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Compliance Policy for Certain Compounding of Oral Oxitriptan (5-HTP) Drug Products for Patients With Tetrahydrobiopterin (BH4) Deficiency

Immediately in Effect Guidance for Industry

FDA is issuing this guidance for immediate implementation in accordance with 21 CFR 10.115(g)(2). Comments may be submitted at any time for Agency consideration. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to https://www.regulations.gov. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

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U.S. Department of Health and Human Services
Food and Drug Administration
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Compounding

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Compliance Policy for Certain Compounding of Oral Oxitriptan (5-HTP) Drug Products for Patients With Tetrahydrobiopterin (BH4) Deficiency
Immediately in Effect Guidance for Industry[1]

This guidance represents the current thinking of the Food and Drug Administration (FDA, the Agency, or we) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance describes the Food and Drug Administration's (FDA, we, or the Agency) policy concerning the conditions under which the Agency does not generally intend to take regulatory action against a licensed pharmacist in a State-licensed pharmacy or Federal facility or a licensed physician using the bulk drug substance oxitriptan (also known as 5-hydroxytryptophan or 5-HTP) to compound oral drug products for patients with tetrahydrobiopterin (BH4) deficiency.[2,3] On February 19, 2019, FDA issued a final rule (84 FR 4696) ("final rule") that established the list of bulk drug substances that can be used to compound drug products under section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act), even though they are not the subject of an applicable United States Pharmacopoeia (USP) or National Formulary (NF) monograph or a component of an FDA approved drug product (503A Bulks List).[4] The final rule, codified at 21 CFR 216.23, placed six bulk drug substances on the 503A Bulks List (21 CFR 216.23(a)), and identified four others, including oxitriptan, that cannot be used to compound drug products under section 503A of the FD&C Act (21 CFR 216.23(b)). Additional bulk drug substances nominated by the public for inclusion on this list are currently under consideration and will be the subject of future rulemaking.

FDA developed this guidance in response to communications from pharmacists and caregivers regarding the use of oxitriptan to treat patients with BH4 deficiency following issuance of the final rule. According to those communications and other information available to the Agency,

[1] This guidance has been prepared by multiple offices in the Center for Drug Evaluation and Research, in consultation with the Office of Regulatory Affairs at the Food and Drug Administration.

[2] Tetrahydrobiopterin (BH4) deficiency is also known as: primary tetrahydrobiopterin deficiency, atypical phenylketonuria (PKU), GTP cyclohydrolase (GTPCH) deficiency, 6-pyruvoyl-tetrahydropterin synthase (6-PTPS) deficiency, and dihydropteridine reductase (DHPR) deficiency.

[3] This guidance does not apply to drugs compounded for use in animals.

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[4] See section 503A(b)(1)(A) of the FD&C Act [21 U.S.C. 353a(b)(1)(A)].

oxitriptan is the standard of care for the treatment of BH4 deficiency, which is caused by several different rare enzyme defects that result from gene mutations. Thus, this guidance addresses the conditions under which FDA does not intend to take regulatory action against a licensed pharmacist in a State-licensed pharmacy or Federal facility or a licensed physician for the use of bulk oxitriptan to compound oral drug products for the treatment of identified individual patients with BH4 deficiency.

We are issuing this guidance consistent with our good guidance practices (GGP) regulation (21 CFR 10.115). This guidance is immediately effective because FDA has determined that prior public participation is not feasible or appropriate due to the public health need for patients with BH4 deficiency to access compounded oxitriptan oral drug products (21 CFR 10.115(g)(2)).

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

A. Compounding From Bulk Drug Substances Under Section 503A of the FD&C Act

Section 503A of the FD&C Act describes the conditions that must be satisfied for human drug products compounded by a licensed pharmacist in a State-licensed pharmacy or Federal facility, or by a licensed physician, to qualify for exemptions from certain requirements of the FD&C Act related to FDA approval prior to marketing, current good manufacturing practice requirements, and labeling with adequate directions for use (sections 505, 501(a)(2)(B), and 502(f)(1)) [21 U.S.C. 355, 351(a)(2)(B), and 352(f)(1)].

One of the conditions that must be met for a compounded drug product to qualify for these exemptions is that a licensed pharmacist or licensed physician compounds the drug product using bulk drug substances that (1) comply with the standards of an applicable USP or NF monograph, if a monograph exists, and the USP chapter on pharmacy compounding; (2) if such a monograph does not exist, are drug substances that are components of drugs approved by FDA; or (3) if such a monograph does not exist and the drug substance is not a component of a drug approved by FDA, appear on a list of bulk drug substances developed by FDA through regulation.[5]

B. History of Rulemaking Involving Oxitriptan Under Section 503A of the FD&C Act

Because oxitriptan is neither the subject of an applicable USP or NF monograph nor a component of an FDA-approved drug, use of bulk oxitriptan to compound a drug product under section 503A

[5] See section 503A(b)(1)(A)(i) of the FD&C Act [21 U.S.C. 353a(b)(1)(A)(i)].

of the FD&C Act requires that oxitriptan be placed on the 503A Bulks List.[6] Oxitriptan was nominated and evaluated for inclusion on the 503A Bulks List for use in the treatment of insomnia and depression, not BH4 deficiency. FDA convened an advisory committee to seek its advice about whether to include a number of bulk drug substances, including oxitriptan, on the 503A Bulks List.[7] Based on its review and applying the criteria identified in the Federal Register (79 FR 37747), FDA proposed to the Pharmacy Compounding Advisory Committee (PCAC) that oxitriptan not be included on the 503A Bulks List.[8] At the PCAC meeting on June 17, 2015, the committee voted to recommend to FDA not to include oxitriptan on the 503A Bulks List.[9] Taking into consideration the PCAC's advice, and after consultation with USP, FDA determined that, on balance, the criteria that it considers when conducting evaluations for the 503A Bulks List weighed against inclusion of oxitriptan on the 503A Bulks List.

On December 16, 2016, FDA published a proposed rule (81 FR 91071) to not include oxitriptan on the 503A Bulks List and provided for a 90-day period to allow for comments to be submitted for FDA's consideration in finalizing the rule. In the preamble to the December 16, 2016 proposed rule, FDA stated that, on balance, the criteria weighed against the inclusion of oxitriptan on the 503A Bulks List. In particular, the Agency's evaluation of oxitriptan revealed serious safety concerns related to the use of oxitriptan for depression, a potentially life-threatening condition, in lieu of, or causing a delay in, treatment with an available approved product and the lack of adequate warnings that would inform patients and prescribers of the risks associated with taking a compounded oxitriptan drug product. Such risks include, for example, the concomitant use of oxitriptan with antidepressant drugs, which could result in serotonin syndrome, a serious and life-threatening drug interaction (81 FR 91078).

The Agency received comments to the 2016 proposed rule, some of which related to oxitriptan. None of the comments identified treatment of BH4 deficiency as a proposed use of compounded oxitriptan drug products. On February 19, 2019, FDA issued a final rule in the *Federal Register* that identified four bulk drug substances, including oxitriptan, that FDA considered and did not include on the 503A Bulks List (84 FR 4696). The rule became effective on March 21, 2019.

Following publication of the February 19, 2019 final rule, several pharmacists and caregivers contacted FDA to advise the Agency that oxitriptan is an essential and standard treatment for patients with BH4 deficiency, a rare genetic disorder characterized by deficiency of the cofactor BH4 which leads to deficiency of the neurotransmitter serotonin (and its precursor 5-hydroxy-tryptophan) within the central nervous system. As noted above, FDA did not consider BH4 deficiency during its initial review of this substance for the 503A Bulks List.

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[6] See section 503A(c)(2) of the FD&C Act [21 U.S.C. 353a(c)(2)].
[7] See section 503A(c)(1) of the FD&C Act [21 U.S.C. 353a(c)(1)].
[8] See https://wayback.archive-it.org/7993/20170405230419/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/UCM449535.pdf.
[9] See https://wayback.archive-it.org/7993/20170404155231/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/UCM458513.pdf.

III. POLICY

In light of the information brought to the Agency's attention about the standard of care for treating patients with BH4 deficiency, FDA does not intend to take action for violations of sections 501(a)(2)(B), 502(f)(1), or 505 of the FD&C Act against a licensed pharmacist in a State-licensed pharmacy or Federal facility or a licensed physician who compounds with the bulk drug substance oxitriptan, provided the following conditions are met:

- The compounded oxitriptan-containing drug product is intended only for oral administration;
- The compounder provides the oxitriptan-containing oral drug product solely for identified individual patients with BH4 deficiency, after receiving a valid prescription for such identified individual patient indicating the diagnosis;[10]
- The compounder maintains records documenting that the drug product was compounded for a patient with BH4 deficiency; and
- All other conditions of section 503A and other applicable requirements of the FD&C Act and FDA regulations are met.

FDA intends to take regulatory action against entities that compound drug products using bulk oxitriptan for non-oral routes of administration or to treat conditions other than BH4 deficiency. FDA intends to evaluate compliance during inspections by reviewing information (e.g., documentation on prescriptions) stating whether the drug product was compounded for an identified individual patient with BH4 deficiency.

In light of the new information regarding use of oral oxitriptan to treat BH4 deficiency, FDA is considering whether to reevaluate the exclusion of oxitriptan from the 503A Bulks List.

[10] If the prescription does not specify that the identified patient has been diagnosed with BH4 deficiency, the compounder should contact the prescriber to obtain and document this information.