BULK DRUG SUBSTANCES AND FDA EVALUATION

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Purpose

Provide with a general understanding of the efforts to develop the 503B Bulks List including the basic regulatory framework and the clinical need evaluation.

Outline

- Knowledge Check - Question
- 503B Regulatory Framework
- 503B Bulks List Development
  - Status of list (current entries on and off, FRN process and history)
- Clinical Need Evaluation
  - FDA guidance
  - Challenges to establishing clinical need
    - Historical use - Requirement to submit product reports
- Knowledge Check - Answer
- Questions and Answers

Knowledge Check

The nomination proposes compounding with a bulk drug substance that is not FDA-approved. Which part of the evaluation will be completed under FDA's clinical need evaluation guidance?

- A. Part 3
- B. Part 2
- C. Part 1
- D. Parts 1 and 2

Section 503B - The Basics

Exemptions under the FD&C Act

- New drug approval requirements (section 505),
- Labeling with adequate directions for use (section 502(f)(1)), and
- Drug supply chain security requirements (section 582).

CGMP requirements

- Outsourcing facilities (OF) remain subject to CGMP requirements

Section 503B - The Basics

Outsourcing facilities may not compound bulk drug substance (BDS) unless:

- BDS appears on a list (503B Bulks List), or
- Drug product appears on the FDA's drug shortage list

Requires a valid certificate of analysis for BDS

Must be manufactured by a registered establishment

Must comply with United States Pharmacopeia or National Formulary, if applicable

Bulk Drug Substances

- Under Sections 503A and 503B, bulk drug substance as means the same as active pharmaceutical ingredient (API).
- API is defined as “any substance that is intended for incorporation into a finished drug product and is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body.”
- API “does not include intermediates used in the synthesis of the substance.”

Clinical Need Evaluation and the 503B Bulks List

- To establish a list of bulk drug substances for which there is a clinical need, FDA must:
  - Publish a notice in the Federal Register proposing bulk drug substances to be included on the list, and its rationale for the proposal;
  - Provide a period of not less than 60 calendar days for comment on the notice; and
  - Publish a notice in the Federal Register designating bulk drug substances for inclusion on the list

503B Bulks List Development

2013

- **Bulk Drug Substances That May Be Used To Compound Drug Products in Accordance With Section 503B of the Federal Food, Drug, and Cosmetic Act, Concerning Outsourcing Facilities; Request for Nominations Docket No. FDA-2013-N-1524**

2014

- **Bulk Drug Substances That May Be Used To Compound Drug Products in Accordance With Section 503B of the Federal Food, Drug, and Cosmetic Act, Concerning Outsourcing Facilities; Revised Request for Nominations; Docket No. FDA-2013-N-1524**

2015

- **Bulk Drug Substances That Can Be Used To Compound Drug Products in Accordance With Section 503B of the Federal Food, Drug, and Cosmetic Act; Establishment of a Public 10/27/15; Docket No. FDA-2015-N-3469**

Information to Support Bulks List Nominations

- FDA requested the following information about the nominated bulk drug substance and the drug product(s) that will be compounded using such substance:

Column A—What information is requested?	Column B—Put data specific to the nominated substance
What is the name of the nominated ingredient?	Provide the ingredient name.
Is the ingredient an active ingredient that meets the definition of "bulk drug substance" in § 207.3(a)(4)?	Provide an explanation for why it is considered an active ingredient when it is used in specific compounded drug products, and provide citations to specific sources that describe its active properties.
What is the chemical name of the substance?	Chemical name.
What is the common name of the substance?	Common name.
Does the substance have a UNII code?	UNII code.
What is the chemical grade of the substance?	Provide the chemical grade.
What is the strength, quality, stability, and purity of the ingredient?	Provide the strength, quality, stability, and purity information and attach a certificate of analysis.
How is the ingredient supplied?	Describe how the ingredient is supplied (e.g., powder, liquid).
Is the substance recognized in foreign pharmacopeias or registered in other countries?	List the foreign pharmacopeias or other countries in which it is registered.
Has information been submitted about the substance to the USP for consideration of monograph development?	Put yes, no, or unknown. If yes, state the status of the monograph, if known.

Information to Support Bulks List Nominations

Column A—What information is requested?	Column B—Put data specific to the nominated substance
What medical condition(s) is the drug product compounded with the bulk drug substances intended to treat?	Describe the medical condition(s) that the drug product compounded with the bulk drug substances is intended to treat.
Are there other drug products approved by FDA to treat the same medical condition?	List the other approved treatments.
If there are FDA-approved drug products that address the same medical condition, why is there a clinical need for a compounded drug product?	Provide a justification for clinical need, including an estimate of the size of the population that would need the compounded drug.
Are there safety and efficacy data on compounded drugs using the nominated substance?	Provide a bibliography of safety and efficacy data for the drug compounded using the nominated substance, if available, including any relevant peer-reviewed medical literature.
If there is an FDA-approved drug product that includes the bulk drug substance nominated, is it necessary to compound a drug product from the bulk drug substance rather than from the FDA-approved drug product?	Provide an explanation of why it is necessary to compound from the bulk drug substance.
What dosage form(s) will be compounded using the bulk drug substance?	State the dosage form(s).
What strength(s) will be compounded from the nominated substance?	List the strength(s) of the drug product(s) that will be compounded from the nominated substance, or a range of strengths, if known.
What are the anticipated route(s) of administration of the compounded drug product(s)?	List the route(s) of administration of the compounded drug product(s).
Has the bulk drug substance been used previously to compound drug product(s)?	Describe previous uses of the bulk drug substance in compounding.
Is there any other relevant information?	Provide any other information you would like FDA to consider in evaluating the nomination.

503B Bulks List Development

Interim Policy on Compounding Using Bulk Drug Substances Under Section 503B

- 503B Category 1 –Substances Nominated for the Bulks List Currently Under Evaluation
- 503B Category 2 –Substances Nominated for the Bulks List That Raise Significant Safety Risks
- 503B Category 3 –Substances Nominated for the Bulks List Without Adequate Support

Interim Bulks List – Last Updated July 30, 2020

503B Bulk Drug Substance (BDS) Nominations

503B Nominations with Adequate Support for FDA to Evaluate	Unique Bulk Drug Substance Nominated	Total Nominations
Component of FDA-Approved and Marketed Product(s)	261	591
Component of FDA-Approved Product(s) but Discontinued	19	42
Not a Component of FDA-Approved Product(s) (Marketed or Discontinued)	72	141
TOTAL	352	774

Clinical Need Evaluation

Final guidance published March 2019: *Evaluation of Bulk Drug Substances Nominated for Use in Compounding Under Section 503B*

- Clarifies how FDA interprets "bulk drug substances for which there is a clinical need" and provides related policy.
- The 503B Bulks List may include a bulk drug substance if:
  - There is a **clinical need** for an outsourcing facility to compound the **drug product**, and
  - The **drug product** must be compounded using **the bulk drug substance**.

Identifying Bulk Drug Substances for Which There is a Clinical Need: Two-Part Analysis

Part I – Applies to:	Part II – Applies to:
Bulk drug substances that are components of FDA-approved drug products	Bulk drug substances that are components of FDA-approved products for which FDA did not make a finding against clinical need under Part I
	Bulk drug substances that are not components of FDA-approved drug products

Identifying Bulk Drug Substances for Which There is a Clinical Need

Part I Analysis (bulks that are components of approved drugs)

a) Is there a basis to conclude, for each FDA-approved product that includes the nominated bulk drug substance, that

i. an attribute of the FDA-approved drug product makes it medically unsuitable to treat certain patients for the condition that FDA has identified for evaluation, and

ii. the drug product proposed to be compounded is intended to address that attribute?

Identifying Bulk Drug Substances for Which There is a Clinical Need

Part I Analysis (bulks that are components of approved drugs)

b) 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?

Identifying Bulk Drug Substances for Which There is a Clinical Need

Part II Analysis – Balancing Test

- The physical and chemical characterization of the substance;
- Any safety issues raised by the use of the substance in compounding;
- The available evidence of effectiveness or lack of effectiveness of a drug product compounded with the substance, if any such evidence exists; and
- Current and historical use of the substance in compounded drug products, including information about the medical condition(s) that the substance has been used to treat and any references in peer-reviewed medical literature

List of Bulk Drug Substances for Which There is a Clinical Need Under Section 503B of the FD&C Act

Aug 2018

- FDA proposes not to include 3 bulk drug substances.

March 2019

- FDA identified 2 bulk drug substances that FDA is **not including** on the list at this time as FDA does not find clinical need.

List of Bulk Drug Substances for Which There is a Clinical Need Under Section 503B of the FD&C Act

Sept 2019

- FDA proposes not to include 9 bulk drug substances.

July 2020

- FDA proposes to include 4 bulk drug substances.
- FDA proposes not to include 19 bulk drug substances.
- Comments due by September 29, 2020.

July 2020 Federal Register Notice Regarding 23 Bulk Drug Substances and 503B List

- Along with the proposed evaluation of 23 bulk drug substances, FDA is soliciting comment on two options for listing the four bulk drug substances we are proposing to include on the 503B Bulks List; either:
  - (1) To allow compounding of drug products containing only the listed bulk drug substance and no other active ingredients; or
  - (2) To allow compounding of drug products that contain the listed bulk drug substance without limits on compounding a drug product that contains other active ingredients.

Challenges to establishing clinical need

- Lack of clarity in nominations about the products proposed to be compounded using nominated BDS
  - For example, some nominations specify a number of routes and dosage forms, ranges of strengths, and lists of conditions the drug may be used to treat, rather than delineating each for specific compounded products.
- Some literature references do not provide support for compounding the proposed product
  - For example, nominations do not include references supporting each of the nominated conditions

Challenges to establishing clinical need

- Clinical need for a compounded product unclear. For example:
  - Rely on “boilerplate” or general explanation of clinical need for compounding that is not specific to a particular product
  - Fail to identify a population who cannot be treated with the approved drug product or why the approved drug product is not suitable for a particular patient population
  - Provide little to no information on how common treatment conditions are that would need a compounded drug product, for example, people allergic to an ingredient
  - Plan to make products that are similar to an approved product without adequate justification

Challenges to establishing clinical need

- Clinical need for a compounded product unclear. For example:
  - List multiple fixed dose combination products but do not provide a clinical need for combining them together when approved products are available
  - Fail to acknowledge the FDA-approved product and why the formulation is not medically suitable for certain patients
  - Fail to identify an attribute of the approved product(s) that the proposed compounded drug product is intended to address

Clinical Need Evaluation - Historical and Current Use

- Nominations do not always reflect current outsourcing facility data reported to FDA
- Discrepancies between product nomination and actual product reported by outsourcing facilities
- Lack of clarity in product produced by OFs (e.g., concentration units)
- Reporting is retrospective and may not reflect current production activities
- Use caution when duplicating reports or overwriting submissions
- Use On-line Searchable Database for Products Reported by Outsourcing Facilities to check what you have submitted
- Quantities produced should not be zero

Conclusion

- Section 503B established the statutory framework for the 503B Bulks List
- FDA guidances facilitate the implementation of the Section 503B including the bulks nomination and evaluation process.
- The 503B Bulks List Development is ongoing and requires FDA to evaluate, propose, and finalize bulk drug substances for the Bulks List.
- The clinical need evaluation is the underpinning for FDA's determination of what is considered for the Bulks List.
- Accurate and complete reporting of outsourcing facility product reporting data help to understand current and historical use.

Knowledge Assessment

- The nominated drug product proposes compounding with a bulk drug substance that is not FDA-approved. Which part of the evaluation will be completed under FDA's evaluation guidance?
- A. Part 3
- B. Part 2
- C. Part 1
- D. Parts 1 and 2


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