Evaluation of the U.S. Food and Drug Administration's 2020 Proposed 503B Bulk Drug Substances

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Abstract

This is an evaluation of the U.S Food and Drug Administration (FDA)'s July 2020 proposal for inclusion of 4 bulk drug substances to the 503B Bulks List.

The Drug Quality and Security Act, which was enacted by Congress in 2013, added section 503B to the Federal Food, Drug, and Cosmetic Act. Section 503B outlines the conditions under which outsourcing facilities, a new category of compounders, may produce a compounded drug product starting from a bulk drug substance; the substance must appear on the 503B Bulks List or the FDA's drug shortage list. Development of the 503B Bulks List has been underway at the FDA. In July of 2020, proposals for inclusion and exclusion of certain drug substances on the 503B Bulks List were published in the Federal Register. The drug substances proposed for inclusion are diphenylcyclopropenone (DPCP), glycolic acid, squaric acid dibutyl ester (SADBE), and trichloroacetic acid (TCA). Nineteen other drug substances were proposed to not be included on the list. Referenced evidence that was provided to the public in the July 2020 Federal Register Notice is highlighted to illustrate the decision-making process involved in the review of the proposals. The FDA's general progress with reviewing nominated bulk drug substances is also discussed with the goal of educating the public on the 503B nomination review process.

Background

What is 503B Human Drug Compounding?

- Compounding is, generally, the practice of combining, mixing, or altering drug ingredients to fit the specific need of a patient by a licensed pharmacist, physician or a person under their supervision.
- Drug products produced through compounding are not FDA approved; the FDA has developed a program directed at protecting patients from harm while providing access to those who need a compounded drug.
- Section 503B of the Federal Food, Drug, and Cosmetic (FD&C) Act (21 U.S.C. 353b) allows for, under certain conditions, FDA registered outsourcing facilities to manufacture and distribute compounded drugs with or without an individual patient prescription.

What does section 503B allow for?

- If the conditions of that section are met, drugs produced by outsourcing facilities are exempt from the following sections of the FD&C Act:
  - o Section 505 relating to the approval of drugs under new drug applications or abbreviated new drug applications
  - o Section 502(f)(1) which concerns the labeling of drugs with adequate directions for use
  - o Section 582 regarding drug supply chain security requirements
- 503B outsourcing facilities are not exempt from adhering to the FD&C Act Section 501(a)(2)(B) relating to current good manufacturing practice.

What bulk drug substances can a 503B outsourcing facility compound under section 503B?

- Those used to compound a drug on FDA's drug shortage list.
- Those appearing on the 503B Bulks List which identifies drug substances where there is a clinical need.

A Federal Register notice (FRN) published in July 2020 (85 Fed. Reg. 46126) proposed four drug substances for inclusion and 19 bulk substances not for inclusion on the 503B Bulks List.

Evaluation Methods

Document Evaluation: To understand how the evaluation of 503B bulk substances was conducted, all public FDA documents were reviewed. This includes Federal Register notices, Clinical Need Guidance, Pharmacy Compounding Advisory Committee Meetings materials, Nominator Submissions and the FD&C Act. Regulations.gov docket was also consulted.

Nominated 503B Substance Evaluation: Each substance is nominated for inclusion on the 503B Bulks List. The nominator identifies drug products to be compounded from the substance for specific conditions. Each nomination is evaluated on a case-by-case basis. According to the Clinical Need Guidance, two questions that are asked to evaluate substances that are components of FDA-approved drugs are:

> "(1) Is there a basis to conclude, for each FDA-approved product that includes the nominated bulk drug substance, that:
> (a) An attribute of the FDA- approved drug product makes it medically unsuitable to treat certain patients for a condition that FDA has identified for evaluation
> (b) the drug product proposed to be compounded is intended to address that attribute?

> (2) Is there a basis to conclude that the drug product proposed to be compounded must be produced from a bulk drug substance rather than from an FDA-approved drug product?"

If the answer to either question was no, then the FDA would generally not include the substance. Because of this, 19 substances included in the federal register were proposed not for inclusion for not reaching this threshold. The 19 substances proposed to not be included on the 503B Bulks List were; diazepam, dobutamine HCl, dopamine HCl, edetate calcium disodium, folic acid, glycopyrrolate, hydroxyzine HCl, ketorolac tromethamine, labetalol HCl, mannitol, metoclopramide HCl, moxifloxacin HCl, nalbuphine HCl, polidocanol, potassium acetate, procainamide HCl, sodium nitroprusside, sodium thiosulfate, and verapamil HCl. FDA did not need to answer these questions for the four nominated substances proposed for inclusions because they are not components of FDA-approved drugs. Instead, these four substances proceeded directly to the second part of the clinical need analysis, in which the following questions were asked (see Fig. 1).

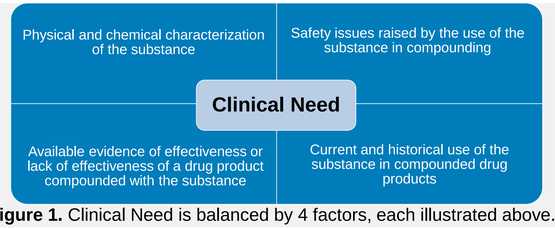

Figure 1. Clinical Need is balanced by 4 factors, each illustrated above.

The four substances that were evaluated for clinical need, based on the four factors listed above, and then proposed for inclusions on the 503B Bulks List for topical dermal use included: diphenylcyclopropenone (DPCP), glycolic acid, squaric acid dibutyl ester (SADBE), and trichloroacetic acid (TCA). In the results and discussion, we will review FDA's consideration of each factor in its evaluation of the clinical need for each substance.

Results and Discussion

FDA evaluated four substances to evaluate whether there is a clinical need for their use in compounding by balancing four factors: physical and chemical characterization, safety issues raised by use of the bulk in compounding, evidence or lack of evidence of, effectiveness, and current and historical use in compounding: DPCP (see Figure 2), glycolic acid (see Figure 3), SADBE (see Figure 4), and TCA (see Figure 5). The proposals, as illustrated below, were described in the July 2020 FRN. FDA balanced the four factors listed above and found the factors weighed in favor of proposing to add the substances to the 503B Bulks List for topical dermal use only. In practice these substances would traditionally be used after FDA approved drug products failed to provide a complete benefit or in addition to traditional therapy. This allows for substances to be made to fit the specific need of the patient.

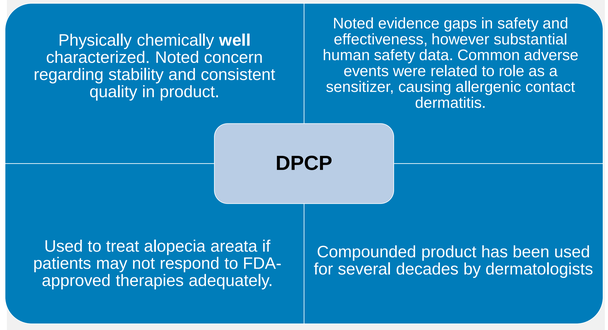

Figure 2. FDA proposed diphenylcyclopropenone be added to the 503B Bulks List for topical dermal use at variable concentrations

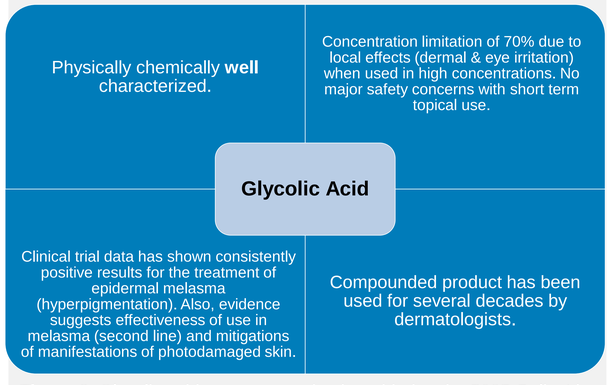

Figure 3. Glycolic acid was proposed to be added to the 503B Bulks List for topical dermal use in concentrations up to 70 percent. This concentration limitation is due to the safety issues noted and very limited data and evidence regarding use of higher concentrations.

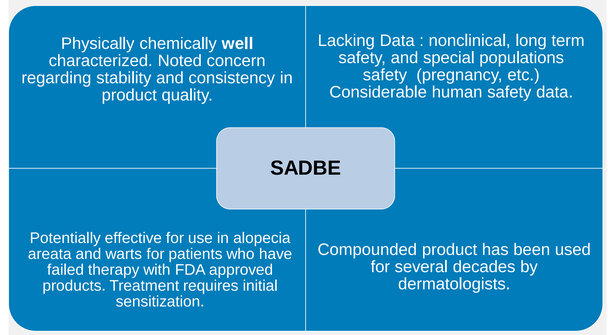

Figure 4. Squaric Acid Dibutyl Ester was proposed to be added to the 503B Bulks List for topical dermal use only.

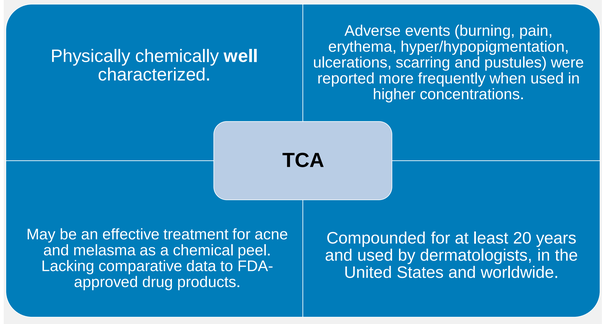

Figure 5. FDA proposed Trichloroacetic Acid be added to the 503B Bulks List for topical dermal use at variable concentrations

Conclusion

Review of the July 2020 FRN illustrated FDA's general decision-making process when evaluating clinical need for substances proposed for compounding by outsourcing facilities. FDA proposed to add to the 503B Bulks List bulk drug substances DCPC, glycolic acid, SADBE and TCA. FDA has also preliminarily concluded that there is no clinical need for 19 substances and proposed to not include them on the list. FDA still has to finalize the determination before the substance are/are not added to the 503B Bulks List. 503B Bulk List evaluation remains underway for additional publicly nominated substances.

Acknowledgement

This project was supported in part by an appointment to the Research Participation Program at the Office of New Drugs/Center for Drug Evaluation and Research, U.S. Food and Drug Administration, administered by the Oak Ridge Institute for Science and Education through an interagency agreement between the U.S. Department of Energy and FDA.