meaning raising the temperature and humidity (and the standard or common approach to test this condition is 40 degrees Celsius and 75% relative humidity) to model the effect of a longer time duration than if the product had been stored at room temperature and standard humidity. While Exela's FDA submission is not public, the patent claim language is consistent with the testing that Exela itself

very likely already did, on information and belief, to demonstrate the pH and stability maintenance, so that it could obtain FDA approval, both referring to the real-time room temperature testing (consistent with the claimed 25 degrees Celsius and 60% relative humidity) and to the accelerated testing (consistent with the claimed 40 degrees Celsius and 75% relative humidity). Whether or not Exela did the testing to confirm the claimed pH stability, on information and belief Exela's Akovaz PFS Product does in fact meet this limitation because of the known issues with pH on ephedrine sulfate stability that Exela would have had to address and confirm before it could demonstrate to FDA, as it has done, that its product will maintain adequate ephedrine sulfate levels for the entire 24-month shelf life and still maintain the expressly disclosed pH range on the label of 4.5 to 6.5.

78. In the alternative, and at a minimum, Exela's product meets this pH claim limitation under the doctrine of equivalents. The Exela product label confirms that the pH range of the Akovaz PFS Product must be 4.5 to 6.5 for the entire 24-month shelf life. It is standard practice to select a pH target and then measure the pH over time to confirm the product stability for the duration of the shelf life. Here, given the pH range on the Akovaz PFS Product label of 4.5 to 6.5, it is reasonable to assert on information and belief that the target pH is 5.5. For a target pH of about 5.5, the maximum drift allowed by the Akovaz PFS Product label is plus or minus 1.0, as compared to the claimed drift of plus or minus 0.5. Thus, although Nexus does not expect Exela's product to drift as much as 1.0 pH units during the shelf life, still that would be well within the doctrine of equivalents as a reasonable extension of the claimed range. As the claimed drift range is plus or minus 0.5 pH units, it would be an insubstantial difference for purposes of infringement even if the Exela product were to drift as much as 1.0 pH units. And if the target pH is lower than about 5.5 or higher than about 5.5, then the acceptable drift range to stay within the label's required

4.5 to 6.5 pH range would be even less, at least at one end. For example, if the target pH is about 5.0, then the acceptable drift range could not be more than 0.5 on the lower end in order to still stay within the label's required pH range.

79. Upon information and belief and given that the Akovaz PFS Product is approved by the FDA including to meet stringent FDA standards regarding stability, Exela's Akovaz PFS Product meets the requirement for having a pH level within 0.5 units of the initial pH level—either literally or under the doctrine of equivalents—for the claimed temperature and humidity conditions.

80. On information and belief, Exela directly infringes under 35 U.S.C. § 271(a) by manufacturing or having manufactured or using the claimed invention according to the steps as explained above. The Akovaz PFS Product label shows that the product is manufactured for Exela, and that Exela is the NDA holder, meaning that Exela is the company that obtained FDA approval and directs the manufacture of the infringing product. On information and belief, Exela indirectly infringes under 35 U.S.C. § 271(b) by inducing, such as a contract manufacturing entity, to manufacture the claimed invention according to the approved product label and other specifications as described herein, with the specific intent to infringe because of the actual knowledge of the patent and the steps therein. Exela's Akovaz PFS Product label says that the product is "[m]anufactured for" Exela and because Exela is the NDA holder, that obtained FDA approval for all of the requirements as outlined above, that means Exela is the entity that directs the manufacturing process. On information and belief, Exela indirectly infringes under 35 U.S.C. § 271(c) by importing or selling a material or apparatus for use in practicing the patented process, knowing the same to be adapted for infringement. Exela obtains the ingredients and provides the

material including the equipment, filters, and raw ingredients that meet the criteria suitable for the claimed invention and designed to be used in practicing the patented process.

81. Upon information and belief, Exela has infringed and is continuing to infringe, the patented invention of at least claim 1 of the '369 patent by making, using, offering for sale, selling, and/or importing the Akovaz PFS Product, including by offering the Akovaz PFS Product for sale in the United States, in violation of 35 U.S.C. § 271(a), (b), and (c).

82. The foregoing actions and continued sales by Exela constitute and will constitute infringement of the '369 patent in violation of 35 U.S.C. § 271(a), (b), and (c).

83. Nexus has sufficiently pled infringement and will at trial demonstrate based on these allegations (as supplemented with discovery) a substantial likelihood exists that the product was made by the patented process, so that if Exela resists further confirmation of the claimed elements, then the burden will shift in the litigation to Exela to show non-infringement. 35 U.S.C. § 295.

84. Upon information and belief, Exela has acted with full knowledge of the '369 patent and without a reasonable basis for believing that it would not be liable for infringing the '369 patent.

85. Before the '369 patent issued, the Patent Office published the application and pending claims. Nexus provided to Exela actual notice of the ongoing applications, including the application that resulted in the '369 patent. Exela makes, uses, offers for sale, and sells products made by the claimed process as claimed in the published patent application. Exela is liable for at least a reasonable royalty for the time period from the published patent application through patent issuance, under 35 U.S.C. §154(d).

86. For manufacturing, using, offering to sell, and selling beginning on the date of patent issuance, Exela is liable for full patent damages, including lost profits and/or a reasonable royalty.

87. Nexus informed Exela of the issuance of the '369 patent. Exela was placed on actual notice of the '369 patent at least by the Nexus Letters, yet Exela persisted with its infringing activity, and is continuing to do so willfully.

88. This case is "exceptional," and Nexus is entitled to an award of reasonable attorneys' fees under 35 U.S.C. § 285.

89. Unless Exela is enjoined from infringing the '369 patent, Nexus will suffer irreparable injury.

**COUNT II – INFRINGEMENT OF**
**U.S. PATENT NO. 11,464,752 UNDER 35 U.S.C. § 271(a), (b), (c), and § 154(d)**

90. Nexus repeats and re-alleges each of the foregoing paragraphs as if fully set forth herein.

91. Nexus is the assignee and owner of all right, title, and interest in the '752 patent and Nexus has the legal right to enforce the patent, sue for infringement, and seek equitable relief and damages.

92. The '752 patent is valid, enforceable, and was duly issued in compliance with Title 35 of the United States Code.

93. Claim 10 of the '752 patent, reproduced below, is directed to single use packaged pharmaceutical products containing shelf-stable, sterilized ready-to-use ephedrine compositions:

> 10. A pharmaceutical product comprising:
>
> a packaged ready-to-use single-use container comprising a shelf-stable sterilized pharmaceutical composition comprising:
>
> a packaged concentration of ephedrine sulfate of 5 mg/mL,

9 mg/mL sodium chloride,

water,

no preservative,

an initial pH level of about 4.5 to about 7; and

having, after storage in the syringe at 25°C and 60% relative humidity for 12 months or after storage at 40°C and 75% relative humidity for 6 months:

an ephedrine sulfate concentration of at least 95% of the packaged concentration, and

a pH level within 0.5 pH units of an initial pH level.

94. The Akovaz PFS Product embodies every limitation of at least claim 10 of the '752 patent, literally or under the doctrine of equivalents, as set forth below. Each heading below provides a claim term, and associated sufficient basis for showing infringement of each claim term. It is fully expected that discovery will provide additional factual support and details.

**A pharmaceutical product comprising:**

**a packaged ready-to-use single-use container comprising a shelf-stable sterilized pharmaceutical composition comprising:**

95. The FDA-approved Akovaz PFS Product label provides that "AKOVAZ injection, 5 mg/mL in a pre-filled syringe, is a premixed formulation. Do not dilute prior to use." Exhibit C at Dosage and Administration. It is therefore ready to use, because it does not require dilution, and in fact the product label confirms it must not be further diluted before administration because it is already "premixed" for the syringe product. The approved labeling also provides that the Akovaz PFS product is "ephedrine sulfate in a 5 mL single-dose prefilled syringe." *Id.* at Dosage Forms and Strengths. The label further confirms that "[t]he single-dose prefilled syringe is intended for use in one patient during one surgical procedure" and requires users to "Discard any unused portion." Exhibit C at Section 2.1. It is therefore a single-use container.

96. The composition inside the syringe must meet stringent FDA criteria to maintain the shelf life for the duration of the product, while remaining stable and sterile. Stability is important to protect the drug potency, because if a product is unstable then the FDA will not approve it since a patient may not get the proper amount of ephedrine sulfate. Sterility is important to protect the drug safety, because if a product is unsterile then the FDA will not approve it since a patient may get microbial or other contamination without required sterility assurances. By virtue of FDA approval by Exela for the Akovaz PFS Product, it has deployed a formulation approach that meets the claimed criteria of a product that is "shelf-stable" and "sterilized." In fact, the product shelf life is believed to be 24 months with adequate sterility, based on the FDA Review Approval Package for the Akovaz PFS Product, which reports that Exela documented sufficient "in-process controls in the manufacturing process to ensure quality assurance, adequate sterility assurance, and adequate stability data to support the proposed shelf-life of 24 months."

97. Upon information and belief and given that the Akovaz PFS Product was approved by the FDA including to meet stringent FDA standards regarding stability and sterility, the Akovaz Product is a ready-to-use, single-use, shelf-stable sterilized pharmaceutical composition as required by claim 10 of the '752 patent.

**a packaged concentration of ephedrine sulfate of 5 mg/mL,**

**9 mg/mL sodium chloride,**

**water,**

**no preservative, and**

**an initial pH level of about 4.5 to about 7; and**

98. Exela reports on its Akovaz PFS Product label that the individual units are sealed with a "tamper evident seal." Exhibit C at Section 2.4. In addition, Exela sells individual syringes, which must meet stringent FDA criteria for safety and efficacy as to each individual unit, so that

they are sealed in order to ensure consistency. As Exela instructs on its Akovaz PFS Product label, "The single-dose 5 mL prefilled syringe is intended for use in one patient during one surgical procedure." Exhibit C at Section 16. These facts confirm that each individual syringe container is individually sealed. Each syringe thus includes a packaged concentration of ephedrine sulfate as required by claim 10.

99. Section 11 of the Akovaz PFS Product label provides that "[e]ach mL of the 5 mL single-dose prefilled syringe contains 5 mg ephedrine sulfate" and "9 mg Sodium Chloride, USP" and "in Water for Injection." Exhibit C at Section 11. The Akovaz PFS Product label makes no mention of using any preservative. *See id.* As pharmaceutical products are expected to disclose on the label the ingredients contained in the product, and no preservative is listed, on information and belief Akovaz PFS Product does not include a preservative.

100. The same Section 11 of the Akovaz PFS Product label confirms that the specified pH range for the entirety of the product shelf life is "4.5 to 6.5." *Id*. The release specifications for the Exela product must therefore require all commercial syringes to meet this requirement, otherwise the FDA would not have approved the labeling requirement. Because the entire labeled range of 4.5 to 6.5 falls within the claimed range of "about 4.5 to about 7," the Exela Akovaz PFS Product meets this pH requirement as well.

**having, after storage in the syringe at 25°C and 60% relative humidity for 12 months or after storage at 40°C and 75% relative humidity for 6 months:**

**an ephedrine sulfate concentration of at least 95% of the packaged concentration, and**

**a pH level within 0.5 pH units of an initial pH level.**

101. The composition inside the syringe must meet stringent criteria to maintain a pH as specified on the product label itself. The Akovaz PFS Product label provides that the pH range of the syringe product must be between 4.5 to 6.5. Exhibit C at Section 11. The product shelf life is

believed to be 24 months, based on the FDA Review Approval Package for the Akovaz PFS Product, which reports that Exela documented sufficient "in-process controls in the manufacturing process to ensure quality assurance, adequate sterility assurance, and adequate stability data to support the proposed shelf-life of 24 months." Nexus is not aware of ways to maintain this shelf life duration with adequate tight potency controls at the 95%-105% range without maintaining pH within the tight specifications as required by the claims.

102. To obtain FDA approval, maintaining pH within a tight range is important in order to show to FDA that the pH level is consistent and stable. The pH is a controlled specification because drug stability, in general, depends on pH. The pH-stability relationship is especially true for ephedrine sulfate. As Nexus explained in its patent, "[e]phedrine sulfate compositions are known to be susceptible to light, pH changes, and humidity." Exhibit A at 1:63-2:2. In other words, if pH is allowed to stray, then the product will lose ephedrine sulfate potency over time, as the drug will become unstable and turn into something other than ephedrine sulfate and lose more than 5% of the starting ephedrine sulfate and therefore fall short of the 95% threshold in this claim.

103. The FDA requires stringent controls and tests to make sure product potency is maintained, and for a drug like ephedrine sulfate that is pH-sensitive, that in turn means monitoring pH for purposes of product stability. On information and belief, therefore, Exela's FDA approval on the ephedrine sulfate syringe product meets the stringent FDA requirement for injectable products that maintain a potency of 95%-105% of the product throughout its shelf life, and given that range, then Exela infringes just as Nexus invented for the claimed formulation that meets this criteria. On information and belief, therefore, Exela's FDA approval on the ephedrine sulfate syringe product must throughout the shelf life of the product maintain the pH because otherwise the pH will vary over time, and in turn will affect the product stability.

104. Companies routinely submit two types of stability testing to the FDA. Stability testing means evaluating a product's properties—including potency—over time. One type of stability testing is real-time, meaning leaving the product at room temperature with standard humidity (and the standard or common approach to test this condition is 25 degrees Celsius and 60% relative humidity). The other type of stability testing is accelerated, meaning raising the temperature and humidity (and the standard or common approach to test this condition is 40 degrees Celsius and 75% relative humidity) to model the effect of a longer time duration than if the product had been stored at room temperature and standard humidity. While Exela's FDA submission is not public, the patent claim language is consistent with the testing that Exela itself very likely already did, on information and belief, in order to demonstrate the pH and stability maintenance, so that it could obtain FDA approval, both referring to the real-time room temperature testing (consistent with the claimed 25 degrees Celsius and 60% relative humidity) and to the accelerated testing (consistent with the claimed 40 degrees Celsius and 75% relative humidity). Whether or not Exela did the testing to confirm the claimed pH stability, on information and belief Exela's Akovaz PFS Product does in fact meet this limitation because of the known issues with pH on ephedrine sulfate stability that Exela would have had to address and confirm before it could demonstrate to FDA, as it has done, that its product will maintain adequate ephedrine sulfate levels for the entire 24-month shelf life and still maintain the expressly disclosed pH range on the label of 4.5 to 6.5.

105. In the alternative, and at a minimum, Exela's product meets the pH claim limitation under the doctrine of equivalents. The Exela product label confirms that the pH range of the Akovaz PFS Product must be 4.5 to 6.5 for the entire 24-month shelf life. It is standard practice to select a pH target and then measure the pH over time to confirm the product stability for the

duration of the shelf life. Here, given the pH range on the Akovaz PFS Product label of 4.5 to 6.5, it is reasonable to assert on information and belief that the target pH is 5.5. For a target pH of about 5.5, the maximum drift allowed by the Akovaz PFS Product label is plus or minus 1.0, as compared to the claimed drift of plus or minus 0.5. Thus, although Nexus does not expect Exela's product to drift as much as 1.0 pH units during the shelf life, still that would be well within the doctrine of equivalents as a reasonable extension of the claimed range. As the claimed drift range is plus or minus 0.5 pH units, it would be an insubstantial difference for purposes of infringement even if the Exela product were to drift as much as 1.0 pH units. And if the target pH is lower than about 5.5 or higher than about 5.5, then the acceptable drift range to stay within the label's required 4.5 to 6.5 pH range would be even less, at least at one end. For example, if the target pH is about 5.0, then the acceptable drift range could not be more than 0.5 on the lower end in order to still stay within the label's required pH range.

106. Similarly in the alternative, and at a minimum, Exela's product meets the 95% potency claim limitation under the doctrine of equivalents. The Exela product label confirms that the Akovaz PFS Product must remain adequately potent for the entire 24-month shelf life. As noted above, there is very likely to be literal infringement by Exela's PFS product, based on information and belief, in view of the stringent FDA requirements for injectable drugs and the general standard to maintain a 95%-105% potency level. Even if, however, the Exela product strays somewhat from the claimed 95% threshold, even still there would be infringement under the doctrine of equivalents because ranges slightly less than 95%--which, on information and belief, Exela's product could not exceed to maintain the FDA-approved 24-month shelf life--would be an insubstantial difference for purposes of infringement.

107. Upon information and belief and given that the Akovaz PFS Product is approved by the FDA including to meet stringent FDA standards regarding stability, Exela's Akovaz PFS Product meets the requirement for having a pH level within 0.5 units of the initial pH level and at least 95% of the ephedrine sulfate level—either literally or under the doctrine of equivalents—for the claimed temperature and humidity conditions.

108. On information and belief, Exela directly infringes under 35 U.S.C. § 271(a) by making, using, offering to sell, and selling the claimed invention according to the claimed elements as explained above. The Akovaz PFS Product label shows that the product is manufactured for Exela, and that Exela is the NDA holder, meaning that Exela is the company that obtained FDA approval and directs the manufacture of the infringing product and is the company authorized to sell commercial product that infringes the claims. On information and belief, Exela indirectly infringes under 35 U.S.C. § 271(b) by inducing, such as a contract manufacturing entity, to manufacture the claimed invention according to the approved product label and other specifications as described herein, with the specific intent to infringe because of the actual knowledge of the patent and the requirements therein. Exela's Akovaz PFS Product label says that the product is "[m]anufactured for" Exela and because Exela is the NDA holder, that obtained FDA approval for all of the requirements as outlined above, that means Exela is the entity that directs the manufacturing process. On information and belief, Exela indirectly infringes under 35 U.S.C. § 271(c) by importing or selling a component of a patented product, knowing the same to be adapted for infringement. Exela obtains the ingredients and provides the material including the equipment, filters, and raw ingredients that meet the criteria suitable for the claimed invention and designed to be used to make the infringing product.

109. Upon information and belief, Exela has infringed and is continuing to infringe, the patented invention of at least claim 10 of the '752 patent by making, using, offering for sale, selling, and/or importing the Akovaz PFS Product, including by offering the Akovaz PFS Product for sale in the United States, in violation of 35 U.S.C. § 271(a), (b), and (c).

110. The foregoing actions and continued sales by Exela constitute and will constitute infringement of the '752 patent in violation of 35 U.S.C. § 271(a), (b), and (c).

111. Upon information and belief, Exela has acted with full knowledge of the '752 patent and without a reasonable basis for believing that it would not be liable for infringing the '752 patent.

112. Before the '752 patent issued, the Patent Office published the application and pending claims. Nexus provided to Exela actual notice of the ongoing applications, including the application that resulted in the '752 patent. Exela makes, uses, offers for sale, and sells products made by the claimed pharmaceutical products as claimed in the published patent application. Exela is liable for at least a reasonable royalty for the time period from the published patent application through patent issuance, under 35 U.S.C. §154(d).

113. For manufacturing, using, offering to sell, and selling beginning on the date of patent issuance, Exela is liable for full patent damages, including lost profits and/or a reasonable royalty.

114. Nexus informed Exela of the issuance of the '752 patent. Exela was placed on actual notice of the '752 patent at least by the Nexus Letters and later correspondence, yet Exela persisted with its infringing activity, and is continuing to do so willfully.

115. This case is "exceptional," and Nexus is entitled to an award of reasonable attorneys' fees under 35 U.S.C. § 285.

116. Unless Exela is enjoined from infringing the '752 patent, Nexus will suffer irreparable injury.

**REQUEST FOR RELIEF**

WHEREFORE, Nexus requests the following relief:

a. A judgment, pursuant to 35 U.S.C. § 271(a), (b), and/or (c), declaring that the commercial manufacture, use, offering to sell, or sale within the United States, and/or importation into the United States of Exela's Akovaz PFS Product before the expiration of the '369 and '752 patents (including any regulatory extension), will infringe the '369 and/or '752 patents;

b. A judgment that the '369 and '752 patents are valid and enforceable;

c. An order for preliminary and permanent injunction;

d. An award, pursuant to 35 U.S.C. §§ 154(d) and 284, of damages or other monetary relief to compensate Nexus for Exela's engagement in the manufacture, use, offer for sale, sale, marketing, distribution, and/or importation of Exela's Akovaz PFS Product, or any product the making, using, offering for sale, selling, marketing, distribution, or importation of which infringes the '369 and/or '752 patents;

e. Awarding Nexus enhanced damages;

f. A judgment pursuant to 35 U.S.C. § 285 that this case against Exela is an exceptional case and an award of attorneys' fees and costs; and

g. Such further and other relief as this Court may deem just and proper.

*/s/ Kelly E. Farnan*

Kelly E. Farnan (#4395)
Christine D. Haynes (#4697)
Richards, Layton & Finger, P.A.
One Rodney Square
920 North King Street
Wilmington, DE 19801
(302) 651-7700
farnan@rlf.com
haynes@rlf.com

*Attorneys for Plaintiff Nexus Pharmaceuticals, Inc.*

OF COUNSEL:

Imron T. Aly
Kevin M. Nelson
Helen H. Ji
Chad F. Watson
ARENTFOX SCHIFF LLP
233 South Wacker Drive
Suite 7100
Chicago, IL 60606
(312) 258-5500
imron.aly@afslaw.com
kevin.nelson@afslaw.com
helen.ji@afslaw.com
chad.watson@afslaw.com

Dated: July 5, 2023