John E. Morrone, Esq.
Frier Levitt
84 Bloomfield Avenue
Pine Brook, NJ 07058

Re: Docket No. FDA-2015-P-4601

NOV 0 5 2018

Dear Mr. Morrone:

This letter responds to the citizen petition (Petition) received on December 4, 2015, submitted on behalf of your licensed pharmacy and outsourcing facility clients. In the Petition, you request that the Food and Drug Administration (FDA or Agency) "refrain from naming implantable testosterone pellets to the demonstrably difficult to compound list which will be codified pursuant to 21 U.S.C. §353a(b)(3)(A) and 21 U.S.C. 353b(a)(6)."

We have carefully considered the information submitted in the Petition. For the reasons stated below, the Petition is denied.

I. BACKGROUND

A. Statutory Framework

Section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 353a) describes the conditions under which a human drug product compounded for an identified individual patient based on a prescription is exempt from three sections of the FD&C Act: (1) section 501(a)(2)(B) (21 U.S.C. 351(a)(2)(B)) (concerning current good manufacturing practice (CGMP) for drugs); (2) section 502(f)(1) (21 U.S.C. 352(f)(1)) (concerning the labeling of drugs with adequate directions for use); and (3) section 505 (21 U.S.C. 355) (concerning the approval of human drug products under new drug applications or abbreviated new drug applications). One of the conditions for these exemptions is that the "drug product is not a drug product identified by the Secretary by regulation as a drug product that presents demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety or effectiveness of that drug product" (section 503A(b)(3)(A) of the FD&C Act). Section 503A(c)(1) of the FD&C Act provides that, "[b]efore issuing regulations to implement [section 503A(b)(3)(A)], the Secretary shall convene and consult an advisory committee on compounding."

Section 503B of the FD&C Act (21 U.S.C. 353b) describes the conditions under which human drugs compounded by or under the direct supervision of a licensed pharmacist in an outsourcing facility are exempt from three sections of the FD&C Act: (1) section 502(f)(1); (2) section 505; and section 582 (21 U.S.C. 360eee-1) (concerning drug supply chain security requirements). One of the conditions for these exemptions is that the drug either (1) is not identified (directly or as part of a category of drugs) on a list published by the Secretary, of drugs or categories of drugs that present demonstrable difficulties for compounding that are reasonably likely to lead to

an adverse effect on the safety or effectiveness of the drug or category of drugs, taking into account the risks and benefits to patients, or (2) is compounded in accordance with all applicable conditions identified on the list as conditions that are necessary to prevent the drug or category of drugs from presenting such demonstrable difficulties (section 503B(a)(6)(A) and (a)(6)(B) of the FD&C Act). Section 503B(c)(2) of the FD&C Act provides that "[b]efore issuing regulations to implement [section 503B(a)(6)], the Secretary shall convene and consult an advisory committee on compounding."

B. Establishment of the Difficult to Compound List

In a notice published in the *Federal Register* on December 4, 2013 (78 FR 72840), FDA stated that it intended to develop and publish a single list of drug products and categories of drug products that cannot be compounded and qualify for any of the exemptions set forth in sections 503A and 503B because they present demonstrable difficulties for compounding (hereinafter the "Difficult to Compound List"). 78 FR 72841. In this notice, FDA invited all interested persons to nominate drug products or categories of drug products for inclusion on the Difficult to Compound List. Nominators were asked to include the name of the drug product or category of drug products being nominated, as well as the reason the drug product or category of drug products should be included on the list, considering the risks and benefits to patients. The notice also included a non-exhaustive list of factors that may be relevant to determining whether a drug product or category of drug products should be included on the Difficult to Compound List. Approximately 71 unique drug products or categories of drug products were nominated for this list. As noted in your Petition, the public comment period for this notice closed on March 4, 2014.

On June 18, 2015, the Pharmacy Compounding Advisory Committee (PCAC) reviewed and discussed the criteria FDA described in its 2013 *Federal Register* notice for evaluating whether drug products or categories of drug products are demonstrably difficult to compound under sections 503A and 503B of the FD&C Act. After considering the PCAC's discussion, FDA refined the criteria and presented the changes to the PCAC on March 9, 2016. The six criteria presented to the PCAC for evaluating whether a drug product or category of drug products is demonstrably difficult to compound are the following: (1) the complexity of the formulation; (2) the complexity of the drug delivery mechanism; (3) the complexity of the dosage form; (4) the complexity of achieving bioavailability; (5) the complexity of the compounding process; and (6) the complexity of physicochemical or analytical testing.

On July 28, 2017, FDA published a *Federal Register* notice entitled *Drug Products That Present Demonstrable Difficulties for Compounding Under the Federal Food, Drug, and Cosmetic Act; Establishment of a Public Docket* (82 FR 35214) (FDA-2017-N-2562).[1] The purpose of this notice was to establish a public docket to permit interested parties to nominate additional drug products or categories of drug products for inclusion on the Difficult to Compound List, resubmit previous nominations (submitted in response to the December 4, 2013 notice) with additional supporting information, or submit comments about newly or previously nominated products or categories of products. The docket established by the 2017 *Federal Register* notice remains

[1] Available at https://www.federalregister.gov/documents/2017/07/28/2017-15900/drug-products-that-present-demonstrable-difficulties-for-compounding-under-the-federal-food-drug-and.

open for public comment, and comments may be submitted at any time.

FDA has begun evaluating drug products or categories of drug products for inclusion on the Difficult to Compound List, including metered dose inhalers, dry powder inhalers, drug products that employ transdermal and topical delivery systems, oral solid modified release drug products that employ coated systems, liposome drug products, and drug products produced using hot melt extrusion. The PCAC recommended that FDA place each of these categories of drug products on the Difficult to Compound List.

As a procedural matter, FDA publishes a *Federal Register* notice to announce when it intends to convene and consult the PCAC to discuss whether specific drug products or categories of drug products should be included on the Difficult to Compound List, among other recommendations. In advance of these meetings, FDA generally posts background materials that include the Agency's scientific opinion for why specific drug products or categories of drug products should be proposed for inclusion on the Difficult to Compound List, using the criteria listed above, and taking into account the risks and benefits to patients. As noted in the *Federal Register* notice, interested persons are invited to present data, information, or views in writing on issues pending before the committee. All electronic and written submissions can be made at the addresses listed in the *Federal Register* notice. Additionally, interested parties have the opportunity to present relevant data, information, or views orally during a portion of the advisory committee meeting called the open public hearing. The *Federal Register* notice also provides instructions on how interested parties can request time during the open public hearing to deliver a formal oral presentation to the PCAC.

After consultation with the PCAC, FDA intends to develop and promulgate the Difficult to Compound List in accordance with sections 503A(b)(3), 503A(c)(1), and 503B(a)(6) of the FD&C Act through notice and comment rulemaking procedures. During the notice-and-comment rulemaking process, interested parties will have another opportunity to comment on drug products and/or categories of drug products that FDA proposes to include on the Difficult to Compound List. FDA will review and consider all significant comments received before promulgating the Difficult to Compound List in a final rule. To date, FDA has not published a notice of proposed rulemaking to establish the Difficult to Compound List.

II. SUMMARY OF THE PETITION

In the Petition, you explain that implantable testosterone pellets are used to treat patients with a deficiency or absence of testosterone.[2] You state that testosterone pellets are surgically implanted and reside beneath the skin for several months. You note that Testopel is currently the only FDA-approved implantable testosterone pellet. Testosterone pellets have been nominated for inclusion on the Difficult to Compound List.[3]

You assert that testosterone pellets should not be included on the Difficult to Compound List for

[2] Petition at 4.
[3] Id.

a number of reasons.[4] First, you argue that implantable testosterone pellets do not present demonstrable difficulties for compounding under the factors that FDA considers for potential inclusion on the List.[5] Second, you state that the parties who nominated testosterone pellets for the Difficult to Compound List have a financial interest in precluding compounding of these products, and thus a conflict of interest exists.[6] Third, you assert that comments submitted by one of the nominators regarding the usage of testosterone pellets in the compounding industry are inaccurate and misleading.[7] Finally, the Petition argues that the interests of the public health require patients to have access to compounded testosterone pellets.

III. DISCUSSION

The Petition requests FDA to refrain from including implantable testosterone pellets on the Difficult to Compound List.[8] As discussed above, as part of the process of implementing the Difficult to Compound List under sections 503A(b)(3)(A), 503A(c)(1), and 503B(c), FDA has established a public docket (FDA-2017-N-2562) to permit interested parties to nominate additional drug products or categories of drug products for inclusion on the Difficult to Compound List, resubmit previous nominations with additional supporting information, or submit comments about newly or previously nominated products or categories of products. That public docket remains open and interested parties can continue to submit comments about newly or previously nominated products or categories of products.[9] Accordingly, your Petition is denied and you should instead direct your input regarding inclusion of implantable testosterone pellets on the Difficult to Compound List to that docket.

Additionally, as noted above, a drug product or category of drug products is not prohibited from being compounded under sections 503A or 503B unless and until FDA adds it to the Difficult to Compound List, or unless it is independently prohibited by another provision of law. We remind you that, to date, FDA has taken no action to include implantable testosterone pellets on the Difficult to Compound List. Should the Agency propose to do so, you will have the opportunity to raise the considerations in your Petition during the PCAC consultation and rulemaking process.

---

[4] Id. at 5.
[5] Id. at 3.
[6] Id. at 9.
[7] Id. at 9.
[8] Id. at 1.
[9] Note that the Endocrine Society has submitted information to the recently established docket for the Agency to consider in evaluating compounded testosterone products for inclusion on the Difficult to Compound List, FDA-2017-N-2562-0006.

IV. CONCLUSION

For the reasons described in this response, the Petition is denied.

Sincerely,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research