BULK SUBSTANCES AND ESSENTIAL COPIES: DRAFT GUIDANCE AND RECENT LITIGATION

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Key Questions re Bulk Substances

- What bulk substances can a compounder use?
- When can a compounder start from a bulk substance?

Policy Issues at Play

- Access:
  - clinical need; patient/provider preference
- Quality:
  - minimize risk of contamination/ error
- Incentives:
  - preserve approval process

FDA's Guidance for Section 503A and 503B Facilities

The Legal Basis for Compounding with Bulks – Section 503A

- Default: May use bulks subject to certain limitations
  - May only use bulk drug substances:
    - That comply with an applicable United States Pharmacopeia (USP) / National Formulary (NF) monograph if one exists, and the USP chapter on pharmacy compounding;
    - Are components of FDA-approved drug products if an applicable USP or NF monograph does not exist; or
    - Appear on an FDA list of bulk drug substances that can be used in section 503A compounding
  - The bulk drug substance must be:
    - Made at an FDA-registered facility; and
    - Accompanied by a Certificate of Analysis (COA)

The Legal Basis for Compounding with Bulks – Section 503B

- Default: May not use bulk drug substances unless:
  - Are used to compound drug products that appear on FDA's drug shortage list at the time of compounding, distribution, and dispensing; or
  - Appear on FDA's 503B list of bulk drug substances for which there is a clinical need, based on a notice and comment process
- The bulk drug substance must be:
  - Made at an FDA-registered facility; and
  - Accompanied by a COA

Relevant Lists

- Bulks list
  - 503A(b)(1)(A)(i)(III)
  - 503B(a)(2)(A)(i))
- Withdrawn or Removed List
  - 503A(b)(1)(C)
  - 503B(a)(4))
- Demonstrably Difficult to Compound
  - 503A(b)(3)(A)
  - 503B(a)(6)

Also, 506E drug shortage list used for determining when permissible to compound because of a shortage.

FDA's Pharmacy Compounding Advisory Committee (PCAC)

- Composition: Twelve core voting members
  - 503A: NABP, USP, pharmacy, physician, and consumer organizations, and other experts
  - 503B: NABP, USP, pharmacists with compounding experience/expertise, physicians w/ compounding background/knowledge, patient and public health advocacy organizations
- Authority
  - Must review substances for inclusion on all 3 503A lists
  - Must review demonstrably difficult 503B list; may be consulted on others
- Progress
  - Met quarterly in 2015 and 2016; met twice in 2017; once in 2018 (9 times)
  - Reviewed about 53 substances to date
- Voting: PCAC has voted "no" to several substances for 503As
  - Domperidone, chondroitin sulfate, acetyl-L-carnitine, NAD, etc.
  - "No" to powdered dose inhalers, transdermal or topical delivery systems
- Next Steps
  - Per statute, all 3 503A lists and 503B demonstrably difficult list must be finalized via regulation
  - First proposed rule for Section 503A published in December 2016 (6 substances recommended for inclusion, and 4 against); nothing happened since

FDA's "Bulks" List for Section 503A and 503B: What Happened Initially?

- In December 2013, FDA invited nominations of bulk drug substances for inclusion on a list of bulk drug substances that can be used for compounding under sections 503A and 503B
  - Received voluminous substances (e.g., whole compendia); but FDA deemed the nominations incomplete
- In July 2014, FDA reopened the nomination process, providing more detailed instructions regarding required information
  - Many, but not all substances, re-nominated
- In July 2017, FDA finalized "Interim Policy" on use of bulk drug substances under sections 503A and 503B

FDA's "Bulks" List for Section 503A and 503B

- FDA website publication in January 2017 addressing bulks
  - Released new interim bulks lists for Sections 503A and 503B
- May compound from substances only if on Category 1 (enforcement discretion)
  - **Category 1** – Substances nominated currently under evaluation
  - **Category 2** – Substances nominated that raise significant safety risks
  - **Category 3** – Substances nominated without adequate support
- How are substances added to list?
  - Process differs for Section 503A and Section 503B
- FDA investigators and states are paying attention to the "types" of drugs compounded and substances used in compounding.

FDA's "Bulks" List for Section 503A and 503B: What's Happened since January 2017?

- Beginning in Spring 2017, FDA updated bulks lists.
- Stated would update lists on @ monthly basis
- Discussions between FDA and industry followed concerning the propriety/legality of FDA's bulk substance nomination process.
- FDA added vasopressin and some other substances to Bulks List 1 after nomination by an outsourcing facility
- As lawsuit loomed, FDA temporarily stopped updating 503B and 503A lists in July 2017.

FDA's "Bulks" List for Section 503B: What Happened...

- Vasopressin happened ...
- Several compounders (Athenex, QuVa, Nephron) nominated vasopressin for the 503B bulks list in 2017
- FDA added vasopressin to List 1 in July of 2017
- The commercial manufacturer who received approval pursuant to FDA's UDI for its product Vasostrict® likely "expressed displeasure" to FDA about the List 1 designation
- In October 2017, the commercial manufacturer (Par Sterile Products and Endo Par Innovation Company (Endo/Par)) sued FDA
- Par claims FDA violated notice and comment rulemaking provisions of the Administrative Procedures Act by use of Interim Policy to nominate and permit use of bulk substances

FDA's "Bulks" List for Section 503B: What Happened...

- Vasopressin has been used intravenously in hospitals (mostly in emergency scenarios) from almost 100 years.
- Would be a popular 503B product
- Par received FDA approval (for Vasostrict®) via FDA's Unapproved Drugs Initiative; thus, all other unapproved vasopressin products were required to leave the market.
- After Par approval, "average wholesale price of intravenous vasopressin surged 3141% — from $4.27 to $148.40 per vial."
- From 2013 to the present, annualized sales increased from $4 million to $400 million.
- Lawful compounds are exempt from drug approval requirements.
- (Athenex Memorandum in Support at 8, 21).

FDA's "Bulks" List for Section 503B: Endo/Par Happened...

- In March 2018 FDA proposed through draft guidance to revamp the nomination process for 503B.
- FDA interprets "bulk drug substances for which there is a clinical need" to mean a clinical need for using a bulk drug substance instead of compounding from the approved drug
- Proposes stringent factors for considering clinical need of each substance:
  - 1) Whether attributes of the approved drug may make it unsuitable to treat certain patients for particular conditions
    - Is the compounded drug is intended to address that attribute, and
    - Must the compounded drug be prepared from a bulk drug substance rather than an approved drug?
  - 2) A balancing test for each substance weighing its physical and chemical characterization, possible or known safety issues, evidence or lack of thereof of effectiveness, and historical use
- Note: If finalized, FDA's restriction against compounding from bulk vs. approved drugs is enforceable – with no need to wait for a finalized "bulks list"

FDA's "Bulks" List for Section 503B: Endo/Par Happened...

- July 2018
  - FDA published a revised bulks list
  - Vasopressin still remains on List 1
  - Athenex Pharma, compounder of vasopressin moves to intervene
  - Court grants motion to intervene
- August 2018
  - FDA publishes draft notice seeking to ***remove*** 3 substances – vasopressin, bumetanide and nicardipine hydrochloride from List 1
  - Par seeks a preliminary injunction
  - FDA opposes motion and states that the case not ripe because guidance is not final agency action, among other reasons.
  - Case is now stayed (third time) pending issuance of final decision on vasopressin.

The Path Forward – Permanent Lists of "Bulks" That May Be Used in Compounding

- Section 503A permanent list
  - Proposed rule outstanding (proposed 12/16; no action in this Administration)
  - PCAC continues to meet
  - Substances can be placed on the list for specific routes of administration, but *not* for restricted uses
- Section 503B permanent list
  - FDA plans to maintain a "positive" and "negative" list
    - Commissioner Gottlieb expected FDA would complete review of ~5 in 2018, more in the coming years
  - To date, zero substances on permanent list (3 currently proposed for exclusion)
    - FDA received 28 public comments on its August 2018 notice – both in support and opposition
    - Several commenters raised new bases for determining clinical need (e.g., allergens not referenced in prior nominations)
  - FDA may place substances on the list for restricted uses (e.g., only for patients with specified allergy)
    - How could FDA enforce these restrictions...

What about Copies of Commercially-available Products? Everyone's Doing it....

The Legal Basis for Prohibiting Compounding What Are "Essentially Copies" of Approved Drugs

- Section 503A defines "essentially a copy" as not including
  - "a drug product in which there is a change, made for an identified individual patient, which produces for that patient a significant difference, as determined by the prescribing practitioner...."
- Section 503B defines "essentially a copy" to mean:
  - a drug that is identical or nearly identical to an approved or marketed drug, unless the drug is in shortage; or
  - "a drug, a component of which is a bulk drug substance that is a component of an approved drug... unless there is a change that produces for an individual patient a clinical difference, as determined by the prescribing practitioner...."

"Essentially a Copy" of Commercially Available Drug Products FINAL Guidance (January 2018) – Section 503A

- **Essentially a Copy:**
  - Same API
  - Same, similar or easily substitutable strength
  - Within 10% of the commercial product
  - Easily substitutable: e.g.., 2 25mg v 1 50 mg
  - Same route of administration
- **"Statement of Significant Difference":**
  - Significant benefit that the prescriber identifies must be produced by the change
  - Specific notation of the difference, including date, on the prescription

"Essentially a Copy" – Section 503A (continued)

"Regularly or in Inordinate Amounts"

- May compound essentially copies of commercially available drugs so long as not "regularly or in inordinate amounts."
- "Regular" and "Inordinate": If a drug "is compounded more frequently than needed to address unanticipated, emergency circumstances or in more than the small quantities needed to address unanticipated, emergency circumstances."
    - FDA guidance considers this to be greater than four prescriptions per month.

"Commercially Available"

- Drug is not "commercially available" – and thus EOC prohibition does not apply – if:
    - It has been discontinued and Is no longer marketed OR
    - It is "currently in shortage" on FDA's 506E drug shortage list

"Essentially a Copy" Final Guidance – Section 503B (January 2018)

- **CANNOT** compound "identical or nearly identical" drugs (exception: drug shortages)
  - Products are "identical or nearly identical" if the compound and the approved drug have the SAME: (1) active ingredient; (2) route of administration; (3) dosage form; (4) dosage strength; and (5) excipients
- **ALSO**, if compounded drug contains a bulk drug substance that is a component of an approved drug, the compounder must receive documentation of a prescriber determination of clinical difference.
  - Prescriber should provide to outsourcing facility statement that specifies that the compound will only be used in those patients for whom the "change" between the compound and the commercially available drug produces the clinical difference.

"Essentially a Copy" – Section 503B (continued)

- Prescriber determination needed "whether it was compounded from bulk drug substances or from drugs in finished form."
  - In describing enforcement plan, Commissioner Gottlieb stated FDA will "prioritize review of situations that could adversely impact the public health and premarket approval process, such as compounding using a bulk drug substance" rather than manipulating an approved drug.
- To date, few Form-483's cite outsourcing facilities for failing to obtain prescriber documentation
  - FDA may link enforcement to the permanent 503B bulks list (if/when substances are added for particular types of patients)

QUESTIONS?

THANK YOU!