Quality Considerations for Transition Biological Products

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Learning Objectives

- Understand the chemistry, manufacturing, and controls (CMC) considerations for biological products subject to the transition provision, upon being deemed BLAs on March 23, 2020.

Challenge Questions

- Name three CMC considerations for biological products subject to the transition provision, upon being deemed BLAs on March 23, 2020.

Outline

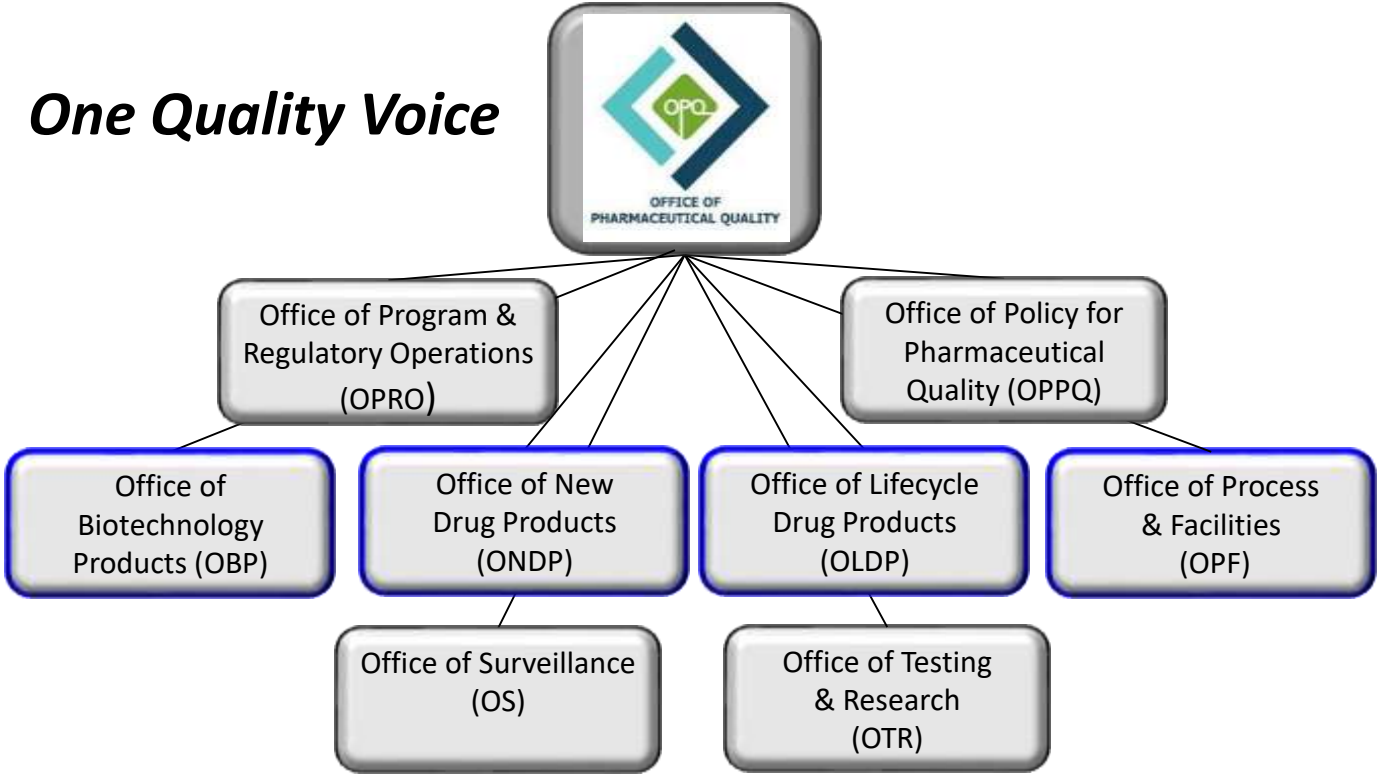
- Review responsibility of OPQ offices with regard to drug substances composed of amino acids polymers
- Expectations after March 23, 2020
  - CMC/quality considerations

CMC/quality considerations

Quality Assessments Responsibilities

CDER Office of Pharmaceutical Quality

One Quality Voice



The Office of Pharmaceutical Quality (OPQ) assures that quality medicines are available for the American public.

Quality Assessment Responsibility in OPQ for Products Containing Drug Substances Composed of Amino Acid Polymers

Size (# aa)	Manufacturing Process	Responsibilities
≤40	• Made entirely by chemical synthesis • Derived from a biological source	ONDP for INDs ONDP and OPF for original applications OLDP and OPF for supplements to approved applications
41-99	• Made entirely by chemical synthesis	
	• Derived from a biological source	OBP for INDs OBP and OPF for original applications and supplements to approved applications
≥100	• Derived from a biological source • Made entirely by chemical synthesis	

MAPP 5016.3: *Responsibility in OPQ for the Integrated Quality Assessment of Products Containing Drug Substances Composed of Amino Acid Polymers*

CMC/quality considerations

Expectations after March 23, 2020

Section 7002(e)(4) of the BPCI Act

<u>On March 23, 2020</u>, an ***approved application*** for a biological product under section 505 of the FD&C Act ***shall be deemed to be a license*** for the biological product under section 351 of the PHS Act [i.e., an approved BLA].

CMC Considerations for Deemed BLAs

- Expected impact should be minimal
  - CMC requirements under both the PHS Act and the FD&C Act address many of the same types of CMC considerations for ensuring quality biological products
  - FDA anticipates most biological products subject to the transition provision, upon being deemed BLAs, will meet related general BLA requirements (e.g., **potency, sterility, purity, and identity**) under the PHS Act based on the products having been previously approved under the FD&C Act

CMC Considerations:

Requirements to report or provide different information

1. Lot Release
2. Distribution reports
3. Notification of manufacturing problems involving distributed products

CMC Considerations:

Requirements to report or provide different information

1. Lot Release (21 CFR 601.2)

- FDA may require BLA holders to submit samples and CMC data for each lot of product for FDA review and release.

FDA generally does not anticipate that lot release requirements will apply to deemed BLAs

- Eliminated for well-characterized biotechnology products (60 FR 63048, December 8, 1995; 61 FR 24227, May 14, 1996)
- Once a company has demonstrated its ability to consistently produce acceptable lots and has procedures in place to prevent the release of lots that do not meet release specifications based on product history, it is not necessary to verify lot release – FDA generally considers this the case for deemed BLAs

CMC Considerations:

Requirements to report or provide different information

2. Distribution reports (21 CFR 600.81)

- 6 months report (in contrast to annual reporting for NDAs under 21 CFR 314.81); more granular information than required by NDAs
  - anticipate that the information is already available
  - may request a waiver to provide product distribution reports annually (21 CFR 600.90)

CMC Considerations:

Requirements to report or provide different information

3. Notification of manufacturing problems involving distributed products (21 CFR 600.14)

- change in reporting from Field Alert Report (FAR) for NDAs to Biological Product Deviation Report (BPDR) for BLAs
  - BPDR submitted within 45 calendar days / FAR submitted within 3 calendar days
  - FDA expects the change in reporting will present minimal burden to holders of deemed BLAs

CMC Considerations:

Post-approval changes

At the time that FDA deems the approved NDA for a biological product to be a BLA on March 23, 2020, FDA intends to also **administratively convert any pending supplement** to such approved NDA to a pending supplement to the deemed BLA, and **to review such supplements under applicable standards for BLAs**

CMC Considerations:

Post-approval changes

- Same expectations to demonstrate the post-change product continues to be of acceptable quality
- Limited differences with respect to:
  - **Timing and evaluation** of certain data in submissions
  - **Verification** of these data during review cycle and inspection
  - **Validation data** (e.g., required to be submitted in BLA supplements)

CMC Considerations:
Post-approval changes

- Supplements for process or manufacturing site changes must contain process validation (PV) data (21 CFR 601.12)
  - process performed at commercial manufacturing scale
  - PV to be conducted prior to submission of supplement; data to be included in supplement
- Comparability data: extent commensurate with the type of change (e.g., extended characterization per ICH Q5E)
  - Assess the impact of the change on Critical Quality Attributes (e.g., Potency) as it relates to safety and efficacy
- Batch analysis data
- Stability data

CMC Considerations:

Post-approval changes

- Supplements for site changes or for major manufacturing changes may be subject to an **inspection**
  - Provide production schedules for the complete product in the sBLA
  - Ready for inspection and manufacturing the product for which the change is requested during the supplement review time
  - Must comply with the inspection requirement specified in relevant regulations of 21 CFR 600

Summary

- Definition of “biological product” includes “protein (except any chemically synthesized polypeptide)”
- On March 23, 2020, an approved application for a biological product under section 505 of the FD&C Act will be “deemed to be a license” (BLA) under the PHS Act
- CMC considerations:
  - Lot release, distribution reports, post-approval changes, inspections

Thank you for your attention!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ADMINISTRATION

CMC/quality considerations

Master Files

BLAs and Master Files

- FDA currently does not permit BLAs for biological products to incorporate by reference drug substance (DS), drug substance intermediate (DSI), or drug product (DP) information contained in Drug Master Files (DMFs)

- Biological products regulated under section 505 of the FD&C Act have been able to incorporate by reference information on DS, DSI, or DP contained in DMFs

BLAs and Master Files (proposed rule)

- An application for a biological product approved under section 505 of the FD&C Act and deemed to be a license on March 23, 2020, and, on March 23 2020, incorporated by reference DS, DSI or DP information contained in a DMF under § 314.420 **may continue to incorporate by reference information contained in that DMF after being deemed a BLA**.

- Would codify FDA's existing practice that an application for a biological product under the PHS Act may rely on a master file, except for information regarding a DS, DSI, or DP.

- Would codify FDA's existing practice that information from a master file, including DS, DSI, or DP information, may be relied on at the investigational phase of any BLA.