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January 5, 2022

Division of Dockets Management (HFA-305)
U.S. Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

**RE: FDA-2021-P-0358, Citizen Petition from Nexus Pharmaceuticals Inc.—Second OFA Comment**

The Outsourcing Facilities Association ("OFA") submits this comment in response to Nexus's Comment dated November 24, 2021.[1] The OFA previously commented in response to Nexus's citizen petition on July 8, 2021. OFA is submitting this response to Nexus's Comment to point out Nexus's violations of the regulations governing citizen petitions and to correct the record in response to its new erroneous assertions. The FDA should deny Nexus's Citizen Petition and refer the matter to the FTC due to anticompetitive practices, like the FDA has recently stated it intends to do with a similar petition that did not include all information referred to or relied upon.

## I. Nexus's Citizen Petition and Comment/Response both violate FDA regulations.

Like its original petition, Nexus's "Comment"—really, a supplement to its petition—violates 21 CFR § 10.30(b)(3) because it does not contain the "full … factual and legal grounds on which the petitioner relies, including ***all*** relevant information …, as well as representative information known to the petitioner which is ***unfavorable*** to the petitioner's position." (Emphasis added.)[2] Nor did Nexus abide by the requirement that "[i]nformation referred to or relied upon in a submission is to be ***included in full*** and may not be incorporated by reference, unless previously submitted in the same proceeding." 21 CFR § 10.20(c). Just like the FDA noted in its response to Par Sterile Products, LLC's ("Par's") Citizen Petition,[3] Nexus also makes numerous unsubstantiated assertions and refers to information it has withheld from FDA and the public. The most glaring example of its disregard for the regulations is Nexus's unsubstantiated assertion that it supposedly "has information that outsourcing facilities are supplying healthcare providers whose patients' medical needs could be met by Emerphed" and that unidentified "[p]rospective customers have communicated to Nexus that they obtain their ephedrine sulfate products from outsourcing

[1] Comment from Nexus Pharmaceuticals, Inc, RE: FDA-2021-P-0358, Citizen Petition from Nexus Pharmaceuticals Inc., Comment ID FDA-2021-P-0358-0007 (Nov. 24, 2021) [hereinafter Nexus Comment].
[2] 21 CFR § 10.30(b)(3) ("A petition submitted under paragraphs (b)(1) or (b)(2) of this section must be in accordance with § 10.20 and in the following format… A full statement, in a well-organized format, of the factual and legal grounds on which the petitioner relies, including all relevant information and views on which the petitioner relies, as well as representative information known to the petitioner which is unfavorable to the petitioner's position").
[3] FDA Ltr. To Chad A. Landmon, Re: Docket No. FDA-2021-P-1211 (Dec. 15, 2021)[hereinafter FDA Response to Par]

facilities."[4] Despite referring—and asking FDA to rely on— this information Nexus supposedly has, Nexus provides none of it, let alone all of it, as required by 21 CFR § 10.20(c). Nexus's direct violation of the regulations and FDA's policies warrant immediate withdrawal of its citizen petition and should be treated like Par with a referral to the proper sister federal agency.[5] Otherwise, the veracity of its claims about the information supposedly in its possession at the time of its Comment should be investigated and if found to be a misrepresentation, action should be taken under the False Reports to the Government Act.[6]

Worse still, Nexus provides none of the "representative information known to the petitioner which is unfavorable to the petitioner's position," as required by 21 CFR § 10.30(b)(3). In its rush to blame what appears to be its own poor product forecasting on competition from outsourcing facilities, Nexus asserts that underlying OFA's comment is the "false premise that compounded drug products are preferable to approved drug products when they are less expensive or available in a more convenient form."[7] Setting aside the fact OFA said no such thing, Nexus withheld from its submission the information it knows about competition for its product from at least one competing FDA-approved drug: AKOVAZ. There is no question Nexus knows this information because its own application states that "[t]he proposed drug product's entire label is based on the information mentioned from the AKOVAZ label, ***the only difference*** being that the proposed drug product is a 'ready-to-use' solution for patient administration compared to the [Reference Listed Drug] RLD that requires prior dilution with sodium chloride before administration." (Emphasis added.)[8] Nexus fails to acknowledge the competition it faces from AKOVAZ when healthcare providers see through its manipulation of the drug approval process and instead prepare injectable doses according to the FDA-approved labeling for AKOVAZ. If Emerphed's label is based on the information mentioned from the AKOVAZ label, it certainly stands to reason that healthcare providers may choose to purchase AKOVAZ instead of Emerphed.

In addition, Nexus violates FDA regulations by using the petition process for an impermissible purpose by seeking to compel FDA to take enforcement action. It blatantly encourages FDA to post untitled letters or warning letters, or pursue seizures or injunctions against outsourcing facilities, beyond the Form FDA-483s issued to outsourcing facilities at present.[9] The regulations specifically state that citizen petitions cannot be used to request enforcement actions against companies. 21 CFR 10.30(k) ("This section does not apply to the referral of a matter to a United States attorney for the initiation of court enforcement action and related correspondence, or to

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[4] Nexus Comment at 2.
[5] FDA referred Par to the FTC. ("FDA intends to refer this matter to the FTC, which has the administrative tools and the expertise to investigate and address anticompetitive business practices.") FDA Response to Par at 8.
[6] *See* 21 CFR § 10.20(i) ("All submissions to the Division of Dockets Management are representations that, to the best of the knowledge, information, and belief of the person making the submission, the statements made in the submission are true and accurate. ***All submissions are subject to the False Reports to the Government Act (18 U.S.C. 1001) under which a willfully false statement is a criminal offense***.") (Emphasis added.).
[7] Nexus Comment at 1.
[8] Center for Drug Evaluation and Research Application Number: 213407Orig1s000, Summary Review, at 4 https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/213407Orig1s000SumR.pdf.
[9] Nexus does not establish that any of the Form FDA-483s listed in Nexus Citizen Petition (at n.16) identified ephedrine sulfate products as products that were essentially copies.

requests, suggestions, and recommendations made informally in routine correspondence received by FDA").[10]

## II. Nexus's Comment is full of incorrect statements.

In addition to ignoring the regulations, Nexus also fails to heed the facts. Nexus states that "compounders that produce copies of FDA-approved drug products undermine the incentive for manufacturers to obtain FDA approvals, including supplemental new drug approvals for drug products that are in ready-to-administer form."[11] In fact, Nexus's product, Emerphed, is not in a **ready-to-administer** form. Emerphed is in a **ready-to-use** form. This factual distinction is important for patient safety and the FDA's essentially a copy analysis. Simply put, a Ready-to-Administer (RTA) product does not require any further manipulation to administer to a patient but a Ready-to-Use (RTU) product does. Taking ephedrine sulfate as an example, an RTA product is one that is sold in a syringe for direct injection, whereas an RTU product is one that is sold in a container such as a vial, where at a minimum the vial must be pierced, and drug product must be withdrawn before it may be injected. Because RTA products require no human manipulation in the clinical setting, they are less susceptible to human-error, potentially making them a safer alternative in the medical judgment of doctors. There is great incentive for manufacturers to obtain FDA approvals, including supplemental new drug approvals for drug products that are in ready-to-administer form. Had Nexus simply submitted a supplemental application for an RTA form of ephedrine sulfate, then perhaps it would not now be seeking to abuse the citizen petition process to stake out a monopoly on ephedrine sulfate.

Nexus is also guilty of obfuscating the distinction between "clinical need" and "clinical difference." Nexus points FDA to the 503B *clinical need* determination regarding vasopressin as supposed support for its petition.[12] But *clinical need* is not the same as *clinical difference*. Indeed, the distinction was a basis for the federal district court's decision in the litigation regarding FDA's clinical need determination for vasopressin:

> Plaintiffs complain that reading Section 503B in this way is impermissible because, through its pre-market "clinical need" inquiry, FDA is in effect making the "clinical difference" determination that the statute leaves to treatment providers. The agency is thus impermissibly regulating the practice of medicine, say Plaintiffs. *See* Pls.' Mem. at 27. Not so. Take the case of vasopressin. FDA's decision not to recognize a "clinical need" for vasopressin does not interfere with a physician's decision whether to treat a patient with the approved product, Vasostrict, or a compounded version of Vasostrict that meets a patient's individual need. FDA's vasopressin decision only regulates the type of drug that reaches the marketplace.[13]

As seen from the court's own words, the "clinical difference" determination is left to treatment providers.

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[10] Nexus pays lip service to this admonition, then flaunts it. *See* Nexus Citizen Petition Fn 48 ("Requests to the Agency to initiate enforcement actions are not with the scope of FDA's citizen petition procedures").
[11] *Id.*
[12] Nexus Comment at 3 citing 84 Fed. Reg. 7383, 7388 (2019).
[13] Athenex Inc. v. Azar, 397 F. Supp. 3d 56, 72 (D.D.C. 2019).

If Nexus made an unlucrative business decision or is not reaping the full benefits of its forecasted monopoly gains, that is no grounds for requesting the FDA to impermissibly practice medicine and make "clinical difference" determinations for healthcare providers.[14] Denying Nexus's citizen petition is the only way for the FDA to not interfere with a physician's decision whether to treat a patient with the approved product, AKOVAZ, the approved product Emerphed, or a compounded version starting with AKOVAZ or Emerphed that meets a patient's individual need.

## III. Antitrust Violations

The FDA should review and consider Nexus's actions in a similar light to those by Par and take similar actions.[15] In addition to violating the FDA regulations, Nexus's citizen petition is part of a pattern of conduct that appears to be in violation of the Sherman Anti-Trust Act ("Sherman Act"). That Act prohibits "monopolization[,] attempted monopolization or conspiracy or combination to monopolize."[16] Monopolies refer to the dominance of a market by one company or firm while cutting out competitors, and harming consumers, by means other than competing on the merits. This means regulators must ensure monopolies are the result of business acumen and innovation, and not through exclusionary or predatory practices. When a competitor achieves or maintains monopoly power through conduct that serves no purpose other than to exclude competition, such conduct is clearly improper and in violation of the Sherman Act. Nexus is doing just that with a pattern of conduct, including the current FDA's citizen petition and other nefarious actions, to achieve or maintain a monopoly over ephedrine sulfate products sold in the United States.

Specifically, the Sherman Act prohibits (1) monopoly power that is (2) willfully acquired or maintained as distinguished from growth or development as a consequence of a superior product, business acumen, or historic accident. Regarding the first element, there is no question that Nexus has monopoly power over ephedrine sulfate products sold in the United States. Nexus has a patent listed in FDA's Orange Book for 20 years, until 2040 on Emerphed (ephedrine sulfate) Vial 50 mg/10 mL (5,g/mL). Nexus has leveraged its exclusivity to gain dominance over all ephedrine sulfate products. For decades, compounders have compounded ephedrine sulfate products. When FDA granted approval to its first ephedrine sulfate product, compounders have since used Akovaz as a base ingredient for compounding ephedrine products. As noted above, Nexus capitalized off of the compounding market by seeking a 505(b)(2) approval and thus, exclusivity on the commonly compounded ephedrine sulfate product. Nexus's monopoly power is confirmed by its ability to maintain its power over time, even while imposing large increases in prices.[17]

Nexus also has achieved or maintained its market power through anticompetitive conduct, the Sherman Act's second element.[18] This conduct includes Nexus's use of sham litigation to stifle

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[14] *See* Nexus Citizen Petition at n.43 ("EMERPHED was projected to be Nexus's top selling product for 2020, but Nexus now forecasts that in view of outsourcing facilities' compounding of copies, Nexus may earn only approximately 20% of the ready-to-use ephedrine sulfate product market, as opposed to the nearly 100% that it could have tried to claim if it competed only with the FDA-approved high-concentrate product").

[15] *See* FDA Response to Par *supra* note 5.

[16] 15 U.S.C. § 2.

[17] *Verizon Commc'ns Inc. v. Law Offices of Curtis V. Trinko, LLP*, 540 U.S. 398, 407 (2004). Market power being the ability to raise prices profitability above those that would be charged in a competitive market.

[18] *Trinko*, 540 U.S. at 407. Such conduct often is described as "exclusionary" or "predatory" conduct.

competition. Prior to its citizen petition, Nexus pursued six (6) lawsuits designed to exclude competition in ephedrine sulfate products. All of these suits were dismissed, confirming they lacked merit and were pursued for no reason other than to harass and harm other market participants.[19] Nexus's citizen petition raises the same issues already rejected repeatedly by courts, also confirming Nexus's serial use of these proceedings to burden and deter competition. More to the point, Nexus's citizen petition omits material information as shown above, which even further demonstrates its nefarious means of conduct.

Nexus also has utilized coercion and intimidation, rather than fair competition, to achieve and maintain its power. Nexus has sent numerous cease and desist letters threatening lawsuits and other punishment of participants that dared try to compete. This conduct, backed up by sham litigation and now a citizen petition, has forced actual and potential competitors, including and most notably compounders, off the ephedrine sulfate market. As stated, the ephedrine sulfate products that Nexus complains are essentially copies of Emerphed have been on the market for decades prior to Nexus's 505(b)(2) approval. Nexus relied on Akovaz's clinical research which did not conduct any studies to support its NDA. Instead, Akovaz's approval was predicated on the fact that "Ephedrine has been used in the United States for decades as marketed unapproved products. In support of the clinical pharmacology submission, the sponsor reviewed published literature and submitted supporting information."[20] Much of the marketed unapproved product that was used in the United States for decades was compounded. Despite neither sponsor of Emerphed or Akovaz expending its owner resources to establish safety and efficacy, Nexus continues to declare all ephedrine sulfate products essentially copies of Emerphed.

In addition, Nexus has tried to create a monopoly unlawfully by claiming that it is illegal to use FDA-approved finished products for compounding, except when compounders use Nexus's FDA-approved product, Emerphed. In essence, compounders are lawfully compounding ephedrine sulfate products when Nexus can make a profit. But if compounders use other ephedrine sulfate products as a baseline ingredient, it is considered unlawful by Nexus. This effort by Nexus to force compounders to buy a more expensive product that they do not need or want is another version of anticompetitive behavior that supports a violation of the Sherman Act.

This summary of Nexus's anticompetitive conduct is more than enough evidence to show that it has unlawfully monopolized the ephedrine sulfate market. But even if there were a question, it would be certain that Nexus is unlawfully attempting to monopolize that market.

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[19] *See* Nexus Pharmaceuticals, Inc. v. Cent. Admixture Pharmacy Services, Inc., C.D. Cal. No. SACV2001506CJCJDEX, 2020 WL 6555052 (C.D. Cal. Oct. 29, 2020), appeal dismissed, 9th Cir. No. 20-56157, 2020 WL 8409681 (9th Cir. Dec. 1, 2020); Nexus Pharmaceuticals, Inc. v. Quva Pharma, Inc., C.D. Cal. No. CV2007518CJCJDEX, 2020 WL 6498970 (C.D. Cal. Oct. 29, 2020); Nexus Pharmaceuticals, Inc. v. Leiters, Inc., C.D. Cal. No. CV2007328CJCJDEX, 2020 WL 10356606 (C.D. Cal. Oct. 29, 2020); Nexus Pharmaceuticals Inc. v. SCA Pharmaceuticals Inc., C.D. Cal. No. 2:20-CV-07520 (C.D. Cal. Nov. 5, 2020); Nexus Pharmaceuticals, Inc. v. U.S. Compounding, Inc., C.D. Cal. No. CV2007331CJCJDEX, 2021 WL 342573, (C.D. Cal. Jan. 7, 2021); Nexus Pharmaceuticals, Inc. v. Fagron Compounding Services LLC, C.D. Cal. No. 2:20CV07329 (C.D. Cal. Aug. 13, 2020).

[20] Center for Drug Evaluation and Research Application Number: 208289Orig1s000, Clinical Pharmacology and Biopharmaceutics Review, at 3, https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/208289Orig1s000ClinPharmR.pdf.

The Sherman Act also prohibits attempted monopolization when there is (1) anticompetitive conduct, (2) a specific intent to monopolize, and (3) a dangerous probability of achieving monopoly power.[21] The first element is satisfied by the above evidence demonstrating Nexus's anticompetitive conduct to monopolize. The second element, specific intent to monopolize, means "a specific intent to destroy competition or build monopoly."[22] Again, that element is satisfied by the above, where Nexus has attempted to "destroy competition" through its coercion, cease and desist letters, many failed lawsuits, and now a citizen petition raising the same unmeritorious arguments again. For element three, it is "not necessary to show that success rewarded [the] attempt to monopolize;" rather, "when that intent and the consequent dangerous probability exist, this statute, like many others and like the common law in some cases, directs itself against the dangerous probability as well as against the completed result."[23] In other words, should FDA grant Nexus's citizen petition, there is a dangerous probability of Nexus achieving monopoly power over the ephedrine sulfate market.

As identified above, Nexus is in violation of the Sherman Act's monopolization and attempted monopolization of the ephedrine sulfate market.

## IV. Conclusion

Nexus has failed to offer factual or legal grounds by which FDA could grant Nexus' requests. Nexus is also in violation of the Sherman Act with its anti-competition actions. The FDA must deny Nexus's petition and should refer this matter to the FTC. Alternatively, Nexus should withdraw its citizen petition, provide the evidence it claims to possess, or the veracity of its claims should be investigated and if found to be a misrepresentations, action should be taken under the False Reports to the Government Act.

Respectfully submitted,

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[21] *Spectrum Sports, Inc. v. McQuillan*, 506 U.S. 447, 456 (1993).
[22] *Times-Picayune Publ'g Co. v. United States*, 345 U.S. 594, 626 (1953).
[23] *Spectrum Sports*, 506 U.S. at 455 (quoting *Swift & Co. v. United States*, 196 U.S. 375, 396 (1905)).