POLICY AND PROCEDURES

OFFICE OF PHARMACEUTICAL QUALITY

Responsibility for the Quality Assessment of Products Containing Peptide or Protein Drug Substances

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PURPOSE

- This MAPP describes how the responsibility for the quality assessments[1] of products containing peptide or protein drug substances will be divided among the suboffices of the Office of Pharmaceutical Quality (OPQ).[2]

- This MAPP serves as a guide for the Office of New Drugs and the OPQ Office of Program and Regulatory Operations (OPRO) to direct submissions and manage other interactions regarding the quality assessments among the Office of Biotechnology Products (OBP), the Office of Lifecycle Drug Products (OLDP), the Office of New Drug Products (ONDP), and the Office of Pharmaceutical Manufacturing Assessment (OPMA), including OPMA's Division of Biotechnology Manufacturing (DBM).

- The policy and procedures described in this MAPP apply to the quality assessments performed by OPQ for all original investigational new drug applications (INDs), IND amendments, original new drug applications

[1] Original new drug applications (NDAs) and biologics license applications (BLAs) are assessed by an integrated quality assessment team. Investigational new drug applications (INDs) and supplements to applications are assessed by an application assessment team, which may not involve team members who typically would be assigned to an integrated quality assessment team. For convenience, this MAPP uses *quality assessment* throughout.

[2] The assignment of responsibility for a quality assessment as described in this MAPP does not constitute an Agency determination of whether a product is or is not a biological product or whether a product will be regulated under the Public Health Service Act or the Federal Food, Drug, and Cosmetic Act.

(NDAs), original biologics license applications (BLAs), NDA and BLA amendments, supplements to approved NDAs and BLAs, and emergency use authorizations (EUAs) for products containing peptide and/or protein drug substances.

- This MAPP does not apply to:
  - Abbreviated new drug applications (ANDAs)
  - Products containing an amino acid polymer that is used solely as an excipient.[3]

BACKGROUND

- Currently, OPQ suboffices including OBP, OLDP, ONDP, and OPMA perform product quality assessments for products ranging in size and complexity from small peptides to large glycoproteins. The manufacturing processes used by sponsors and applicants for these products include, but are not limited to, chemical synthesis, purification from a naturally occurring biological source, and application of biotechnology.

- The Biologics Price Competition and Innovation Act of 2009 clarified the statutory authority under which certain protein products will be regulated by amending the definition of *biological product* in section 351(i) of the Public Health Service Act (PHS Act) to include "a protein (except any chemically synthesized polypeptide)" and describing procedures for submission of a marketing application for certain biological products.[4] Section 605 of the Further Consolidated Appropriations Act, 2020 (Public Law 116-94) removed the parenthetical "(except any chemically synthesized polypeptide)" from the category of *protein* in the definition of *biological product* in section 351(i)(1) of the PHS Act.

- FDA's regulations in 21 CFR 600.3(h)(6) state that the term *protein* means "any alpha amino acid polymer with a specific, defined sequence that is greater than 40 amino acids in size. When two or more amino acid chains in an amino acid polymer are associated with each other in a manner that occurs in nature, the size of the amino acid polymer for purposes of this [definition] will be based on the total number of amino acids in those chains, and will not be limited to the number of amino acids in a contiguous sequence."

[3] The terms *excipient* and *inactive ingredient* often are used interchangeably. In this MAPP, *excipient* means any inactive ingredient that is added intentionally to therapeutic and diagnostic products and is not intended to exert therapeutic effects at the intended dosage, although it may act to improve product delivery.

[4] Sections 7001–7003 of the Patient Protection and Affordable Care Act (Public Law 111-148).

- FDA considers any amino acid polymer composed of 40 or fewer amino acids to be a peptide and not a protein.[5]

POLICY

- OPQ will divide the responsibilities for the quality assessments of products containing peptide or protein drug substances among the suboffices (OBP, OLDP, ONDP, and OPMA, including OPMA/DBM) based on whether the size of the drug substance molecule is either ≤40 amino acids or ≥41 amino acids, regardless of its method of manufacture (whether chemically synthesized, purified from a naturally occurring biological source, or biotechnologically derived).

- Additional considerations for determining the responsibility for the quality assessments of products containing peptide or protein drug substances are described below:

    - For a combination product[6] that contains both a protein drug substance as a constituent part and a non-protein drug substance as a constituent part and for which the responsibility for the quality assessment of the constituent parts falls to different OPQ sub-offices, the quality assessment will be a collaborative effort within OPQ.

    - For a product in which the drug substance is composed of a mixture of identified protein and/or peptide components,[7] the amino acid polymer component with the greatest number of amino acids will be used to determine where the responsibility in OPQ for the quality assessment.

    - For a product in which a drug substance is composed of an amino acid polymer, but the above scenarios do not apply, the responsibility in OPQ for the quality assessment will be determined on a case-by-case basis.

    - OPQ suboffices will collaborate with each other when multiple offices have expertise that could contribute to the quality assessments of these products including policy, review, and/or inspectional issues.

    - OPQ suboffices will address and resolve, if possible, any disputes

[5] See the proposed rule, "Definition of the Term 'Biological Product'" ("FDA proposes to consider any polymer composed of 40 or fewer amino acids to be a peptide and not a protein.") (83 FR 63817, December 12, 2018, codified at 21 CFR 600.3(h)(6)).
[6] See the definition of *combination product* at 21 CFR 3.2(e).
[7] For example, a product in which the drug substance is composed of a mixture of peptides and/or proteins extracted from a plant part or an animal tissue.

concerning the responsibility for the quality assessments of these products. If a resolution cannot be obtained, the matter will be brought to the OPQ Deputy Director of Science.

PROCEDURES

- OPRO will use the criteria summarized in the table in the attachment and any applicable additional considerations described above when requesting assessor assignments, directing submissions, and managing other interactions regarding the responsibilities for the quality assessments for INDs, NDAs, BLAs, and supplements (including amendments) submitted for products containing peptide or protein drug substances.

- OPQ suboffices will provide information to help OPRO decide which OPQ suboffice is responsible for the quality assessment, when requested by OPRO.

- OPQ will use established procedures and responsibilities for the implementation of this MAPP.

REFERENCES

- Draft guidance for industry and review staff *Good Review Management Principles and Practices for New Drug Applications and Biologics License Applications* (September 2018)[8]

- MAPP 4150.1 *Role and Procedures of the CDER Ombudsman*

- MAPP 4151.8 Rev. 1 *Equal Voice: Collaboration and Regulatory and Policy Decision-Making in CDER*

- MAPP 6025.1 *Good Review Practices*

- 21 CFR 600.3, Definitions

EFFECTIVE DATE

- This MAPP is effective upon date of publication.

[8] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

CHANGE CONTROL TABLE

Effective Date	Revision Number	Revisions
12/11/2018	n/a	Initial
6/21/2023	1	Updated policy and procedures to conform to Section 605 of the Further Consolidated Appropriations Act, 2020 and the codification of 21 CFR 600.3(h)(6). Other updates are also included to reflect current policy and procedures.

ATTACHMENT

Responsibilities for Quality Assessments of Products Containing Peptide or Protein Drug Substances

Size (Expressed in Number of Amino Acids)	Submission Type[a]	Responsible OPQ Suboffice[b]
≤40	IND	ONDP
	Treatment IND or treatment protocol	ONDP and OPMA
	Original NDA	ONDP and OPMA
	Supplement to approved NDA	OLDP and OPMA
	EUA	ONDP and OPMA
≥41	IND	OBP
	Treatment IND or treatment protocol	OBP and OPMA/DBM
	Original BLA	OBP and OPMA/DBM
	Supplement to approved BLA	OBP and OPMA/DBM
	EUA	OBP and OPMA/DBM

[a] Submission types include amendments.
[b] Assignments also apply to meetings that occur under respective submission types.