Kristen L. Gullo
Vice President, Development & Regulatory Affairs
US WorldMeds
4441 Springdale Rd.
Louisville, KY 40241

May 21, 2020

Re: Docket No. FDA-2019-P-6049

Dear Ms. Gullo:

This letter responds to your citizen petition received by the Food and Drug Administration (FDA or Agency) on December 23, 2019 (Petition). You request that FDA:

(1) Require any abbreviated new drug application (ANDA) referencing Apokyn (apomorphine hydrochloride) injection, seek approval of both the drug and device constituent parts of Apokyn;

(2) Establish a policy framework clarifying the circumstances, if any, under which the drug constituent part of a generic drug-device combination product can be approved in an ANDA that does not also seek approval of the device constituent part

(Petition at 4).

We interpret the second request to ask that FDA establish such a policy framework within the timeframe for final Agency action on a petition subject to section 505(q) of the Federal Food, Drug, and Cosmetic Act (FD&C Act). We have carefully considered the Petition and a comment submitted to the docket. For the reasons described below, we are denying the actions requested in your Petition. [1]

I. APOKYN

Currently, the only approved drug-device combination product containing apomorphine and intended for use in the advanced Parkinson's disease population is Apokyn (apomorphine hydrochloride) injection, new drug application (NDA) 021264, held by US WorldMeds LLC. FDA approved Apokyn on April 20, 2004, for the acute, intermittent treatment of hypomobility,

[1] US World Meds submitted a substantially similar citizen petition on July 1, 2019, Docket No. FDA-2019-P-3192 (July 2019 Petition). The Agency denied the July 2019 Petition on November 27, 2019 without comment on the substance of the actions requested.

"off" episodes ("end-of-dose wearing off" and unpredictable "on/off" episodes) associated with advanced Parkinson's disease. The Dosage Forms and Strengths section of Apokyn's approved labeling states: "APOKYN 30 mg/3 mL (10 mg/mL) containing apomorphine hydrochloride (as apomorphine hydrochloride hemihydrate), USP is supplied as a clear, colorless, sterile, solution in a 3 mL (30 mg) cartridge. The 3 mL (30 mg) glass cartridge for single-patient use is used with a manual reusable pen injector (APOKYN Pen)."[2]

II. APPLICABLE STATUTORY AND REGULATORY FRAMEWORK

A. ANDA Approval

The Drug Price Competition and Patent Term Restoration Act of 1984[3] (the Hatch-Waxman Amendments) amended the FD&C Act to add, among other things, section 505(j) (21 U.S.C. 355(j)), which established an abbreviated approval pathway for generic drugs. The Hatch-Waxman Amendments reflect Congress's efforts to balance the need to "make available more low cost generic drugs by establishing a generic drug approval procedure" with new incentives for drug development in the form of exclusivity and patent term extensions.[4]

To obtain approval, an ANDA applicant is not required to provide evidence to independently establish the safety and effectiveness of the proposed drug product. Instead, an ANDA relies on FDA's previous finding that the reference listed drug (RLD) is safe and effective.[5] To rely on this finding, an ANDA applicant must, among other things, provide sufficient information to show that its drug product is bioequivalent to the RLD.[6] An ANDA applicant generally must also demonstrate, among other things, that the proposed drug product has the same active ingredient(s), route of administration, dosage form, strength, and (with certain permissible differences) labeling as the RLD.[7]

FDA must approve an ANDA unless it finds that, among other things: (1) the ANDA applicant has not provided sufficient evidence of the foregoing; (2) the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of the drug are inadequate to assure and preserve its identity, strength, quality, and purity; (3) the inactive ingredients of the

[2] Drugs@FDA, Apokyn Approved Labeling, DOSAGE FORMS AND STRENGTH section, May 1,, 2020, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/021264s018lbl.pdf.

[3] Public Law 98-417.

[4] See House Report No. 98-857, part 1, at 14-15 (1984), reprinted in 1984 U.S.C.C.A.N. 2647 at 2647-2648.

[5] An RLD is "the listed [i.e., approved] drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its ANDA" (§ 314.3(b) (21 CFR 314.3(b)). RLDs are identified in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluation* (the Orange Book).

[6] See, e.g., section 505(j)(2)(A)(iv) of the FD&C Act (21 U.S.C.355(j)(2)(iv)) (requiring "information to show that the new drug is bioequivalent to the listed drug"); § 314.3(b) (defining reference listed drug); § 314.94(a)(7) (21 CFR 314.94(a)) (requiring, as part of ANDA content and format, information to show that the drug product is bioequivalent to the RLD); and § 314.127(a)(6)(i) (21 CFR 314.127 (a)(6)(i) (stating that FDA will refuse to approve an ANDA if information submitted is insufficient to show that the drug product is bioequivalent to the listed drug referred to in the ANDA).

[7] Section 505(j)(2)(A), (j)(2)(C), and (j)(4) of the FD&C Act; *see also* § 314.94(a).

proposed drug are unsafe for use under the conditions prescribed, recommended, or suggested in the proposed labeling; or (4) the composition of the drug is unsafe under such conditions because of the type or quantity of inactive ingredients included or the manner in which the inactive ingredients are included.[8]

B. Combination Products

As set forth in section 503(g) of the FD&C Act and 21 CFR part 3, a combination product is a product composed of two or more different types of medical products (i.e., a combination of a drug, device, and/or biological product with one another). The drugs, devices, and biological products included in combination products are referred to as "constituent parts" of the combination product.

C. Section 505(q) of the FD&C Act

Section 505(q) of the FD&C Act was added by section 914 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law 110-85, 121 Stat. 823) and was amended by the Food and Drug Administration Safety and Innovation Act (Public Law 112-144, 126 Stat. 993). Section 505(q) of the FD&C Act, as originally added by FDAAA, applies to certain citizen petitions and petitions for stay of Agency action that request that FDA take any form of action relating to a pending application submitted under section 505(b)(2) or (j) of the FD&C Act and governs the way these petitions are treated. Among other things, section 505(q)(1)(F) of the FD&C Act governs the time frame for final Agency action on a petition subject to section 505(q). Under this provision, FDA must take final Agency action on such a petition no later than 150 days after the date on which the petition is submitted.

III. DISCUSSION

A. ANDAs citing Apokyn as the Reference Listed Drug

The Petition requests that FDA "require that any ANDA referencing Apokyn seek approval of both the drug and device constituent parts of Apokyn."[9]

The Petition states that "when the device constituent part is included as part of the RLD and was approved under the NDA, an ANDA must include a corresponding device constituent part in the ANDA submission, and the required showing of sameness must take account of the device constituent part."[10] Additionally, according to the Petition, the Apokyn Pen is approved only for use with the Apokyn cartridge, and there are no other approved or cleared devices with technical specifications and/or intended uses consistent with the administration of apomorphine hydrochloride for its approved use.[11] Therefore, the Petition concludes that an ANDA

[8] Section 505(j)(4) of the FD&C Act; *see also* § 314.127 (21 CFR 314.127).

[9] Petition at 4.

[10] Petition at 11.

[11] Petition at 15.

referencing Apokyn must "include its own device constituent part," because the alternative—approving an ANDA for the cartridge only and "using a generic drug constituent part with the Apokyn Pen—would be improper[.]"[12]

The Petition asserts that not only would approving an ANDA for a drug constituent part to be used with the Apokyn Pen invite an unapproved use of the Apokyn Pen, but it cannot be presumed that individuals receiving the generic apomorphine hydrochloride cartridges will have access to the Apokyn Pen.[13] For example, the Petition notes that the "Apokyn Pen is dispensed by specialty pharmacies only in connection with an Apokyn prescription."[14] Therefore, the Petition states that if a patient were not previously prescribed Apokyn, and only receives the generic version of apomorphine hydrochloride, then the patient would not have access to the Apokyn Pen. Additionally, the Petition notes that even for patients who were previously prescribed Apokyn, there is a risk that the Apokyn Pen they previously received will require replacement, but "such patients will not be able to obtain a replacement Apokyn Pen if they no longer are prescribed Apokyn."[15]

The Petition contends that even if an ANDA applicant were able to seek approval of only the drug constituent part for use with the device constituent part of the RLD, such an ANDA applicant could not comply with its applicable current good manufacturing practices (cGMP) requirements.[16] Specifically, the Petition contends that such an ANDA applicant would not be able to comply with its design control obligations because the ANDA applicant would not have any relationship with the manufacturer of the RLD's device constituent part. Therefore, according to the Petition, the ANDA applicant "would be unable to ensure initial or continued compliance with its cGMP obligations with respect to the device constituent part[.]"[17] Moreover, the Petition contends that this lack of a relationship between the ANDA applicant and the manufacturer of the RLD's device constituent part will prevent the ANDA applicant from being able to ensure continued compatibility between its cartridges and the RLD's device constituent part in the future.[18]

The Petition also asserts that an ANDA applicant that seeks approval of only the drug constituent part of a drug-device combination product would not be able to comply with its post-market safety reporting obligations.[19]

Additionally, the Petition responds to a comment submitted to the docket for your previous petition, docket no. FDA-2019-P-3192 (July 2019 Petition). For the most part, these responses

[12] Petition at 15.

[13] Petition at 20-21.

[14] Petition at 20.

[15] Petition at 21.

[16] Petition at 16-17.

[17] Petition at 17.

[18] Petition at 19-20.

[19] Petition at 18-19.

to the prior comment reiterate the assertions outlined above, which mirror the assertions in the July 2019 Petition. In these responses, the Petition also asserts that it is not aware of any legal or regulatory authority for FDA to approve an ANDA for only the drug constituent part of a drug-device combination product RLD.[20] In addition, the Petition contends that the precedent cited by the commenter as support for approval of an ANDA for only the drug constituent part of Apokyn is not relevant because the precedent involved a device cleared in a 510(k).[21]

As described in section I.C of this response, section 505(q)(1)(F) of the FD&C Act requires FDA to take final Agency action on the Petition within 150 days of submission. Therefore, we must take action on the Petition at this time. For the reasons explained below, we deny without comment on the specific requests in your Petition regarding any specific ANDA referencing Apokyn as its RLD.

FDA has made no final determination on whether to approve or not approve any ANDA referencing Apokyn. In the case of ANDAs referencing Apokyn, FDA's consideration of one or more applications will necessarily inform our decisions on the nature of the data and information regarding the approvability of such applications. Therefore, we must determine whether it would be appropriate for us to take final Agency action on the approvability of a specific aspect of an ANDA before taking final action on the approvability of ANDAs as a whole. To make this determination, we believe it is appropriate to evaluate the statutory and regulatory provisions governing the content and review of ANDAs in connection with the statutory provision of section 505(q) of the FD&C Act governing the time frame for action on the Petition.

The FD&C Act and FDA regulations establish procedural protections for applicants in the context of application review. Section 505 of the FD&C Act and FDA's regulations in 21 CFR part 314 describe certain procedures by which the Agency reviews an ANDA, and notifies an applicant if it determines that an application is approved[22] or may not be approved,[23] or identifies the deficiencies in the application and the steps an applicant may take to respond to the deficiencies.[24] In addition, the statute and regulations describe a specific process through which an applicant whose application the Agency has found does not meet the requirements for approval may challenge the Agency's determination.[25] Under this process, the Agency will give the applicant notice of an opportunity for a hearing on whether the application is approvable, with a specific time frame and process if the applicant requests such a hearing.[26] These procedures ensure that applicants have an adequate opportunity to challenge a finding by the Agency that a product does not meet the requirements for approval.

[20] Petition at 22.

[21] Petition at 24-26.

[22] See § 314.105 (21 CFR 314.105).

[23] See section 505(c) and (j) of the FD&C Act; §§ 314.125 and 314.127 (21 CFR 314.125 and 314.127).

[24] See § 314.110 (21 CFR 314.110).

[25] See section 505(c)(1)(B) and (d) of the FD&C Act; § 314.200 (21 CFR 314.200).

[26] Id.

There is no evidence that in enacting section 505(q) of the FD&C Act, Congress intended to bypass the application review process or to lessen an ANDA applicant's procedural rights by requiring that the Agency make decisions that constitute final Agency action regarding the approvability of certain aspects of pending applications on a piecemeal basis outside of the process established under the FD&C Act and FDA regulations.[27] Therefore, we do not interpret section 505(q) of the FD&C Act to require that FDA render a final Agency decision within the statutory deadline on the approvability of a specific aspect of an ANDA when a final decision on the approvability of any such ANDA has not yet been made.[28] Accordingly, we are denying without comment your request that FDA require that any ANDA referencing Apokyn seek approval of both the drug and device constituent parts of Apokyn.

B. Policy Framework

The Petition requests that FDA establish a policy framework clarifying the circumstances, if any, under which a drug constituent part of a generic drug-device combination product can be approved in an ANDA that does not seek approval of the device constituent part. The Petition further requests that this framework be developed through a transparent public process.

The development of a policy framework clarifying such circumstances, if any, raises complex scientific and policy issues that FDA cannot resolve within the 150-day time frame set forth in section 505(q) of the FD&C Act. Therefore, we deny the request to develop such a policy framework at this time, without comment.

IV. CONCLUSION

For the reasons discussed above, the Petition is denied.

Sincerely,

Douglas C. Throckmorton -S

Digitally signed by Douglas C. Throckmorton -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300121270, cn=Douglas C. Throckmorton -S
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Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

[27] In other citizen petition responses, we have responded to requests related to general standards for approval (e.g., bioequivalence criteria for generic drug products) that may pertain to one or more pending drug applications without commenting on the approvability of any particular aspect of a specific pending application. We believe that this approach of describing our general policies or standards for approval of a drug application (beyond the descriptions provided in this response) would not be appropriate in this case because, as stated, our review of a given ANDA would inform our decisions regarding the sufficiency of the specific data and information needed for approval. We will continue to evaluate each citizen petition on a case-by-case basis on the appropriateness of responding to requests regarding any pending application.

[28] Under applicable statutory and regulatory provisions, we are generally prohibited from disclosing any determinations regarding the receipt or approvability of any pending ANDA before we have reached a final decision on whether to approve or not approve the ANDA. See, e.g., § 314.430 (21 CFR 314.430).