# Center of Excellence Development of 503B Bulks List

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

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# 503B Bulks List: Statutory Framework

- Section 503B condition: the drug is compounded in an outsourcing facility that does not compound using bulk drug substances unless --
  - the bulk drug substance appears on **a list** established by the Secretary **identifying bulk drug substances for which there is a clinical need**, or
  - the drug compounded from such bulk drug substance appears on the drug shortage list in effect under section 506E at the time of compounding, distribution, and dispensing

# 503B Bulks List: Statutory Framework

- 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, including the rationale for such 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

# Request for Nominations

- Request for nominations of bulk drug substances for 503B Bulks List through several Federal Register Notices (FRN):
  - Original docket opened 12/4/13
    - Docket No. FDA-2013-N-1524
  - Revised request published 7/2/14, closed 9/30/14
    - Docket No. FDA-2013-N-1524
  - Established docket 10/27/15, which remains open
    - Docket No. FDA-2015-N-3469
- FRN describes the information about each nominated bulk drug substance and the drug product(s) to be compounded using such substance that FDA needs to conduct an evaluation for clinical need

# Request for Nominations

| 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. |
| 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. |

# Request for Nominations

- Eligibility for Consideration for the 503B Bulks List
  - Bulk Drug Substance
    - Means the same as "active pharmaceutical ingredient" as defined in 21 CFR 207.1
      - *Active pharmaceutical ingredient* means 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, but the term does not include intermediates used in the synthesis of the substance
  - Cannot be subject to approval in a biologics license application (see e.g., Purple Book)
  - Cannot be a substance that is on the list of drugs that have been withdrawn or removed from the market for safety or efficacy reasons ("Withdrawn or Removed List") (21 CFR 216.24)
  - At this time, FDA does not consider drugs that appear on Schedule 1 of the Controlled Substances Act (21 CFR 1308.11)
  - Cannot be a finished drug product (does not meet the definition of a bulk drug substance in 21 CFR 207.1)

# Request for Nominations

- To fully evaluate a bulk drug substance, FDA needs the following information about the nominated bulk drug substance and the drug product(s) that will be compounded using such substance:
- Active Ingredients
  - Confirmation that the nominated substance is a bulk drug substance
  - General background on the Bulk Drug Substance
- Clinical Need to Compound
- Information on the Drug Product That Will Be Compounded With the Bulk Drug Substance

# Request for Nominations

- General background on the Bulk Drug Substance
  - Ingredient name
  - Chemical name
  - Common name(s)
  - Identifying codes, as available
    - Unique Ingredient Identifiers (UNII) code
  - Chemical grade of the ingredient
  - Description of the strength, quality, stability, and purity of the ingredient
    - Copy of a certificate of analysis that is representative of the characteristics of the ingredient
  - How the bulk is supplied (e.g., powder, liquid)
  - Information about whether information has been submitted to the United States Pharmacopeia for consideration of monograph development
  - Information about recognition in foreign pharmacopeias and status of registration in other countries, e.g.:
    - European Pharmacopeia
    - Japanese Pharmacopeia

# Request for Nominations

- Information on the drug product that will be compounded with the bulk drug substance
  - Strength of the proposed compounded drug product
  - Dosage form
  - Route of administration
  - Information about the previous use of the compounded drug product

# Request for Nominations

- Information about clinical need
  - A statement describing the medical condition(s) that the drug product to be compounded with the nominated bulk drug substances is intended to treat;
  - A list of FDA-approved products, if any, that address the same medical condition;
  - If there are FDA-approved drug products that address the same medical condition, an explanation of why a compounded drug product is necessary;
  - If the approved drug product is not suitable for a particular patient population, an estimate of the size of the population that would need the compounded product
    - Should include citations to the literature regarding the incidence of the condition, if it exists
  - A bibliography of safety and efficacy data for the drug product compounded using the bulk drug substance, if available; and
  - If there is an FDA-approved drug product that includes the bulk drug substance nominated, an explanation of why the drug product proposed to be compounded must be compounded from bulk rather than with the FDA-approved drug product

# Guidance: Interim Policy

- Final guidance published January 2017: *Interim Policy on Compounding Using Bulk Drug Substances Under Section 503B of the Federal Food, Drug, and Cosmetic Act*
- Guidance describes interim regulatory policy concerning compounding by outsourcing facilities using bulk drug substances while the 503B Bulks List is under development

# Guidance: Evaluation of Bulk Drug Substances

- Final guidance published March 2019: *Evaluation of Bulk Drug Substances Nominated for Use in Compounding Under Section 503B of the Federal Food, Drug, and Cosmetic Act*
- Guidance states that FDA interprets section 503B to mean that the 503B Bulks List may include a bulk drug substance if:
  - There is a clinical need for an outsourcing facility to compound a drug product, and
  - The drug product must be compounded using the bulk drug substance

# Clinical Need to Compound

- General or “boilerplate” explanations of clinical need generally will not be considered sufficient to provide adequate support for a nomination of a bulk drug substance
  - E.g., broad statements that a compounded drug product with an attribute that differs from the FDA-approved drug is necessary for certain patients, without sufficient evidence that the attribute makes the FDA-approved drug medically unsuitable for specific patients for the condition that has been identified for evaluation
- FDA may not identify a clinical need to compound from a bulk drug substance under section 503B where:
  - There are only minor changes in dosage form compared to an FDA-approved drug
    - E.g., tablet to capsule
  - The proposed product consists of a combination of multiple active ingredients to allow for administration of fewer products
  - A drug product is proposed to be compounded in a lower concentration than an FDA-approved product
- FDA does not consider supply issues such as backorders, or cost to be within the definition of "clinical need" under section 503B
- Compounding a ready-to-use product from a bulk drug substance to seek improved efficiency for prescribers or healthcare providers, or to address the possibility that the approved drug might be mishandled by a medical professional, would not constitute clinical need to compound with a bulk drug substance under section 503B.

# Request for Nominations

- Public docket number FDA-2015-N-3469
  - Submit new nominations
  - Submit comments either in support of or in opposition of other nominations
  - Request withdrawal of a nomination
  - Describes information needed by FDA to meaningfully evaluate nominations

# 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

# 503B Bulk Drug Substance Evaluations (2018-2022)

| Decision or Proposal to Include | Decision or Proposal Not to Include | | |
|---|---|---|---|
| • **DPCP for topical use only (F)**<br>• **Glycolic acid for topical use only in concentrations up to 70 percent (F)**<br>• **SADBE for topical use only (F)**<br>• **TCA for topical use only (F)**<br>• Quinacrine HCl for oral use only (P) | • **Diazepam (F)**<br>• **Dipyridamole (F)**<br>• **Dobutamine HCl (F)**<br>• **Dopamine HCl (F)**<br>• **Edetate calcium disodium (F)**<br>• **Folic acid (F)**<br>• **Glycopyrrolate (F)**<br>• **Nicardipine HCl (F)**<br>• **Sodium thiosulfate (F), except for topical administration**<br>• **Vasopressin (F)**<br>• Bromfenac sodium (P)<br>• Bumetanide (P)<br>• Ephedrine sulfate (P)<br>• Famotidine (P) | • Hydralazine HCl (P)<br>• Hydroxychloroquine sulfate (P)<br>• Hydroxyzine HCl (P)<br>• Ketorolac tromethamine (P)<br>• Labetalol HCl (P)<br>• Mannitol (P)<br>• Methacholine chloride (P)<br>• Metoclopramide HCl (P)<br>• Mitomycin-C (P)<br>• Moxifloxacin HCl (P)<br>• Nalbuphine HCl (P)<br>• Nepafenac (P)<br>• Polidocanol (P) | • Potassium acetate (P)<br>• Procainamide HCl (P)<br>• Sodium bicarbonate (P)<br>• Sodium nitroprusside (P)<br>• Sodium tetradecyl sulfate (P)<br>• Trypan blue (P)<br>• Vecuronium bromide (P)<br>• Verapamil HCl (P) |

P: Proposed; **F: Final**

Link to 503B Bulks List


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