FDA U.S. FOOD & DRUG ADMINISTRATION

FEB 18 2020

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Re: Docket No. FDA-2019-P-0537

Dear Mr. Kulkarni:

This letter responds to your citizen petition received February 2, 2019 (Petition). In the Petition, you request that the Food and Drug Administration (FDA or Agency) "consistently ensure that the requirements to manufacture Methscopolamine Bromide USP are adhered to by all Active Pharmaceutical Ingredient (API) and finished product manufacturers of Methscopolamine Bromide tablets" (Petition at 1). Specifically, you express concern that not all manufacturers of methscopolamine bromide (with respect to both the API and the finished product) are "compliant with" the recommendations outlined in FDA's guidance for industry *Botanical Drug Development* (December 2016) (Petition at 2).[1] Accordingly, we interpret your Petition as a request that FDA: 1) require compliance with a guidance document, and 2) take specific enforcement action.

FDA has considered your Petition. For the reasons stated below, your Petition is denied.

I. BACKGROUND

Federal laws and regulations dictate the standards for the manufacture of drugs. Under the Federal Food, Drug, and Cosmetic Act (FD&C Act), a drug with a name that "is recognized in an official compendium" must comply with compendial identity standards, and the "determination as to the strength, quality, or purity" of the drug "shall be made in accordance with the tests or methods of assay set forth in such compendium . . . ," unless labeled to show all respects in which the drug differs from compendial standards.[2] Thus, where a monograph for the drug is included in a compendium such as the United States Pharmacopeia/National Formulary

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

[2] Section 501(b) of the FD&C Act (21 U.S.C. 351(b)); 21 CFR 299.5(c).

(USP/NF), a drug must meet the standards outlined in that monograph as described above.[3] In addition, drugs, including APIs, must be manufactured in compliance with current good manufacturing practices.[4]

In addition to the requirements outlined above, FDA provides recommendations for industry in the form of guidance documents to aid manufacturers in meeting current quality standards.[5] In general, these guidances do not establish legally enforceable rights or responsibilities.[6] Instead, they describe the Agency's current thinking on a topic, and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited.[7]

II. DISCUSSION

In your Petition, you cite FDA's guidance for industry *Botanical Drug Development* and request that "FDA consistently ensure that all Manufacturers are in full compliance with the outlined requirements in the guidance" (Petition at 2). In general, Agency guidances constitute recommendations to industry and cannot be viewed as "requirements" (21 CFR 10.115(d)). Therefore, your request that FDA *require* manufacturers to comply with the guidance is inconsistent with the parameters of the Agency's authority under Federal regulation.

In any case, with respect to methscopolamine bromide specifically, the considerations laid out in the *Botanical Drug Development* guidance generally do not apply. The guidance contemplates a unique class of products that require "regulatory policies that differ from those applied to nonbotanical drugs, such as synthetic, semi-synthetic, or otherwise highly purified or chemically modified drugs . . . ."[8] Highly purified substances are excluded from the scope of the guidance as outside the meaning of the term "botanical" as it is interpreted in the guidance. As the guidance explains, "[b]otanical drugs are generally heterogenous mixtures. As such, their chemical constituents often are not well defined; in some cases, their active constituents are not identified and their biological activities are not well characterized."[9]

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[3] Id. See also 21 CFR 299.5(c).

[4] FD&C Act 501(a)(2)(B); see also §§ 210 and 211 (21 CFR 210 and 211).

[5] See § 10.115 (21 CFR. 10.115); e.g., guidance for industry *Q1A(R2) Stability Testing of New Drug Substances and Products* (International Conference on Harmonisation (ICH)) (November 2003); guidance for industry *Q3A Impurities in New Drug Substances and Products* (ICH) (June 2008); guidance for industry *Q3B(R2) Impurities in New Drug Products* (ICH) (July 2006); and guidance for industry *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances* (ICH) (December 2000).

[6] § 10.115(d).

[7] § 10.115.

[8] Guidance for industry, *Botanical Drug Development*, at 1.

[9] Id. at 5.

Here, in contrast to the "chemical constituents [that] are not well defined" that the guidance contemplates, methscopolamine bromide is a highly purified, well-characterized substance included in a USP/NF monograph.[10] As discussed, Federal law requires that the standards set forth in that monograph dictate the determination of the drug's "strength, quality, or purity."[11] Furthermore, Federal regulations on current good manufacturing practices apply to the manufacture of methscopolamine bromide, with respect to both its API and the finished drug product.[12] Because methscopolamine bromide is well-characterized and highly purified, it is not appropriate to apply the unique considerations laid out in the *Botanical Drug Development* guidance.[13]

To the extent that your Petition is asking FDA to take an enforcement action, your request is denied. Requests for the Agency to initiate enforcement actions are not within the scope of FDA's citizen petition procedures (see 21 CFR 10.30(k)). Decisions with respect to initiating enforcement action are generally made by the Agency on a case-by-case basis and are within the discretion of the Agency.

III. CONCLUSION

For the reasons discussed above, your Petition is denied.

Sincerely,

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

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[10] See USP41-NF36 2S.

[11] Section 501(b) of the FD&C Act.

[12] See section 501(a)(1)(B) of the FD&C Act (stating that a drug shall be deemed to be adulterated if:

> the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of this Act as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess).

See also §§ 210 and 211.