

US FDA update: Recent Trends in the Regulation of Biopharmaceuticals

CMC Strategy Forum Europe 2019

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Disclaimer

This presentation reflects the views of the presenter and should not be construed to represent FDA's views or policies.

Outline

- Office of Pharmaceutical Quality
- Updates on Biosimilars
- Updates on the “deemed to be a license” provision of the BPCI Act

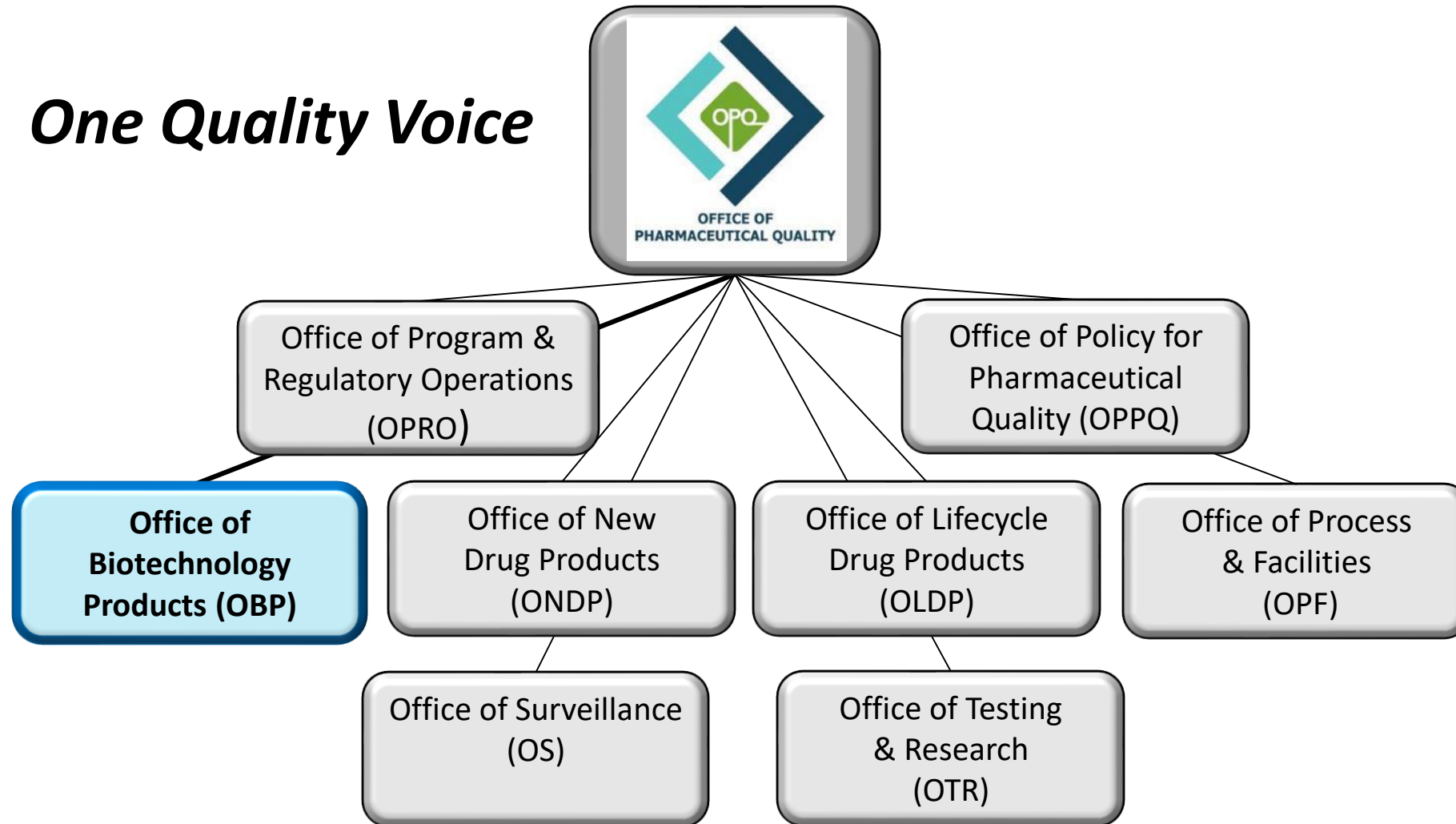


OFFICE OF PHARMACEUTICAL QUALITY

CDER Office of Pharmaceutical Quality

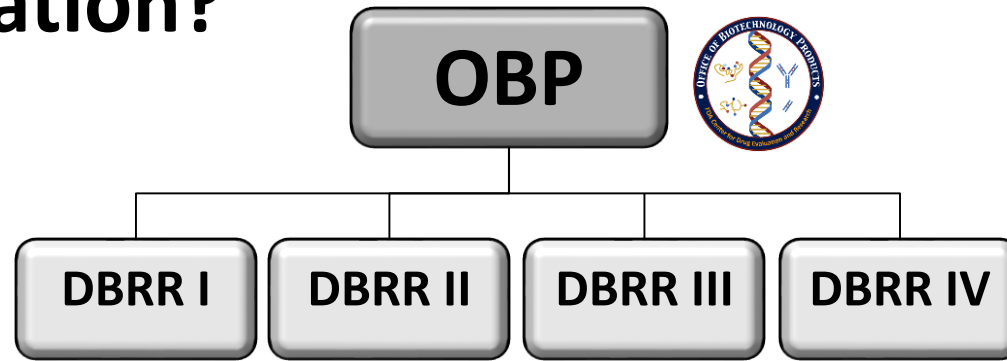


One Quality Voice



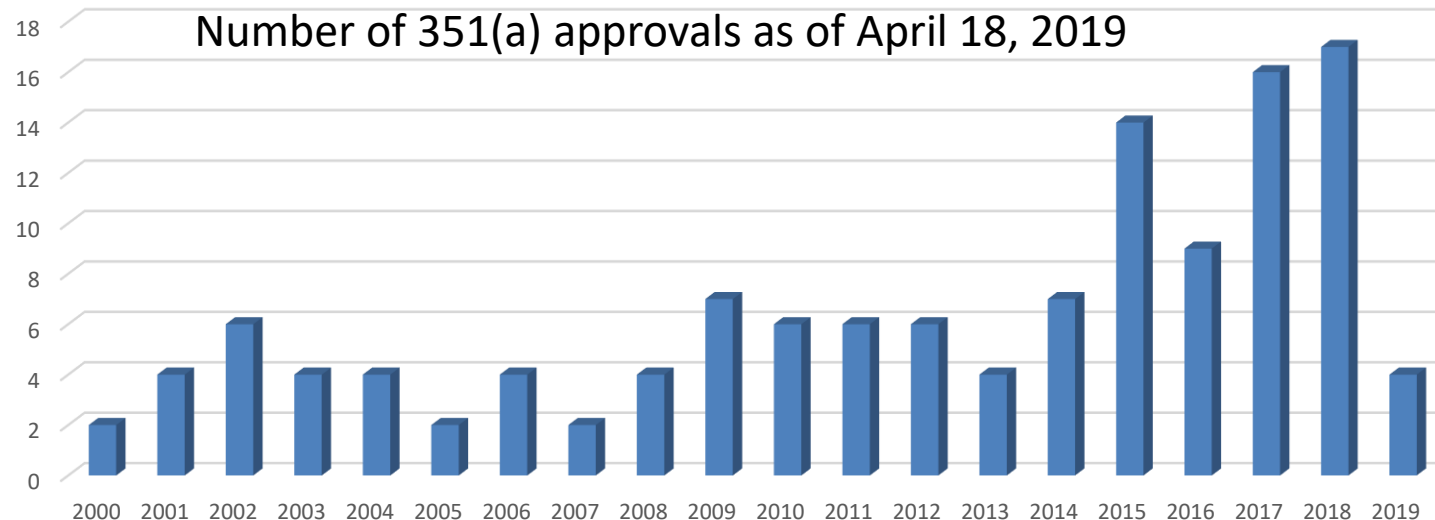
The Office of Pharmaceutical Quality (OPQ) assures that quality medicines are available for the American public.

Who reviews the CMC sections of your Biologic License Application?



*DBRR: Division of Biotechnology Review and Research

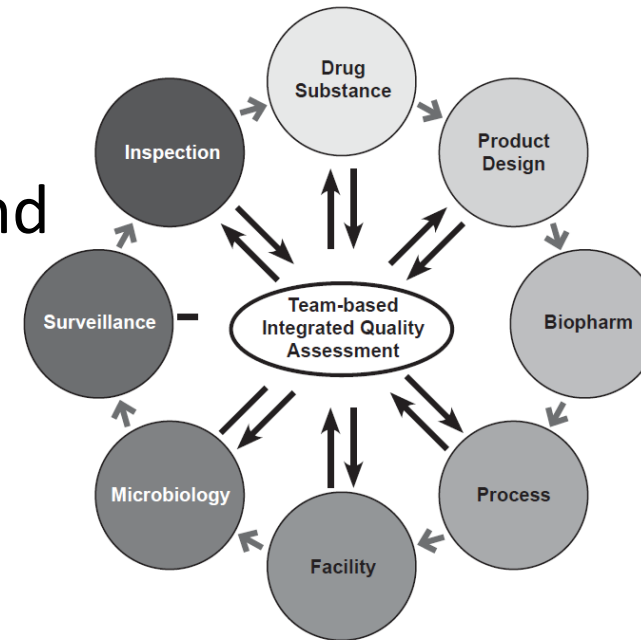
- OBP has four divisions and operates as a fully integrated unit within OPQ
- OBP is responsible for the quality review of BLAs for monoclonal antibodies and therapeutic proteins at CDER



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Team-based Integrated Quality Assessment (IQA)

- Multidisciplinary team, maximize team members expertise
- Integrates review and inspection activities
- Provides aligned patient-focused and risk-based drug product quality recommendations
 - drug substance, drug product, manufacturing, and facilities
- Approximately 20 BLAs have been approved so far employing the IQA approach





UPDATES ON BIOSIMILARS

Biosimilars: Background

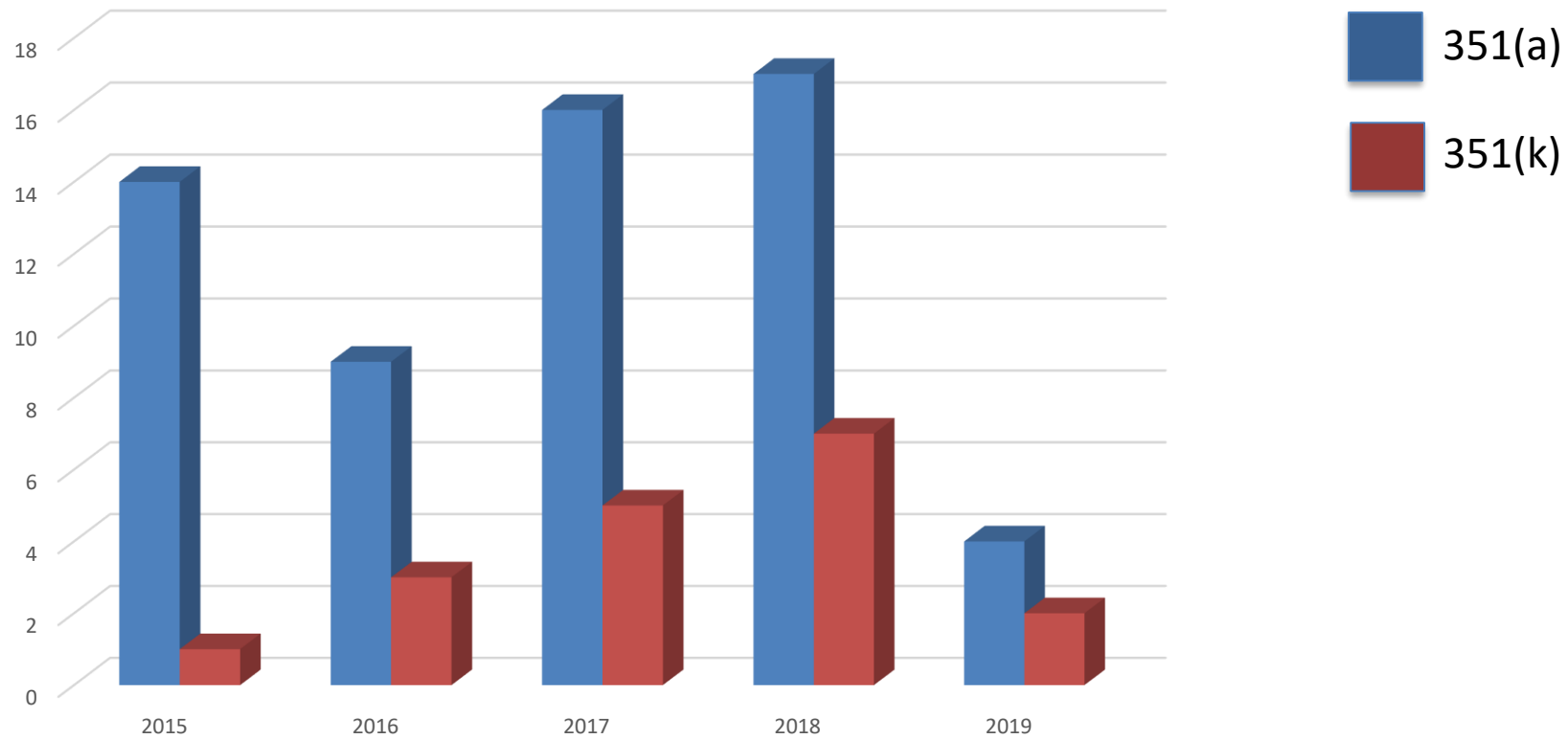


- The Biologics Price Competition and Innovation Act of 2009 (**BPCI Act**) created an ***abbreviated licensure pathway for biological products shown to be biosimilar to or interchangeable with*** an FDA-licensed reference product.
- Biosimilar or Biosimilarity means that:
 - the biological product is **highly similar** to the reference product notwithstanding minor differences in clinically inactive components; and
 - there are **no clinically meaningful differences** between the biological product and the reference product in terms of the safety, purity, and potency of the product.
- The ability to rely on FDA’s previous finding regarding the reference product to support approval of the biosimilar product allows for a potentially shorter and less costly drug development program.
- Once a biosimilar or interchangeable is approved by FDA, patients and health care providers are able to rely upon the safety and effectiveness of an FDA-approved biosimilar or interchangeable product just as they would for the reference product that the biosimilar was compared to.

Status of the biosimilar program

- **As of May 1, 2019, 78 programs** were enrolled in the Biosimilar Product Development (BPD) Program. CDER has received meeting requests to discuss the development of biosimilars for **36** different reference products.
- FDA is prohibited from publicly disclosing the existence of a pending application, unless the existence of the application has been previously publicly disclosed or acknowledged, because this information is confidential and belongs to the manufacturer/sponsor developing the drug.
- Since program inception and as of **May, 2019, 16** companies have publicly announced submission of **29** 351(k) BLAs to FDA.
- **As of May 1, 2019 nineteen** 351(k) BLAs for biosimilar products have been approved.
 - Zarxio (filgrastim-sndz) – Approved 3/6/15 (Neupogen)
 - Inflectra (infliximab-dyyb) – Approved 4/5/16 (Remicade)
 - Erelzi (etanercept-szsz) – Approved 8/30/16 (Enbrel)
 - Amjetiva (adalimumab-atto) – Approved 9/23/16 (Humira)
 - Renflexis (infliximab-abda) – Approved 4/21/17 (Remicade)
 - Cyltezo (adalimumab-adbm) – Approved 8/25/17 (Humira)
 - Mvasi (bevacizumab-awwb) – Approved 9/14/17 (Avastin)
 - Ogivri (trastuzumab-dkst) – Approved 12/1/17 (Herceptin)
 - Ixifi (infliximab-qbtx) – Approved 12/13/17 (Remicade)
 - Retacrit (epoetin alfa-epbx) – Approved 5/15/18 (Epogen)
 - Fulphila (pegfilgrastim-jmdb) – Approved 6/4/18 (Neulasta)
 - Nivestym (filgrastim-aafi) – Approved 7/20/18 (Neupogen)
 - Hyrimoz (adalimumab-adaz) – Approved 10/30/18 (Humira)
 - Udencya (pegfilgrastim-cbqv) – Approved 11/2/18 (Neulasta)
 - Truxima (rituximab-abbs) – Approved 11/28/2018 (Rituxan)
 - Herzuma (trastuzumab-pkrb) – Approved 12/14/18 (Herceptin)
 - Ontruzant (trastuzumab-dttb) – Approved 1/18/2019 (Herceptin)
 - Trazimera (trastuzumab-qyyp) – Approved 3/11/2019 (Herceptin)
 - Eticovo (etanercept-ykro) – Approved 4/25/2019 (Enbrel)

351(a) and 351(k) approvals in CDER



New and Revised Draft Q&A on Biosimilar Development and the BPCI Act (Revision 2)

- Q.I.20. What is the type of information that a sponsor should provide to support a post-approval manufacturing change for a licensed biosimilar product?
 - Principles outlined in the ICHQ5E guidelines
 - Sufficient data and information (commensurate with the type of manufacturing change) to support comparability, using a sufficient number of pre- and post-change lots
 - Comparison with historical data

THE “DEEMED TO BE A LICENSE” PROVISION OF THE BPCI ACT

FDA resources on the interpretation of the “deemed to be a license” and other related BPCI Act provisions

- Definition of the Term “Biological Product”, **proposed rule**
- Interpretation of the “Deemed to be a License” Provision of the Biologics Price Competition and Innovation Act of 2009 Guidance for Industry, **final guidance**
- The “Deemed to be a License” Provision of the BPCI Act Questions and Answers Guidance for Industry, **draft guidance**
- **MAPP 5016.3**: Responsibility in OPQ for the Integrated Quality Assessment of Products Containing Drug Substances Composed of Amino Acid Polymers
- FDA Webpage on the “Deemed to be a License” Provision of the BPCI Act (available at <https://www.fda.gov/drugs/guidance-compliance-regulatory-information/deemed-be-license-provision-bpci-act>)

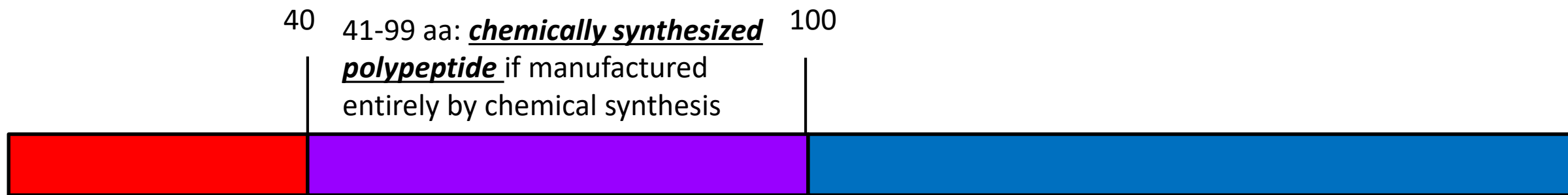
Background



- Although the majority of therapeutic biological products have been licensed under the PHS Act, some protein products (e.g., insulin and insulin analogs, human growth hormone, pancreatic enzymes, reproductive hormones) historically have been approved in new drug applications (NDAs) under the FD&C Act.
- BPCI Act amended the definition of “biological product” in section 351(i) of the PHS Act to include a “protein (except any chemically synthesized polypeptide).”
- Interpretation of Statutory Terms: To implement the amended definition of “biological product,” FDA described its proposed interpretation* of the following statutory terms:
 - **Protein**: Any alpha amino acid polymer with a specific defined sequence that is greater than 40 amino acids in size.
 - **Chemically synthesized polypeptide**: Any alpha amino acid polymer that:
 1. is made entirely by chemical synthesis; and
 2. is greater than 40 amino acids but less than 100 amino acids in size.

* Definition of the Term “Biological Product”, Proposed Rule December 12, 2018 (83 FR 63817); New and Revised Draft Q&As on Biosimilar Development and the BPCI Act (Revision 2): Draft Guidance

Definition of the Term “Biological Product” (Proposed Rule)



40 or fewer aa:
peptide regardless
of the method of
manufacture

> 40 aa: ***protein*** (regulated as a biological product if 41-99 aa and derived from biological sources or ≥100 aa regardless of the method of manufacture)

MAPP 5016.3: policy

- Outline review responsibility of OPQ offices with regard to drug substances composed of amino acids polymers
- OPQ divided products across offices based on the size of the drug substance and method of manufacture
- For mixtures, number of amino acids and manufacturing process are factors for considerations in responsibility for quality assessments
- OPQ offices will consult and collaborate when expertise is shared across offices

MAPP 5016.3: Assignment of Review Responsibilities

Size (number of amino acids)	Manufacturing Process	Responsibilities
≤40	<ul style="list-style-type: none"> 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
	<ul style="list-style-type: none"> Made entirely by chemical synthesis 	
41-99	<ul style="list-style-type: none"> Derived from a biological source 	OBP for INDs
	<ul style="list-style-type: none"> Made entirely by chemical synthesis 	
≥100	<ul style="list-style-type: none"> Derived from a biological source 	OBP and OPF for original applications and supplements to approved applications
	<ul style="list-style-type: none"> Made entirely by chemical synthesis 	

Section 7002(e) of the BPCI Act



- A marketing application for a “biological product” ***must be submitted*** under section 351 of the PHS Act.
 - **Exception**: An application for a biological product ***may be submitted*** under section 505 of the FD&C Act ***not later than March 23, 2020***, if the biological product is in a “product class” for which a biological product in such class was approved under § 505 of the FD&C Act not later than 3/23/10.
 - **Limitation**: The exception does not apply if there is another biological product licensed under section 351(a) of the PHS Act that could be a “reference product” if the application were submitted under section 351(k) of the PHS Act.
- **On March 23, 2020**, 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 [i.e., an approved BLA] under section 351 of the PHS Act.

Q&A Draft Guidance on “Deemed to be a License” Provision

- Procedural information: examples
 - BLA number, license number, identification of products
 - Type of application [(a) vs (k)], discontinued applications, user fee
- Differences in statutory and regulatory requirements; examples
 - Labeling
 - **CMC requirements**
- Transition from Orange Book to Purple Book
- Compliance policy for requirement related to labeling

CMC Considerations for Deemed BLAs

- FDA expects that in many instances the practical implications of differences in CMC requirements between the FD&C Act and PHS Act on holders of deemed BLAs will be minimal because the 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.
- Holders of deemed BLAs may be required to report or provide different information than is required for biological products under the FD&C Act, including for example:
 - Lot release:
 - 21 CFR 601.2, FDA may require BLA holders to submit samples and CMC data.
 - Waived for well-characterized biotechnology products
 - May be waived once company has demonstrated its ability to consistently produce acceptable lots
 - Most biological products subject to transition provision would meet either condition for waiving lot release requirements and FDA generally does not anticipate that lot release requirements will apply for biological products approved in NDAs that are deemed to be BLAs
 - Distribution reports
 - 6 months report, more granular information than required by NDA, anticipate that the information is already available
 - Notification of manufacturing problems involving distributed products - FDA expects the change in reporting between FAR and BPDR will present minimal burden to holders of deemed BLAs

CMC Supplements to Deemed BLAs

- When FDA deems the approved NDA to be a BLA on 3/23/20, FDA plans to administratively convert any pending supplement to such NDA to be a pending supplement to the deemed BLA, and to review such supplements under applicable BLA standards
- Changes to approved application to be submitted in supplements
 - Same expectations to demonstrate the post change product continues to be of acceptable quality
 - Limited differences in timing and evaluation of certain data, and verification of these data during review cycle and inspection (e.g, validation data)
 - Comparability data, extent commensurate with the type of change (e.g, extended characterization)
 - Batch analysis data
 - Stability data

CMC Supplements to Deemed BLAs

- Facility inspections
 - After March 23, 2020 supplement submitted to deemed BLAs must comply with the inspection requirement specified in relevant regulations of 21CFR600
 - Supplements for site changes where facilities are added to the license or supplements for major manufacturing change may be subject to an inspection
 - Ready for inspection and manufacturing the product for which the change is requested during the supplement review time



Thank you for your attention!

Questions?