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# How FDA Thinks…
# About its Bulks Lists Nominations, Bulks Lists Reviews, and Claims and Substantiation

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# FDA's Bulks List: Section 503A

## History

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## The (Tortured) History of the Section 503A Bulks List

- January 7, 1999: FDA proposed rule listing bulk drug substances that may be used in pharmacy compounding).
- November 2013: Congress passed the Drug Quality and Security Act, Title I (Compounding Quality Act)
  - Created "Outsourcing Facilities"
  - Excised unconstitutional advertising provision from Section 503A
  - 503A was reinvigorated
- December 2013: Issued guidance documents on Bulks List Nominations for both 503A and 503B
- Industry (until July 2014): Nominated over 2,000 substances for FDA's Bulks List
- FDA called "uncle" and demanded a "do over"

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## History of the Section 503A Bulks List (Cont'd)

July 2014:

- FDA reopened the nominations process
- Provided "clearer" guidance on the content of nominations
- Approximately 740 substances nominated under the refined process
- FDA engages in consultation with the Pharmacy Compounding Advisory Committee and USP

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## History of the Section 503A Bulks List (Cont'd)

### FDA Review Criteria; October 2014 Federal Register Notice

(1) The physical and chemical characterization of the substance;

(2) Any safety issues raised by the use of the substance in compounded drug products;

(3) Historical use of the substance in compounded drug products, including information about the medical condition(s) the substance has been used to treat and any references in peer-reviewed medical literature; and

(4) The available evidence of effectiveness or lack of effectiveness of a drug product compounded with the substance, if any such evidence exists.

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## History of the Section 503A Bulks List (Cont'd)
## FDA Review Criteria; October 2014 Federal Register Notice

- 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.
- Describe past uses of the bulk drug substance in compounding.
- Provide information on the proposed use of the compounded drug product
- Provide a rationale for the use of a compounded drug product.
- Submit nominations to FDA docket.

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## History of the Section 503A Bulks List (Cont'd)
## FDA Review Criteria

(1) FDA evaluates the entire submission.

(2) FDA evaluates anecdotal evidence of efficacy and safety.

(3) FDA prefers clinical studies, but understands that the studies will not be as robust as clinical trials used in FDA approved drug products.

(4) Industry should update submissions with additional information while the nomination is pending.

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## History of the Section 503A Bulks List (Cont'd)
## FDA Review Criteria

Other considerations?

(1) Lack of rigorous evidence of safety and effectiveness.

(2) Low quality data; mostly anecdotal.

(3) Limited oversight and widespread use.

(4) Is there a public health concern?

(5) What does the PCAC or USP say? And does it matter?

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## History of the Section 503A Bulks List (Cont'd)

February 2016

- Published Proposed Rule for 503A evaluation criteria and bulks list for six substances

January 2017

- Interim Policy on 503A Compounding from Bulk Substances

February 2019

- Published Final Rule for 503A evaluation criteria and bulks list for six substances
  - Brilliant Blue G
  - Cantharidin (topical only)
  - Diphenylcyclopropenone (topical use only)
  - N-acetyl-D-glucosamine (topical only)
  - Squaric Acid dibutyl ester (topical)
  - Thymol iodide (topical)
- Four did not make the cut.
  - Oxitriptan
  - Piracetam
  - Silver Protein Mild
  - Tranilast
- Regulation?: 21 C.F.R. §216.23

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## History of the Section 503A Bulks List (Cont'd)

September 2019

- FDA published a second proposed regulation in September 2019
- Proposed to place five nominated substances on the list
- Proposed not to place 26 other substances on the list.
- After considering public comments, the Agency will issue a final regulation.
- As of today these additions have not been added to the final regulation.

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## History of the Section 503A Bulks List (Cont'd)

- Five Additions: Glutaraldehyde, glycolic acid, L-citrulline, pyruvic acid, and trichloroacetic acid (TCA).
- 26 "No's":

- 7-keto dehydroepiandrosterone (DHEA)
- acetyl-L-carnitine (ALC)
- alanyl-L-glutamine Aloe vera 200:1 freeze dried
- Artemisinin
- astragalus extract 10:1
- Boswellia serrata extract (BWSE)
- cesium chloride
- chondroitin sulfate
- Chrysin
- Curcumin
- D-ribose
- deoxy-D-glucose
- Diindolylmethane
- domperidone
- epigallocatechin gallate (EGCG)
- germanium sesquioxide glycyrrhizin
- kojic acid
- Nettle
- nicotinamide adenine dinucleotide (NAD)
- nicotinamide adenine dinucleotide disodium reduced (NADH)
- rubidium chloride
- sodium dichloroacetate
- vanadyl sulfate
- vasoactive intestinal peptide (VIP)

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## History of the Section 503A Bulks List (Cont'd)
## FDA Review Criteria

### Oxitriptan

One of the substances FDA removed from List 1 via final rulemaking.

- Several compounding pharmacies contacted FDA
- Summit Health Pharmacy (PA) submitted a citizen petition requesting FDA add oxitriptan to the Bulks List; that FDA allow compounding for certain patient population in the interim period.
- Medication is used for patients with BH4 deficiency.
- CP included a review of literature and case histories.

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## History of the Section 503A Bulks List (Cont'd)
## FDA Review Criteria

Oxitriptan

- While FDA has not added oxitriptan to the Bulks List, FDA announced it will not object to oxitriptan being compounded for patients with this condition.
- The Agency informed stakeholders that it does not intend to object to the compounding of oral oxitriptan for patients with BH4 deficiency who have a prescription identifying the disorder, so long as compounded in compliance with all other conditions of section 503A of the FD&C Act.
- **Agency took a patient-centered approach to regulation.**
- **Example of where directed advocacy worked.**

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# Bulks List Today

- Interim List last updated September 29, 2023
- Significant additions to FDA's Bulks List 2
- Multiple substances cannot be used in compounding because they "raise significant safety risks"
- FDA is focusing on "peptide-related" impurities
- Lack of sufficient safety information and related similar concerns for most peptide nominations.

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## FDA's Bulks List II September 23 additions

- AOD 9604
- BPC-157
- Cathelicidin LL-37
- CJC-1295
- Dihexa Acetate
- Emideltide (DSIP)
- Epitalon
- GHK-Cu (for injectable routes of administration)
- Ibutamoren Mesylate
- Ipamorelin Acetate
- Kisspeptin-10
- KPV
- Melanotan II
- Mechano Growth Factor, Pegylated (PEG-MGF)
- MOTs-C
- Selank Acetate (TP-7)
- Semax (heptapeptide)
- Thymosin Alpha-1 (Ta1)
- Thymosin Beta-4, Fragment (LKKTETQ)

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## 503A Bulks List Challenge

- *Evexias Medical Centers, PLLC; Evexias Health Solutions, LLC; and North American Custom Laboratories, LLC, D/B/A Farmakeio Custom Compounding v. FDA*, filed March 29, 2024 (N.D. Texas)
- Lawsuit filed in Federal Court challenging FDA's determination that certain peptide products are ineligible for compounding based on FDA's interim determination.

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## FDA Bulks List Challenge

- *Evexias Medical Centers, PLLC; Evexias Health Solutions, LLC; and North American Custom Laboratories, LLC, D/B/A Farmakeio Custom Compounding v. FDA*, filed March 29, 2024 (N.D. Texas)

- In all practical respects, the FDA's "interim" categorization policy has the force and effect of law. Specifically, as relevant here, the FDA and industry treat substances that are assigned to Category 2 as illegal to compound.
- On September 29, 2023, with no notice or opportunity for comment, the FDA assigned nineteen drug substances to Category 2 of its "interim" policy, thereby effectively prohibiting their use in compounding.
- Four of the peptides assigned to Category 2 are AOD-9604, CJC-1295, ipamorelin acetate ("ipamorelin"), and Thymosin Alpha-1 ("Ta1").

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# Bulks List Challenge

- *Evexias Medical Centers, PLLC; Evexias Health Solutions, LLC; and North American Custom Laboratories, LLC, D/B/A Farmakeio Custom Compounding v. FDA*, filed March 29, 2024 (N.D. Texas)

- **FIRST CAUSE OF ACTION: (Arbitrary and Capricious Agency Action in Violation of APA)**
- **SECOND CAUSE OF ACTION: (Invalid Rulemaking Without Notice and Comment)**
- **THIRD CAUSE OF ACTION: (Agency Action Unlawfully Withheld or Unreasonably Delayed in Violation of APA)**

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## Bulks List Challenge

- *Evexias Medical Centers, PLLC; Evexias Health Solutions, LLC; and North American Custom Laboratories, LLC, D/B/A Farmakeio Custom Compounding v. FDA*, filed March 29, 2024 (N.D. Texas)

**Prayer for Relief**

A. Declare that the FDA's designation AOD-9604, CJC-1295, ipamorelin, and Ta1 to Category 2 is arbitrary and capricious in violation of the APA;

B. Declare that the FDA's "interim" categorization of drug substances without notice and comment violates the APA;

C. Declare that the FDA has unreasonably delayed finalizing the Section 503A Bulks List, including in determining whether AOD-9604, CJC-1295, ipamorelin, and Ta1 should be included on the list;

D. Vacate the FDA's designation AOD-9604, CJC-1295, ipamorelin, and Ta1 to Category 2;

E. Vacate the FDA's "interim" categorization of drug substances without notice and comment;

F. Enjoin the FDA from taking enforcement action against plaintiffs based on its "interim" categorization;

G. Compel the FDA to finalize the Section 503A Bulks List, including determining whether AOD-9604, CJC-1295, ipamorelin, and Ta1 should be included on the list….

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## Levels of Evidence

Substantiation for prescription drug claims

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# Claims and Substantiation

- What is a claim?

Anything said about product

Not all claims are treated equally

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# Evidentiary Support – Legal/Reg Requirements

| | |
|---|---|
| Substantial Evidence | • Same standard for drug approval |
| Substantial Clinical Experience | • For drugs that have not gone through the New Drug Application Process? |
| Competent and Reliable Evidence | • Pharmacoeconomic data presented to formularies |

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# Substantial Evidence

- Two adequate and well controlled studies
  - This is typically FDA's expectation
- Data from one adequate and well-controlled clinical investigation + confirmatory evidence
- In some cases, FDA has determined data from one study is substantial evidence
  - The study provides a degree of statistical persuasiveness comparable to that of two such studies
  - The study demonstrates a clinically meaningful effect on mortality, irreversible morbidity, or prevention of a disease with potentially serious outcome such that conducting another trial would be unethical
- The quantity and quality of the evidence is always considered on a case-by-case basis for each drug

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# Substantial Evidence

## Adequate and Well Controlled

- A clear statement of objectives
- Proposed or actual methods of analysis
- Minimization of bias
- Methods for assessing subject response are well defined
  *See, e.g.,* 21 C.F.R. § 314.126
- Secondary endpoints must be pre-specified and must meet pre-specified statistical requirements (hierarchical testing, correction for multiplicity)
- Data collection points without a statistical analysis plan rarely permitted

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# Substantial Evidence

- Confirmatory Evidence -
  - Evidence generated from quality data derived from “an appropriate source”
    - Clinical evidence from a different stage of the same disease or from a different but closely related disease
    - Compelling mechanistic evidence in the setting of well-understood disease pathophysiology
    - Evidence from a relevant animal model
    - Evidence from other drugs in the same pharmacological class
    - Natural history evidence
    - Real World Data/Evidence
    - Evidence from Expanded Access
  - Quantity of confirmatory evidence may vary
    - Impacted by features and results from the single adequate and well controlled clinical investigation
  - Relevance of disease considerations
    - Are there unmet needs, size of patient population, etc.,

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# Substantial Evidence

- Single Large Multicenter Trial
  - Limited to clinically meaningful and statistically persuasive effect on mortality, severe or irreversible morbidity, or prevention of a disease with a potentially serious outcome
    - Confirmation of results would be impracticable or unethical
  - Adjusted for bias - no single trial site should be the main contributor of the observed effect
    - Either a much bigger effect or many more patients
  - Results are consistent and clinically meaningful based on prospectively specified endpoints
    - Effects on objective endpoints (e.g., imaging) may complement subjective endpoints (e.g., clinician or patient reported outcomes)
  - Broad entry criteria and diverse trial populations help address generalizability of findings
  - Close scrutiny of trial conduct

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# Substantial Clinical Experience

- Experience adequately documented in medical literature or by other data . . . On the basis of which *it can fairly and responsibly be concluded by qualified experts that the drug is safe and effective for such uses*
  - (21 C.F.R. § 202.1(e)(4)(II)(c))
- FDA has taken the position in speeches that this standard is used to support claims for prescription drugs that have not been evaluated by the FDA through the NDA process
  - This position is not reflected in law or regulations

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# Competent and Reliable

- Standard is identified in the Federal Food, Drug, and Cosmetic Act but not defined in the law or implementing regulations
- FDA Guidance from 2018 describes "competent and reliable scientific evidence" as using generally accepted scientific standards, appropriate for the information being conveyed, that yield accurate and reliable results
  - FDA will consider existing current good research practices for substantiation developed by authoritative bodies
- Specifically applies to healthcare economic information provided to payors

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# THANK YOU!

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