Presentation by OFA for the FDA Public Meeting on Drug Compounding by Outsourcing Facilities

MAY 21, 2019

OFA's Mission

- The Outsourcing Facility Association (OFA) is the trade association representing FDA-registered 503B outsourcing facilities
  - OFA members work with patients, healthcare providers, and facilities on a daily basis to ensure the specific needs, of both providers and patients, are satisfied with safe and effective compound and repackaged medications
- OFA will continue to work with industry, governmental agencies, and healthcare providers to educate and advocate for outsourcing facilities and their ability to meet the critical need of ensuring that patients and providers have access to the medications they need

Agenda

- Revised cGMP Guidance
- Addressing FDA's Specific Questions
- State Laws Regarding 503A Office Stock

OFA's Comments to the cGMP Guidance

- OFA submitted a comment to FDA on Feb. 11, 2019
- Overview of comments:
  1. OFA supports one consistent standard for all 503Bs
     - The Revised Draft Guidance appears to apply one standard to all 503Bs, but FDA's public statements have indicated the opposite
     - OFA request that FDA clarify that one cGMP standard applies to all 503Bs no matter their size, revenue, or type of compounding

OFA's Comments to the cGMP Guidance

2. OFA disagrees with FDA's position that 503B compounding poses more risk to patients than drug manufacturing
   - The Revised Draft Guidance mischaracterizes 503Bs as more prone to sterility, strength, and labeling issues with both sterile and non-sterile compounded drug products
   - FDA has yet to provide evidence to support the premise that products produced from a 503B pose a higher risk to consumers than drug products produced from a conventional drug manufacturer
     - In fact, as an example
   - Furthermore, any product poses a threat of patient harm if it is made under improper standards regardless of where that product is made
   - 503Bs and drug manufacturers are subject to cGMPs (21 CFR 210 & 211)
   - 503Bs maintain the same processes as drug manufacturers
     - E.g., supplier verification, raw material testing, product release testing

OFA's Comments to the cGMP Guidance

3. FDA's distinction between "Higher Risk Compounding" and "Lower Risk Compounding" is misplaced
   - The Revised Draft Guidance "distinguishes, where applicable, between higher risk compounding activities (e.g., sterile production, manual manipulations) and lower risk compounding activities (e.g., lower volume of production, nonsterile production, use of automated equipment)."
   - There should be no distinction between higher risk compounding and lower risk compounding because there should be one consistent standard for all 503Bs that engage in sterile compounding regardless of the types of starting material used (i.e., bulk drug substance versus commercially available product)

OFA's Comments to the cGMP Guidance

4. OFA seeks clarification on testing
   - OFA requests that FDA clarify what level of testing is required for container-closures and modifications to container closures (lines 482-86)
   - OFA continues to be concerned about 503Bs ability to obtain COAs from suppliers as it relates to testing each lot of containers and closures (lines 508-15)
5. FDA's COA policy must be modified based on 503Bs current position in the marketplace
   - "To be eligible for the exemptions provided in section 503B of the FD&C Act, each bulk drug substance used in compounding must be 'accompanied by a valid certificate of analysis' (section 503B(a)(2)(D)). FDA interprets this provision to mean that each lot of a bulk drug substance is accompanied by a valid COA."
   - This requirement is outside the control of the 503B. OFA is concerned that 503Bs will not be able to comply because bulk substance manufacturer and/or commercial manufacturers may refuse to provide COAs to 503Bs. Additionally, if source suppliers did not perform sufficient testing on the source products supplied, FDA does not provide guidance on how 503Bs should validate each supplier under such circumstances. The burden should not be on 503Bs to obtain COAs for source products when source suppliers are FDA-regulated entities. Also, the guidance implies that if one develops a Quality Agreement, FDA will not take regulatory action on the lack of testing to verify a COA. OFA requests additional clarification on how FDA proposes that 503Bs validate each supplier.

OFA's Comments to the cGMP Guidance

6. The reserve sample limitation set out in the Revised Draft Guidance is arbitrary

   - "FDA generally does not intend to take regulatory action against an outsourcing facility regarding reserve sample requirements if all of the following apply: Once >10,000 units are produced of a given drug product formulation and container-closure system in a 6-month reporting period, an appropriately identified and representative reserve sample is collected each time 1,000 units of that specific formulation and container-closure system is produced for the remainder of the current reporting period and for the entire subsequent 6-month reporting period."
   - OFA seeks clarification on the threshold referenced above. FDA does not provide scientific rationale or evidence for this arbitrary 10,000-unit threshold requirement.

Addressing FDA's Specific Questions - Demand and supply of office stock

- FDA has asked for ways in which HCPs seek to identify outsourcing facilities that compound the drugs they want for office stock, as well as issues, if any, with this process
  - 503Bs have worked hard to develop close relationships with healthcare providers
  - 503Bs are focused heavily on validation – validation of equipment, manufacturing suites and storage rooms (much like traditional drug manufacturers)
  - One critical concern of 503Bs is that there is no way currently to distinguish a compliant 503B with a non-compliant 503B
  - FDA's inability to issues EIRs after corrective action has occurred, essentially closing out a 483, is impacting 503Bs business
  - Open 483s also impact 503Bs ability to obtain state licenses and enter GPO agreements
  - FDA should release a statement to all HCPs that office stock should only be procured from a FDA-registered 503B and they can verify the potential vendor on the FDA website. Otherwise the HCP will be responsible if purchased office stock from a 503A.

FDA Dialogue/Inspection Closure

- 503Bs are committed to compliance with clear and justified FDA guidance
- OFA requests that FDA issue the final cGMP guidance as quickly as possible
- OFA also requests that FDA be more responsive to inquiries from 503Bs especially following inspections – many 503Bs have submitted inquires and/or responses to 483s and do not hear back from the Agency for 12 months
- OFA requests that FDA focus on closing 483s for entities that have sufficiently responded/taken corrective action

Addressing FDA's Specific Questions - Demand and supply of office stock

- FDA has asked about HCPs' experiences with the availability of office stock products from outsourcing facilities
  - FDA's position on compounding from bulks impacts 503Bs ability to meet office stock demand because 503Bs currently struggle to obtain COAs from finished product manufacturers (to use finished product as a starting material)

Addressing FDA's Specific Questions - Perspectives related to orders for drug products that an outsourcing facility has not made or does not routinely make

- FDA has asked what factors outsourcing facilities consider before deciding whether to fill an order for a requested compounded drug product that it has not previously made or does not routinely make
  - Is the starting material available?
    - Bulks are required/necessary to meet certain patient needs
  - Is the product a shortage product (that could come off the shortage list in the near future)?
  - What duration of time will this product be needed (to address a shortage or market need)?
  - Is there a large enough interest in this product to justify using resources to perform studies and create formulations?
    - For example:
      - Formulation - $10,000 per drug (external resources to examine and prove formulation) + $15,000 (internal resources; 2-3 weeks of development time)
      - Method validation and development of stability testing - $30,000 per drug (external resources) + $50,000 (internal resources; 4 weeks of development time)

Addressing FDA's Specific Questions - Perspectives related to orders for drug products that an outsourcing facility has not made or does not routinely make

- FDA has asked about the impact that FDA's policies proposed in the revised draft guidance would have on outsourcing facilities filling orders for requested products not previously or routinely made
  - Lot testing requirements, COA collection, and BUDs could significantly impact whether a 503B chooses to make a product not previously or routinely made

Addressing FDA's Specific Questions - Perspectives related to beyond use dating for office stock products

- FDA has asked how long HCPs seek to keep office stock drug products before use
  - Example from one member: 90-120 days of BUD

Addressing FDA's Specific Questions - Perspectives related to beyond use dating for office stock products

- FDA has asked about the impact that FDA's policies proposed in the revised draft guidance would have on outsourcing facilities' production of compounded drug products for office stock with beyond use dating desired by HCPs
  - The current Revised Draft Guidance could have a significant impact
  - For this reason, the policy relating to in-use times must be modified
    - "[i]f the compounded drug product requires additional manipulation before administration (e.g., reconstitution and/or dilution), FDA interprets the directions for use requirement to include an in-use time because the health care practitioner who manipulates or administers the drug would need to know how long it is expected to retain its quality after being manipulated."
    - The Draft Guidance is not in agreement with USP undergoing revision. The proposed revision eliminates in-use-times. Additionally, a new paradigm for establishing Beyond-Use Dates ("BUD") is anticipated. For instance, an aseptically prepared compounded sterile product prepared from only sterile starting components with no sterility testing performed will have a BUD of 4 days if stored at room temperature and 9 days if refrigerated. OFA suggests FDA modifies the policy mentioned above to better reflect the anticipated USP BUDs.

State Laws

- Many state laws contradict section 503B of the FD&C Act and FDA's current guidance (e.g., many state laws still allow 503As to produce compounded sterile products for office use)
  - E.g., California
- How is FDA addressing this issue?

Questions

- OFA thanks FDA for the opportunity to speak today
- OFA is happy to take questions from the Agency