



# Compounding Policy Overview

Jane A. Axelrad  
Associate Director for Policy, CDER  
And Agency Lead on Compounding

March 18, 2015

# Guidances Issued During the Past Year

- Final Guidance:
  - 503A
  - Outsourcing Facility Fees
  - Registration of Outsourcing Facilities
- Draft Guidance:
  - Interim CGMPs for Outsourcing Facilities
  - Guidance For Entities Considering Whether to Register as Outsourcing Facilities
  - Adverse Event Reporting for Outsourcing Facilities
  - Revised Product Reporting for Outsourcing Facilities
  - Repackaging
  - Mixing, Diluting, and Repackaging Biologics

# Other Accomplishments

- Issued draft Standard Memorandum of Understanding (MOU) under 503A
- Issued proposed rule describing additions and modifications to the Withdrawn or Removed List (503A and 503B)
- Solicited nominations for 503A and 503B bulks lists and for drugs that are difficult to compound under sections 503A and 503B
- Announced membership of Pharmacy Compounding Advisory Committee and held first meeting covering drugs proposed for withdrawn or removed list and 503A bulks list

# Draft Guidance for Entities Considering Whether to Register as Outsourcing Facilities

- If you register as an outsourcing facility, you are indicating your intent for ALL drugs compounded at the facility to be regulated under section 503B, and not section 503A
- ALL drugs compounded at the facility must be compounded under CGMP requirements
- Must be engaged in compounding of some sterile drugs; cannot do ONLY non-sterile; compounded non-sterile drugs will qualify for the exemptions if compounded in an outsourcing facility in accordance with the provisions of section 503B

## Draft Guidance for Entities Considering Whether to Register as Outsourcing Facilities (cont'd)

- Definition of compounding does not include repackaging; may not do ONLY repackaging under section 503B; repackaging is addressed in the repackaging guidance
- In section 503B, drug does not include a biological product subject to licensure under section 351 of the PHS Act; may not manipulate ONLY biologics; mixing, diluting or repackaging biologics is addressed in the biologics guidance

# Draft Repackaging Guidance

- Describes conditions under which FDA does not intend to take action for violations of sections 505 (approval), 502(f)(1) (labeling with adequate directions for use) and if not an outsourcing facility, 501(a)(2)(B) (CGMP) for repackaging that meets the conditions of the guidance

# Activities Excluded From Draft Repackaging Guidance

- Draft guidance DOES NOT ADDRESS:
  - biological products subject to licensure under section 351 of the Public Health Service Act
  - repackaging drugs for use in animals
  - repackaging by anyone other than a pharmacy, Federal facility or outsourcing facility
  - removing drug from original container for immediate administration at point of care for single patient after receipt of Rx or order for that patient
  - certain repackaging of solid oral dosage forms to fill patient-specific Rx

# Draft Repackaging Guidance Conditions

- Starting material is an FDA-approved drug or unapproved drug on the FDA drug shortage list
- Repackaged drug is not on the withdrawn or removed list
- Repackaging is by or under the supervision of a licensed pharmacist
- Repackaging facility is in compliance with any applicable state requirements
- Repackaging does not conflict with approved labeling, except for labeling statements related to the product being single dose or single use



## Draft Repackaging Guidance Conditions (cont'd 2)

- If pharmacy or Federal facility ONLY:  
prescription or order for identified individual patient obtained directly from practitioner, patient, or patient's agent; or in advance of Rx or order in quantity that doesn't exceed 14 day supply based on history of receipt of Rx or orders within a consecutive 14 day period

# Draft Repackaging Guidance Conditions (cont'd 3)

- Beyond Use Dates (BUDs) for STERILE drugs:
  - if approved product has an in use time, BUD is in accordance with in use time or expiration date, whichever shorter
  - if no in use time on approved label or unapproved drug on shortage list:
    - if repackaged by pharmacy or Federal facility:  $\leq 30$  hours, controlled room temp (CRT) ;  $\leq 9$  days refrig;  $\leq 45$  days frozen (these are based on USP 797 medium risk category)
    - if repackaged by an outsourcing facility and sterility tested, and gets passing results before release:  $\leq 14$  days beyond completion of sterility test or 28 days from repackaging, whichever shorter if CRT or refrig;  $\leq 45$  days beyond completion of sterility test or 59 days from repackaging, whichever shorter if frozen (these are based on interim CGMP for OF Guidance)
- BUDs for NON-STERILE drugs: no longer than expiration date on original product

# Draft Repackaging Guidance Conditions (cont'd 4)

- If state-licensed pharmacy or Federal facility, complies with USP 795 or 797, as applicable; outsourcing facility complies with CGMPs
- Not sold or transferred by an entity other than the one that repackages the drug; sale or transfer does not include administration in a healthcare setting
- Other outsourcing facility conditions: labeling; product reporting; AE reporting

# Draft Mixing, Diluting, or Repackaging Biologics Guidance

- Describes conditions under which FDA does not intend to take action for violations of section 351 of the Public Health Service Act (premarket approval) and FD&C Act sections 502(f)(1) (labeling with adequate directions for use) and if not an outsourcing facility, 501(a)(2)(B) (CGMP) for mixing, diluting, and repackaging biologics that meets the conditions of the guidance

# Activities Excluded From Draft Biologics Guidance

- Draft guidance DOES NOT ADDRESS:
  - mixing, diluting, or repackaging in accordance with a biologics license application (BLA)
  - vaccines, cell therapy, gene therapy, blood or blood components for transfusion (but does apply to plasma derived products)
  - mixing, diluting, or repackaging by anyone other than a pharmacy, Federal facility, or outsourcing facility, or, for allergenic extracts only, by a physician

# Activities Excluded from Draft Biologics Guidance (cont'd)

Draft guidance DOES NOT ADDRESS:

- biologics subject to approval under section 505 of FD&C Act
- mixing, diluting, or repackaging products for animals
- removing biological product from original container for immediate administration at point of care for single patient after receipt of Rx or order

# Draft Biologics Guidance Conditions

- Starting material is a licensed biological product only, and not a biological product licensed for further manufacturing use, or a bulk drug substance
- Mixing, diluting or repackaging is by or under the supervision of a licensed pharmacist
- Mixing, diluting, or repackaging is done in a facility that complies with any applicable state requirements
- Mixing, diluting, or repackaging does not conflict with approved labeling, except for labeling statements related to the product being single dose or single use

# Draft Biologics Guidance Conditions (cont'd 2)

- If pharmacy or Federal facility ONLY: prescription or order for identified individual patient obtained directly from practitioner, patient, or patient's agent; or in advance of Rx or order in quantity that doesn't exceed expected demand within the BUD based on history of receipt of Rx or orders within a BUD period



# Draft Biologics Guidance Conditions (cont'd 3)

- Beyond Use Dates (BUDs) very short because of concerns associated with the characteristics of biological products
- Developed based on reviews of labeling for approved biologics
- If mixed, diluted, or repackaged by a pharmacy or Federal facility:
  - 4 hours or original approved product's "in-use" time, whichever shorter; or
  - up to 24 hours with microbial challenge study
- If mixed or diluted by an outsourcing facility:
  - 4 hours or original approved product's "in-use" time, whichever shorter; or
  - up to 24 hours with microbial challenge study; or
- If repackaged by an outsourcing facility:
  - 4 hours or original approved product's "in-use" time, whichever shorter; or
  - up to 24 hours with microbial challenge study; or 5 days or expiration date of product, whichever shorter, if compatibility studies in container closure conducted in accordance with CGMPs

# Draft Biologics Guidance Conditions (cont'd 4)

- If state-licensed pharmacy or Federal facility, complies with USP 797; outsourcing facility complies with CGMPs
- Not sold or transferred by an entity other than the one that mixes, dilutes, or repackages; sale or transfer does not include administration in a healthcare setting
- Other outsourcing facility conditions: labeling; product reporting; AE reporting

# FDASIA Health Systems Drug Shortage Provisions

- Section 506F of the FD&C Act (added by section 1007 of FDASIA) exempts a health system hospital engaged in certain repackaging of drugs in shortage from registration under section 510 of the act if drugs repackaged for the same health system
- Once repackaging drugs and mixing, diluting, and repackaging biologics guidances are final, section 506F will no longer apply

# Adverse Event Reporting Draft Guidance for Outsourcing Facilities

- Section 503B says outsourcing facilities must submit adverse experience (AE) reports “in accordance with the content and format requirements established through guidance or regulation under section 310.305”
- Guidance specifies **MUST** report all serious, unexpected, AEs associated with the use of their compounded Rx products within 15 days of first receiving information about AE
- Must submit follow-up report within 15 days of receipt of new information about the event, or upon request of FDA

# Threshold for Reporting

- 4 data elements should be actively investigated when considering submission of report to FDA:
  - identifiable patient
  - identifiable reporter
  - suspect drug
  - serious adverse event
- Reports should be submitted as long as there is information on suspect drug and adverse event

# Other Topics Covered By Draft AE Guidance

- Failure to report is a prohibited act under 301(ccc)(3)
- Draft guidance discusses how to report, what should be included in a report, recordkeeping expectations, and review of recordkeeping and reporting during FDA inspections