U.S. FOOD & DRUG ADMINISTRATION

Current Good Manufacturing Practice – Draft Guidance for Outsourcing Facilities

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Outline

- Requirements for current good manufacturing practice (CGMP)
- How the draft guidance describes a risk-based approach
- Overview of CGMP expectations for all outsourcing facilities (OFs)
- Proposed enforcement discretion policies that vary by risk

Requirements for CGMPs

Drug Quality and Security Act (DQSA) added a new section 503B to the FD&C Act

- Compounders can register with FDA as an OF
- Drug products compounded in an OF can qualify for exemptions from:
  - FDA approval requirements (section 505 of the FD&C Act)
  - Requirement to label drug products with adequate directions for use (section 502(f)(1) of the FD&C Act)
  - Drug supply chain security requirements (section 582 of the FD&C Act)

Requirements for CGMPs

OFs must comply with CGMP requirements

- Under section 501(a)(2)(B) of the FD&C Act, a drug is deemed to be adulterated if it is not produced in accordance with CGMP
- Under section 503B(b)(4)(B) of the FD&C Act, OFs are inspected by FDA according to a risk-based schedule

Requirements for CGMPs

Under section 501(a)(2)(B) of the FD&C Act, a drug is deemed adulterated if:

> [T]he methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of this Act as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess . . . .

Requirements for CGMPs

Section 501 of the FD&C Act, as amended by the Food and Drug Administration Safety and Innovation Act, states:

> For purposes of paragraph (a)(2)(B), the term “current good manufacturing practice” includes the implementation of oversight and controls over the manufacture of drugs to ensure quality, including managing the risk of and establishing the safety of raw materials, materials used in the manufacturing of drugs, and finished drug products.

Requirements for CGMPs

- FDA intends to promulgate more specific CGMP regulations for OFs
- Until these final regulations are promulgated
  - OFs are subject to the CGMP requirements in 21 CFR parts 210 and 211
  - Guidance (currently in draft) provides for conditions under which FDA generally does not intend to take regulatory action against an OF regarding certain CGMP requirements during this interim period.

CGMP – Draft Guidance for OFs

- 2014 Draft guidance focused on sterility assurance of sterile drug products and safety more generally, with respect to strength (e.g., subpotency, superpotency), and labeling or drug product mix-ups.
- Revised draft guidance issued, in part, to:
  - Include considerations for non-sterile products.
  - Propose policies that better reflect the size and scope of OF operations (e.g., addressing smaller volume production).
  - Help encourage additional compounders to register as OFs in light of the changes described above.

How Draft Guidance Describes a Risk-Based Approach

- Retain robust production controls regardless of risk
- Higher-risk compounding vs lower-risk compounding
  - Higher volume/product vs lower volume/product
  - Sterile vs non-sterile
  - Manual manipulations vs. use of automated equipment
- Lower-risk compounding allows for enforcement discretion policies that:
  - Reduce end-product release testing
  - Reduce stability testing and reserve sample retention

Overview of CGMP Expectations for OFs

- Quality control unit – responsible for facility oversight, including:
  - Establishment of procedures
  - Release of lots
  - Investigations into failures/complaints
- Facility design and equipment
  - Minimize product mix-ups and contamination
  - Enable aseptic production for sterile products
- Environmental and personnel monitoring
  - Prevent contamination, including cross-contamination & bioburden control
  - Ensure sterility in aseptic production

Overview of CGMP Expectations for OFs

- Controls for equipment
  - Ensure equipment does not adversely affect the drug and functions as intended
- Controls for containers and closures
  - Ensure suitable for intended use
  - Product remains sterile and/or uncontaminated
- Controls for components
  - Establish specifications
  - Test all aspects of quality for each shipment of each lot **or** may test identity only and rely on qualified supplier's COA

Overview of CGMP Expectations for OFs

- Production and process controls
  - Ensure consistent production of a drug that meets quality standards
  - Document through batch records
  - Validate aseptic production or terminal sterilization method, as applicable
  - Manage changes in production and process procedures

Overview of CGMP Expectations for OFs

- Laboratory controls
  - Ensure methods and equipment are suitable for intended use and produce valid results
  - Design sampling/testing procedures to ensure components, in-process materials, and drug products conform to specifications
  - Follow written procedures and document the results
- Packaging controls
  - Ensure protection of drug product
  - Labeling controls to prevent product mix-ups

Proposed Enforcement Discretion Policies

Release Testing: Non-Sterile

- Reduced testing based on the following conditions:
  - Solid dosage form (assumed low water activity)
  - Low water activity
  - Batch size <60 units
  - Starting from FDA-approved product
  - Product tested for strength by method that is highly specific (e.g., high performance liquid chromatography (HPLC))

Conditions	Batch Release Test ○ Test for which FDA generally does **not** intend to take regulatory action under the conditions listed ● Test expected to be performed, if applicable								
	Identity	**Strength**	**Content Uniformity[c]**	**pH**	**Appearance**	**AET/Preservative Content[d]**	**Microbial Enumeration (bacteria and fungi)[e]**	**Tests for Specified Microorganisms[e]**	**Other Appropriate Specifications[f]**
Tests are conducted according to these conditions …									
1. Batch size <60 units,[a] if omitted tests are performed once 60 units are produced[b]									
1a. Starting from FDA-approved product	○	○	○	○	●	○	○	○	○
1b. Starting from bulk drug substance	●	●	○	○	●	○	○	○	○
2. Batch size ≥60 units *or* once 60 units are produced[b] and considering the following characterizations of water activity:									
2a. Water activity >0.6	●	●	●	●	●	●	●	●	●
2b. Water activity ≤0.6 (other than solid dosage forms)	●	●	●	●	●	○	○	○	●
2c. Solid dosage forms	●	●	●	○	●	○	○	○	●
… unless conditions 3 or 4 also apply. If so, choosing the least stringent option for each test among applicable conditions would be consistent with the enforcement policy set forth in this appendix.									
3. Product tested for strength by method that is highly specific (e.g., HPLC) and uses a reference standard	○	●	●	●	●	●	●	●	●
4. Compounded drug product is single dilution of FDA-approved drug product, or is made from one or more dilutions of FDA-approved drug product performed per labeling dilution instructions and using automated equipment calibrated immediately before and after production	○	○	●	●	●	●	●	●	●

Proposed Enforcement Discretion Policies

Release Testing (Non-sterile): Example 1

If all of the following conditions apply:

- Batch size is >60 units
- Water activity is ≤0.6 (it is not a solid dosage form)
- Product is tested for strength by a method that is highly specific (e.g., HPLC) and uses a reference standard.

Then from Table A, conditions 2b and 3 apply:

Under those conditions, FDA generally does not intend to take regulatory action regarding batch release tests for identity, AET/preservative content, microbial enumeration, or tests for specified microorganisms if the OF assessed strength, content uniformity, pH, appearance, and the other appropriate specifications for that product.

Proposed Enforcement Discretion Policies

Release Testing: Sterile

- Reduced testing based on the following conditions:
  - Batch size < 60 units
  - Batch size < 10 units compounded pursuant to a prescription for a single patient
  - Terminally sterilized
  - Dilution of FDA-approved product following instructions in labeling
  - Multi-component injectable drug product using components from FDA-registered manufacturers using automated equipment
  - Product tested for strength by highly specific method (e.g., HPLC)

Table B. Conditions Regarding Batch Release Tests for Sterile Drug Products

Batch Release Test

○ Test for which FDA generally does **not** intend to take regulatory action under the conditions listed

● Test expected to be performed

Conditions	Identity	Strength	Sterility	Endotoxin[c]	pH	Color	Clarity	Visible Particulates	Subvisible Particulates	Other Appropriate Specifications[d]
Tests are conducted according to these conditions ...										
1. Batch size ≥60 units[a] *or* once 60 units are produced[b]	●	●	●	●	●	●	●	●	●	●
2. Batch size <60 units, if omitted tests are performed once 60 units are produced[b]	○	○	●	●	○	●	●	○	○	○
3. Batch <10 units compounded pursuant to prescription for single patient and label bears BUD per Table D in Appendix B, if omitted tests are performed once 60 units are produced[b]	○	○	○	●	○	●	●	○	○	○
… unless conditions 4, 5, or 6 also apply. If so, choosing the least stringent option for each test among applicable conditions would be consistent with the enforcement policy set forth in this appendix.										
4. Product tested for strength (potency) by method that is highly specific (e.g., HPLC) and uses a reference standard	○	●	●	●	●	●	●	●	●	●
5. For solutions or total parenteral nutrition (TPN) only: - Compounded drug product is single dilution of FDA-approved drug product, or is made from one or more dilutions of FDA-approved drug product performed per labeling dilution instructions and using automated equipment calibrated immediately before and after production - OR - - Bulk solution but not finished drug product is tested for identity and strength immediately before filling into final and prelabeled drug product containers - OR – - Drug product is multicomponent injectable drug product (e.g., TPN product, cardioplegia solution) compounded from APIs produced only by FDA-registered manufacturers, finished product is compounded using automated equipment with validated software, and equipment is calibrated immediately before and after each personnel shift	○	○	●	●	●	●	●	●	●	●
6. Product is terminally sterilized using validated sterilization cycle that uses physical, chemical, or biological indicators	●	●	○	●	●	●	●	●	●	●

Proposed Enforcement Discretion Policies

Stability Testing

- Two approaches to establishing expiration date for label
  - Use "default Beyond Use Date (BUD)"
    - Tables in guidance; BUDs vary based on factors such as storage condition, whether sterility testing conducted, risk of microbial growth
  - Conduct limited stability testing (subset of testing performed by commercial manufacturers)
- Approach varies based on risk of volume/product
- Based on aggregate batch size in 6-month reporting period (5,000 units non-sterile; 1,000 units sterile)
  - Default BUD available to use, if below this batch size
  - If above this batch size or a longer BUD is desired, conduct limited stability testing

Proposed Enforcement Discretion Policies

Reserve Samples

- Proposed enforcement discretion policy based on level of production (high volume/product)
- Once >10,000 units are produced of a given drug product formulation and its container-closure system in a 6-month reporting period, reserve samples are collected from production of each subsequent 1,000 units for the remainder of the current reporting period and for the entire subsequent 6-month reporting period.

Proposed Enforcement Discretion Policies

Reserve Samples (continued)

- Reserve sample is retained and stored under the labeled storage conditions and in the same immediate container-closure system in which the drug product is marketed or in one that has essentially the same characteristics
- Reserve sample is held for at least 30 days following the expiration date
- Reserve sample consists of at least the quantity of drug product necessary for all tests required at release, except for sterility and pyrogen testing

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Questions?


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