POLICY AND PROCEDURES

OFFICE OF PHARMACEUTICAL QUALITY

Quality Assessment for Products in Expedited Programs

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PURPOSE

This MAPP outlines policies and procedures used in the Office of Pharmaceutical Quality (OPQ) that are intended to facilitate and expedite the development, time to submission, assessment, and marketing approval of new drug applications (NDAs) and biologics license applications (BLAs) for products that address unmet medical needs in the treatment of serious or life-threatening conditions.[1]

This document is intended to help fulfill the chemistry, manufacturing, and controls (CMC) readiness commitments described in the Prescription Drug User Fee Act (PDUFA) VII commitment letter,[2] including the publication of a MAPP on approaches to address CMC challenges for Center for Drug Evaluation and Research (CDER) regulated products with accelerated clinical development timelines. This document also supports the CMC readiness pilot program outlined in the PDUFA VII commitment letter.

[1] In this MAPP, approval of a BLA refers to approval of a BLA or issuance of a license as described in 21 CFR 601.2(d).

[2] *PDUFA Reauthorization Performance Goals and Procedures – Fiscal Years 2023 through 2027*. PDUFA-related documents can be found on the FDA PDUFA webpage at https://www.fda.gov/industry/fda-user-fee-programs/prescription-drug-user-fee-amendments.

BACKGROUND

As detailed in the PDUFA VII commitment letter, products with accelerated clinical development timelines often face challenges in expediting CMC development activities. Overcoming CMC challenges to achieve earlier patient access to these products often requires additional interactions with the Food and Drug Administration (FDA) and the use of science-based and risk-based regulatory approaches.

This MAPP provides information on OPQ's use of regulatory flexibilities contemplated in 21 CFR 314.105(c) and as interpreted in publicly available guidances,[3] to help overcome CMC readiness challenges. This MAPP applies to OPQ's facilitation of CMC development for breakthrough therapy (BT) products, fast track (FT) products, and products included in the CMC readiness pilot described in the PDUFA VII commitment letter.[4] The approaches described in this MAPP may also be considered for certain other products, such as those that:

Diagnose, treat, mitigate, cure, or prevent a serious disease or medical condition, including products addressing a public health emergency (e.g., COVID-19) for which there is no other appropriate and available treatment

Address drug shortages (e.g., drugs to address shortages during the COVID-19 public health emergency, shortages caused by heparin contamination)

Have an orphan drug designation

This MAPP is specific to products that are seeking approval as NDAs or BLAs[5] and does not cover other mechanisms that may be used to facilitate the availability of critical drugs to patients (e.g., Emergency Use Authorizations).

[3] See the guidance for industry *Benefit-Risk Assessment for New Drug and Biological Products* (September 2021) and the guidance for industry *Expedited Programs for Serious Conditions—Drugs and Biologics* (May 2014). We update guidances periodically. 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. See also the draft guidance for industry *Benefit-Risk Considerations for Product Quality Assessments* (May 2022). When final, this guidance will represent the FDA's current thinking on this topic.

[4] This MAPP is focused on products with breakthrough therapy designation, fast track designation, and those in the PDUFA VII CMC readiness pilot, including products that also are on an accelerated approval pathway or have received a priority review designation. However, accelerated approval or priority review, alone, would not be sufficient for this MAPP to apply.

[5] In this MAPP, the term "BLA" means a "351(a) BLA" – i.e., a BLA submitted under Section 351(a) of the Public Health Service Act (PHS Act) and not a BLA submitted under Section 351(k) of the PHS Act for a biosimilar or interchangeable biological protein product.

POLICY

- As explained in the guidance for industry *Expedited Programs for Serious Conditions—Drugs and Biologics* (May 2014), FDA may exercise some flexibility on the type and extent of manufacturing information that is expected at the time of submission and approval for certain components normally expected in an application (e.g., stability updates, validation strategies, inspection planning, manufacturing scale-up). Although some flexibility on the expected information may be considered, the applicant must ensure the availability of a quality product at the time of approval.

- OPQ will consider applying regulatory flexibility options to marketing applications for products within the scope of this MAPP.[6] Such consideration will be based on adequate clinical, nonclinical, and manufacturing information provided to meet the standards for approval[7] regarding safety, effectiveness, and quality, including Current Good Manufacturing Practice (CGMP) requirements.

- When considering regulatory flexibility options, OPQ will conduct risk assessments according to the principles provided in the guidance for industry *Expedited Programs for Serious Conditions—Drugs and Biologics* (May 2014).

- Regulatory flexibility options will be determined on a case-by-case basis, considering modern pharmaceutical principles such as:

  – The extent of product and process understanding as described in the ICH guidances for industry *Q8(R2) Pharmaceutical Development* (November 2009) and *Q11 Development and Manufacture of Drug Substances* (November 2012).

  – The strength of the quality risk management approach as described in the ICH guidance for industry *Q9(R1) Quality Risk Management* (May 2023).

  – The effectiveness of the pharmaceutical quality system as described in the ICH guidance for industry *Q10 Pharmaceutical Quality System* (April 2009).

  – The adequacy of the sponsor's proposal for an integrated postmarketing plan based on the principles described in the ICH guidance for industry *Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management* (May 2021), such as the use of comparability protocols

[6] For more on regulatory flexibility options, please see section four of the procedures section of this MAPP, titled "Consider Regulatory Flexibility Options."

[7] For NDAs, see section 505 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355). For BLAs, see section 351 of the PHS Act (42 U.S.C. 262).

(CPs), CMC postmarketing commitments (PMC),[8] and product lifecycle management documents, where applicable, to define and manage established conditions.[9]

RESPONSIBILITIES

OPQ will continue to follow current application assessment practices, including those described in MAPP 6025.7 Rev. 1 *Good Review Practice: Review of Marketing Applications for Breakthrough Therapy-Designated Drugs and Biologics That Are Receiving an Expedited Review* (February 2024). Additional responsibilities are noted below.

OPQ Assessment Team[10]

- Works with sponsors to enable early engagement to address CMC challenges for products in expedited development programs when CMC development is scheduled for discussion. Such engagement includes meetings scheduled following the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products* (Rev 1)(September 2023)[11] and CMC-focused meetings — including meetings provided under PDUFA VII for products enrolled in the CMC readiness pilot program.

- Works with sponsors to facilitate overall product quality development and advises sponsors on strategies to prioritize activities to produce a data and information package for the marketing application submission that includes all elements needed to meet approval requirements.

- Consistently communicates with sponsors regarding strategies to expedite CMC development.

- Considers regulatory flexibility options, such as those described in this MAPP, to facilitate expediting CMC development and marketing application submission.

[8] The draft guidance for industry *Benefit-Risk Considerations for Product Quality Assessments* (May 2022) uses the term quality postmarketing agreement (QPA) to mean the same as PMC. When final, this guidance will represent the FDA's current thinking on this topic.

[9] For more information on product lifecycle management and established conditions, please see the draft guidance for industry *ICH Q12: Implementation Considerations for FDA-Regulated Products* (May 2021). When final, this guidance will represent the FDA's current thinking on this topic.

[10] The terms "OPQ assessment team" and "OPQ" are used interchangeably throughout this MAPP.

[11] When final, this guidance will represent the FDA's current thinking on this topic.

Regulatory Business Process Manager (RBPM)

- Acts as the OPQ point of contact for the Office of New Drugs (OND) regulatory project manager.

- Acts as the OPQ point of contact for OPQ-managed meetings (e.g., CMC-focused meetings) and other OPQ communications with the sponsor during the IND phase for products covered in the scope of this MAPP.

- Distributes product quality-specific information from sponsors, and internal communications to the product quality assessment team, so that all assessment team members remain aware of the drug development plan's status.

Product Quality Assessor

- Performs a scientific assessment of incoming investigational new drug application (IND), NDA, and BLA submissions and documents assessment findings, as appropriate.

- Assesses CMC-related IND submission materials prior to meetings to identify key quality issues, assessment concerns, and corresponding manufacturing development priorities.

- Identifies issues with the development program, proposes potential solutions, and communicates issues as soon as possible to the RBPM, discipline secondary assessor, and appropriate management in the OPQ sub-office. Shares any concerns with other relevant disciplines.

Discipline Secondary Assessor

- Identifies CMC development issues (e.g., based on the product quality assessments of the IND submission) and works with the product quality assessor, RBPM, and sub-office management, to determine mechanisms to resolve issues; provides guidance on approaches to facilitate CMC development; and strategically manages negotiations with the sponsor.

PROCEDURES

1. Expedited Program Designation

    a. OND will identify products that qualify for BT or FT expedited program designation, and other expedited development decisions, based on evidence that the product has potential to diagnose, treat, or prevent a

serious disease or condition for an unmet medical need, and otherwise meets the qualifying criteria.[12]

b. OND will inform the OPQ RBPM of the designation.

c. The OPQ RBPM will notify the OPQ assessment team of the OND designation.

2. Meetings and Communications

a. The OPQ assessment team will work with sponsors to schedule a CMC-focused meeting as soon as possible. CMC-focused meetings could be requested, for example as:

i. **Type B** meetings for products with expedited designations of BT,[13] FT, or those enrolled in the PDUFA VII CMC readiness pilot.

ii. **Type C** meetings for products without BT or FT designation that are not enrolled in the CMC readiness pilot.

b. Starting at the initial CMC-focused meeting, OPQ will:

i. Determine the sponsor's progress to date in terms of product development, including manufacturing process development and a plan for commercial manufacturing.

ii. Understand the sponsor's strategy to ensure that the proposed commercial facilities are ready for commercial manufacturing under CGMP.

iii. Identify potential regulatory opportunities to expedite CMC development, within a benefit-risk framework as established in the guidance for industry *Benefit-Risk Assessment for New Drug and Biological Products* (October 2023) and in the draft guidance for industry *Benefit-Risk Considerations for Product Quality Assessments* (May 2022).[14] This includes consideration of the data and information to be submitted and the timing of submission (e.g., in the marketing application at the time of submission, during assessment, or postapproval).

[12] For a description of qualifying criteria for BT and FT designations, see the guidance for industry *Expedited Programs for Serious Conditions—Drugs and Biologics* (May 2014).

[13] For products receiving a BT designation, a CMC-focused Type B meeting is a separate meeting from the multidisciplinary meeting automatically triggered when a product receives the BT designation.

[14] When final, this guidance will represent the FDA's current thinking on this topic.

iv. Establish a communication plan for future interactions with the sponsor to refine and reach agreement on regulatory approaches.

3. Expedited Manufacturing Facility Readiness

a. As described in the guidance for industry *Expedited Programs for Serious Conditions—Drugs and Biologics* (May 2014), early availability of CMC information is important for planning inspection activities and to ensure that manufacturing facilities are ready for inspection.

b. To facilitate a successful marketing application and enable FDA to appropriately expedite any necessary steps for facility assessments, OPQ will convey as early as possible (e.g., at the earliest CMC-focused meeting) the importance of having key information, such as:

i. Information recommended in the guidance for industry *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER: Questions and Answers* (October 2019), including:

1. Identification of the intended commercial facilities (e.g., commercial-scale manufacturing, testing, and packaging facilities), including relevant facilities from cross-referenced drug master files (DMFs) that will be included in the marketing application. This includes the name, address, FDA Establishment Identifier number, Data Universal Numbering System (DUNS) number, and local contacts for all facilities that will be involved in commercial manufacturing activities.

2. Identification, if applicable, of any non-commercial facilities that will generate data needed to support marketing application approval.

3. Letter(s) of Authorization to Type II DMF(s) to be cross-referenced in the application.

4. A description of the proposed commercial manufacturing process, including a comparison to the clinical manufacturing process.

5. The sponsor’s plans to ensure that commercial facilities are CGMP compliant.

6. The proposed commercial launching strategy, if atypical (e.g., launch with stockpiled clinical batches or concurrent validation/concurrent release batches).

c. OPQ will inform the sponsor, as appropriate, that commercial facility information may be submitted as an amendment to the IND.

d. If the commercial facility information has not been submitted by the time of the pre-NDA/BLA meeting, for rolling NDA/BLA submissions, FDA will inform the sponsor that early submission of Form FDA 356h with any complete module is an option.[15] This approach is only an option when changes to commercial facilities are not anticipated before submission of the CMC module.

e. For BLAs, OPQ will advise the sponsor to submit a complete manufacturing schedule that covers the BLA review period for each intermediate (if applicable), drug substance, and drug product. The sponsor should be advised to submit the production schedules before the BLA submission.

f. Upon receiving the facility information, OPQ's Office of Pharmaceutical Manufacturing Assessment (OPMA) will assess the facilities, and, if applicable, will seek input from the Office of Inspections and Investigations (OII). The assessment will be based on the facility information submitted to the IND and other available information, such as:

   i. Past inspections by FDA

   ii. Assessment of records or information previously requested under section 704(a)(4) of the FD&C Act

   iii. Inspection reports from other trusted foreign regulatory partners obtained through mutual recognition agreements

   iv. Adverse event reports

   v. Facility compliance history

   vi. Other FDA records and available information

[15] For BT and FT designated products, the sponsor should be encouraged to submit a request for rolling review as indicated in the guidance for industry *Expedited Programs for Serious Conditions—Drugs and Biologics* (May 2014). Specifically refer to the guidance footnote 41 and Appendix 2.

g. Based on the facility risk assessment, OPQ will make related determinations, such as:

i. Recommend accepting the facility.

ii. Attempt to mitigate identified facility risks using remote regulatory assessments, such as information requested under section 704(a)(4) of the FD&C Act or remote interaction evaluation.

iii. Conduct preapproval inspections (PAI) or pre-license inspections (PLI).

4. Consider Regulatory Flexibility Options[16]

a. Control Strategies[17]

i. The amount of flexibility in a control strategy is based on the totality of product and process understanding (e.g., prior knowledge, development studies) in the context of quality risk management principles described in the ICH guidance for industry *Q9 (R1) Quality Risk Management*.[18] For sponsors with enhanced product and process knowledge, OPQ may allow the use of wider acceptance criteria for certain attributes and process parameter ranges beyond the sponsor's manufacturing and clinical experience with the subject product.

ii. OPQ will communicate as early as possible with sponsors that they need to:

1. Develop a thorough understanding of their product, manufacturing process, and analytical capabilities.

2. Discuss their plans with OPQ to establish commercial control strategies as early as possible. This will ensure that

[16] These are some examples of regulatory flexibility approaches that can be considered by the OPQ assessment team under the guidance for industry *Expedited Programs for Serious Conditions – Drugs and Biologics* (May 2014). This list is not exhaustive. Other approaches consistent with applicable guidances can be considered.

[17] ICH guidance for industry *Q10 Pharmaceutical Quality System* (April 2009) and guidance for industry *Q8, Q9 & Q10 Questions and Answers—Appendix: Q&As from Training Sessions* (August 2012).

[18] See control strategy information in the ICH guidances for industry *Q8(R2) Pharmaceutical Development* (November 2009) and *Q11 Development and Manufacture of Drug Substances* (November 2012).

sponsors have time to generate sufficient CMC information to justify their proposed commercial control strategy for inclusion in the original marketing application.

iii. Based on the sponsor's justification of their commercial control strategy and benefit-risk considerations,[19] OPQ may consider the product context of use[20] and all available sources of information provided by the sponsor, such as:

1. Publicly available information

2. Studies relevant to the context of use (e.g., data from in vitro and in vivo data)

3. Prior knowledge[21]

iv. Where sponsors for expedited development products have more limited product and process understanding due to, for example, limited manufacturing and clinical experience, OPQ can consider an *adapted control strategy* which could include:

1. Additional testing as part of specifications, additional in-process testing, narrower acceptance criteria, more process parameters as established conditions, and narrower process parameter ranges.[22]

2. Use of a CP as provided in 21 CFR 314.70(e) and 601.12(e), to change the control strategy postapproval, including establishing a CMC PMC to revise specifications

[19] See the benefit-risk principles applied by FDA when assessing the CMC information on NDAs and BLAs in the draft guidance for industry *Benefit-Risk Considerations for Product Quality Assessments* (May 2022). When final, this guidance will represent the FDA's current thinking on this topic.

[20] Examples include: dosage form, dosing regimen, route of administration, proposed clinical indication(s), and intended patient population(s).

[21] Prior knowledge includes the sponsor's knowledge gained from experience developing and manufacturing similar products or with similar processes (e.g., platform knowledge), established scientific principles, and information available in peer-reviewed scientific publications. Any use of prior knowledge in an application will be consistent with applicable legal and regulatory constraints.

[22] See ICH guidance for industry *Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management* (May 2021).

once the sponsor gains more knowledge and experience with the product.

3. If there is an orthogonal or replacement method under development at the time of approval, but the control strategy is otherwise approvable, OPQ should consider asking for the method to be added to the control strategy postapproval (e.g., reporting per 21 CFR 314.70(b) and 601.12(b)) as a CMC PMC.

b. Process Validation[23]

i. OPQ will communicate the applicable statutory and regulatory requirements, and guidance recommendations, regarding process validation to sponsors:

1. Process validation for drugs is required to be successfully completed prior to commercial distribution under section 501(a)(2)(B) of the FD&C Act.

2. Process validation is required in both general and specific terms by CGMP regulations at 21 CFR parts 210 and 211.[24]

3. While separate CGMP regulations for drug components—such as active pharmaceutical ingredients and intermediates—have not been promulgated, these components are still subject to the statutory CGMP requirements of section 501(a)(2)(B) of the FD&C Act.[25]

4. Additional FDA recommendations on process validation can be found in existing guidance documents, such as the guidance for industry *Process Validation: General Principles and Practices* (January 2011), which includes

[23] Validation activities are a topic of interest in trying to expedite approval and commercial distribution of products in expedited development programs.

[24] This includes the foundation of process validation in 21 CFR 211.110(a), sampling and testing in § 211.110(a), sampling requirements in § 211.160(b)(3), § 211.165(c) and (d), batch specification requirements in § 211.165(a), in-process specifications in § 211.110(b), product quality reviews in § 211.180(e), facility expectations in § 211.42, and equipment expectations in § 211.63 and § 211.68.

[25] Process validation for active pharmaceutical ingredients is discussed in the ICH guidance for industry *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients* (September 2016).

information on the different types and stages of process validation.

ii. **For NDAs**: Stage 1 of process validation (i.e., development and scale-up activities to define the commercial manufacturing process) should be included in the application. Stage 2 of process validation (i.e., process qualification where the commercial process is evaluated to demonstrate reproducibility) must be completed before commercial distribution, but the information does not need to be submitted to the application. Stage 2 can be reviewed during inspections. However, complete sterility assurance validation data should be submitted in the application.[26]

iii. **For BLAs**: Stage 2 process validation information is generally considered necessary in the application to ensure that the process consistently delivers a product that is safe, pure, and potent.[27] BLAs typically include the data and information from both Stage 1 and Stage 2 validation to support approval, including the Stage 2 validation protocol and report.[28]

iv. OPQ will communicate with sponsors who indicate an intent to pursue an alternate approach to process validation that the approach should be discussed as early as possible in a CMC-focused meeting.

v. For products in expedited development programs, OPQ will consider different approaches to streamline Stage 2 validation activities — if supported by the amount of product and process knowledge, including from Stage 1 process validation activities. Such approaches include, but are not limited to:

[26] See 21 CFR 211.113(b) and guidance for industry *Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products* (November 1994).

[27] 42 U.S.C. 262(a)(2)(C)); see also 21 CFR 601.2(a) and 601.20(c).

[28] For information on validation of biological drug substances, see ICH guidance for industry *Q11 Development and Manufacture of Drug Substances* (November 2012).

1. Performing certain CMC confirmatory studies postapproval

2. Decoupling validation of drug substance and drug product processes

3. Using a concurrent release approach

c. Concurrent Release (CR)

i. OPQ may, on rare occasions, consider accepting an approach involving CR of process performance qualification (PPQ) batches from Stage 2 validation activities as detailed in the guidance for industry *Process Validation: General Principles and Practices* (January 2011). For example, OPQ may consider accepting a plan for the commercial release of Stage 2 validation batches before complete execution of all the validation protocol steps and activities.

ii. OPQ may accept such CR plan proposals when OPQ's evaluation indicates that:

1. Available data supports that the process is in a state of control and is capable of consistently delivering quality product adhering to predetermined specifications and quality attributes. OPQ considerations include process development studies, prior knowledge, platform knowledge, supportive data from small scale models, and data from non-PPQ batches (including clinical batches) manufactured using the commercial manufacturing process.

2. All related commercial equipment and testing methods are appropriately qualified and validated.

iii. For BLAs, OPQ will assess and ensure that the CR protocol contains release specifications, all relevant in-process controls, process parameters, and any additional monitoring and evaluation that is necessary as a part of the process validation activities. This includes ensuring that the proposed acceptance criteria for all tests in the protocol are appropriately justified.

1. OPQ will discuss with the sponsor what data from the CR protocol will be submitted in the original application (e.g., data from one PPQ batch), what data will be submitted postapproval, and how the data will be submitted postapproval (e.g., a changes being effected (CBE) supplement).

iv. For both NDAs and BLAs, OPQ will ensure that there is a commitment to submit the stability data from the PPQ batches to the application postapproval.

d. Decoupling Drug Substance and Drug Product Process Validation

i. Because both drug substance and drug product processes need to be validated, Stage 2 validation protocols often include using drug substance validation batches to manufacture drug product validation batches.[29] To expedite development, OPQ will assess alternate proposals, including performing drug substance PPQ activities in parallel to the drug product PPQ activities based upon finding that such an approach is justified, e.g., there is evidence that the manufacturing process of drug substance used for the drug product PPQ batches is representative of the commercial drug substance manufacturing process.

e. OPQ considers other process validation streamlining approaches. For example, consistent with ICH Q11, validation of certain unit operations can be performed at reduced scale and then confirmed postapproval at commercial scale.

f. Analytical Procedures Validation

i. As described in the guidance for industry *Analytical Procedures and Methods Validation for Drug and Biologics* (July 2015), OPQ will confirm the following:

1. Each NDA includes the analytical procedures necessary to ensure the identity, strength, quality, purity, and potency of the drug substance and drug product.[30]

2. Each BLA includes a full description of the manufacturing process, including analytical procedures, that demonstrate the manufactured product meets prescribed standards of identity, quality, safety, purity, and potency.[31]

3. Data establishes that the analytical procedures used in testing meet proper standards of accuracy, sensitivity,

[29] Guidance for industry *Process Validation: General Principles and Practices* (January 2011).

[30] See 21 CFR 314.50(d)(1).

[31] See 21 CFR 601.2(a) and 601.2(c).

specificity, and reproducibility and are suitable for their intended purpose.[32]

ii. OPQ will consider whether it may be possible for the sponsor to submit certain confirmatory method validation information postapproval when it has been determined that the control strategy is acceptable for approval. For example, if changes are needed in a method validation protocol, OPQ may ask for the changes to be implemented as a postapproval commitment (e.g., confirmation of the method validation as a CMC PMC).

g. Marketing of Batches Manufactured with the Clinical Manufacturing Process

i. In cases where sponsors intend to scale-up their clinical manufacturing process for commercial manufacturing — but scale-up activities will delay commercial launch of the product — OPQ will consider commercial distribution of batches manufactured with the clinical manufacturing process.

ii. In this scenario, commercial distribution could be initiated with batches from the clinical-scale manufacturing process from a facility that has no prior commercial manufacturing experience (e.g., a clinical manufacturing site), or from a preexisting commercial manufacturing facility. OPQ will:

1. Identify the manufacturing facilities that will produce batches for commercial distribution in the application.

2. Ensure that any material that is commercially distributed will meet FDA's standards (e.g., manufactured under CGMP conditions).

3. Assess evidence of facility readiness for inspection of the manufacturing sites, if needed, and ensure that the inspection can be conducted in a timely manner to support approval of the application.

4. For BLAs, ensure that the Stage 2 process validation for the clinical process is submitted in the application and is acceptable. For NDAs, remind the sponsor that this Stage 2 process validation must be completed prior to commercial distribution.

[32] See 21 CFR 211.165(e) and 211.194(a)(2).

5. Ensure, if applicable, that there is a postapproval commitment to complete scale-up activities in a timely manner.

6. Inform the sponsor that scaling up the manufacturing process postapproval can be facilitated by including a CP[33] in the marketing application under 21 CFR 314.70(e) or 601.12(e).

iii. In the scenario above, where the clinical manufacturing process will be the initial commercial process, OPQ will consider proposals from sponsors to commercially distribute stockpiled clinical batches. In this scenario, the facility that manufactured the stockpiled clinical batches will be listed as a commercial manufacturing facility in the marketing application. OPQ will ensure that the criteria above are met (e.g., batches were manufactured under CGMP conditions, readiness of the facility for inspection, as necessary). In addition, OPQ will ensure that stockpiled batches:

1. Were manufactured using a process that is representative of the commercial process.

2. Are reflective of the intended commercial control strategy, including meeting any relevant changes made during the review of the application. For example, batches should meet updated specifications if the sponsor made changes in specifications during review of the application to address FDA concerns.

3. The batches will be distributed with the approved labeling, including the container closure labeling.[34]

h. Stability Studies

i. OPQ will evaluate drug substance and drug product stability as per relevant guidances, including ICH guidances for industry *Q1A(R2)*

[33] See the guidance for industry *Comparability Protocols for Postapproval Changes to the Chemistry, Manufacturing, and Controls Information in an NDA, ANDA, or BLA* (October 2022). See also ICH guidance for industry *Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management* (May 2021).

[34] Sponsors using foreign manufacturing facilities might be encouraged to submit a Pre-Launch Activities Importation Request, so that the product can be in the country, waiting to be labeled and staged upon approval. See the guidance for industry *Pre-Launch Activities Importation Requests (PLAIR)* (March 2022).

Stability Testing of New Drug Substances and Products (November 2003), *Q1E: Evaluation of Stability Data* (June 2004), and *Q5C Quality of Biotechnology Products: Stability Testing of Biotechnology/Biological Products* (July 1996).

ii. OPQ may consider allowing a variety of regulatory flexibility options for potential NDAs and BLAs by considering all the available data and information from the sponsor, including information about process and product knowledge, stability data from supportive batches, and any relevant prior knowledge.

iii. If a sponsor proposes alternate approaches to the stability data intended to support the proposed retest period[35] and shelf life,[36] OPQ will advise the sponsor to:

1. Discuss the proposal with OPQ as early as possible.

2. Provide the proposed stability strategy for establishing a shelf life and/or retest period prior to the pre-NDA or pre-BLA meeting (e.g., at a CMC-focused meeting).

3. Include the proposed final stability strategy in the pre-NDA or pre-BLA meeting package. The proposed final strategy should include what data and information will be provided at the time of filing and what will be provided during application review to ensure that sufficient data will be included in the marketing application to support approval.

4. Seek agreement with OPQ on the proposed final stability strategy at the pre-NDA or pre-BLA meeting.

[35] In this MAPP, the term "retest period" means the time during which the drug substance remains within its specification and, therefore, can be used in the manufacture of a given drug product, provided that the drug substance has been stored under the defined conditions. For most biotechnological/biological substances known to be labile, it is more appropriate to establish a shelf life for the drug substance than a retest period. See the guidance for industry *Q1A(R2) Stability Testing of New Drug Substances and Products* (November 2003).

[36] In this MAPP, the term "shelf-life" means the time during which a drug product remains within the approved shelf-life specification, if it is stored under the conditions defined on the container label. The term is also used for drug substance for biotechnology/biological products. See the ICH guidance for industry *Q1A(R2) Stability Testing of New Drug Substances and Products* (November 2003).

iv. OPQ may apply regulatory flexibility based on a holistic assessment, such as accepting or allowing an application to have:

1. Less than the recommended data for primary stability batches at the time of submission (e.g., submission of 6 months real-time primary stability data, along with accelerated data at the time of filing) with an agreement that additional stability data will be submitted during the review of the marketing application.

2. Stability data from batches that differ in size from the recommendations in ICH guidance for industry *Q1A(R2) Stability Testing of New Drug Substances and Products* (November 2003).

3. The use of real-time stability data from batches other than the primary stability batches of the drug substance or drug product (i.e., supportive stability data). In this situation, the supportive stability data may help to establish a retest or shelf life that is longer than what would be possible if relying on the primary stability batches alone. For supportive stability data, OPQ will assess comparability to ensure that batches are representative of the to-be-marketed product, with any differences explained and justified. If comparability between the primary and supportive stability batches is demonstrated, real-time data from these supportive stability batches can be considered in establishing the retest period or shelf life.

4. Prior knowledge consisting of stability data from other products may support a longer retest or shelf life than the primary stability batches alone. To rely on prior knowledge, OPQ will ensure that there is sufficient information to justify the scientific relevance of the specific data being relied upon from those other products. This could include, for example, a comparison and evaluation of

potential adverse effect of any differences between products in terms of:

a. physical and chemical characteristics of the active pharmaceutical ingredient

b. susceptibility to environmental conditions

c. formulations

d. manufacturing processes

e. analytical testing

f. container closure systems

i. Use of Predictive Stability Models

i. Consistent with ICH guidance for industry *Q1A(R2) Stability Testing of New Drug Substances and Products* (November 2003), NDAs can include mathematical modeling of stability data from drug substance and drug product to establish shelf life and retest dates beyond the long-term data from the primary stability batches. For NDAs, OPQ will consider proposals using predictive stability models.

ii. Predictive stability modeling is not recommended when the attributes that will be used to set the retest period or shelf-life are not amenable to modeling. Since the degradation of a biologic DS or DP is unlikely to be governed by attributes that are amenable to mathematical modeling, we do not generally recommend predictive stability modeling for BLAs at this time. However, predictive stability modeling could be considered for BLAs if sufficiently justified.

iii. Predictive stability modeling may be used to establish comparability of primary and supportive stability batches so that the supportive batches can establish the retest period or shelf-life. For example, modeling on data from accelerated stability studies from both clinical and commercial process batches could be used — as part of a comparability assessment — to support the use of

long-term stability data from clinical batches in establishing the retest period of the drug substance and/or shelf-life of the product.

iv. In this context, OPQ will:

1. Communicate with sponsors that if they intend to pursue predictive stability modeling other than as detailed in the ICH guidance for industry *Q1E Evaluation of Stability Data* (June 2004), the use of the model should be agreed upon between the sponsor and OPQ by no later than the pre-NDA meeting.

2. Inform the Office of Policy for Pharmaceutical Quality (OPPQ) that a sponsor is proposing to use an alternative stability modeling approach.

3. Evaluate the proposed model and the supportive information provided for its reliability and validity, including data on the use of the proposed predictive model for the specific proposed product (described in the NDA) or similar products. For example:

    a. Data and information assuring the capability of the model to capture all relevant stability factors (e.g., temperature, humidity, light conditions).

    b. Validation data demonstrating that the model's kinetic assumptions are appropriate.

    c. Information supporting that the model is applicable to the commercial container closure system.

    d. Information identifying situations when the model would not be appropriate.

    e. Information on whether the product stability-indicating critical quality attributes (CQAs) were considered in establishing the proposed model. If any of the identified stability-indicating CQAs (from the current or related products) were not considered during model qualification, then OPQ should recommend to sponsors that they requalify

the model, adding these new CQAs, or reconsider the use of the model.

REFERENCES

Draft Guidances for Industry[37]

1. Draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products* (Rev 1)(September 2023)

2. Draft guidance for industry *ICH Q12: Implementation Considerations for FDA-Regulated Products* (May 2021)

3. Draft guidance for industry *Benefit-Risk Considerations for Product Quality Assessments* (May 2022)

Guidances for Industry

1. Guidance for industry *Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products* (November 1994)

2. Guidance for industry *Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products* (July 1996)

3. Guidance for industry *Process Validation: General Principles and Practices* (January 2011)

4. Guidance for industry *Q8, Q9 & Q10 Questions and Answers—–Appendix: Q&As from Training Sessions* (August 2012)

5. Guidance for industry *Expedited Programs for Serious Conditions—–Drugs and Biologics* (May 2014)

6. Guidance for industry *Analytical Procedures and Methods Validation for Drug and Biologics* (July 2015)

7. Guidance for industry *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER: Questions and Answers* (October 2019)

[37] When final, these guidances will represent the FDA's current thinking on these topics.

8. Guidance for industry *Comparability Protocols for Postapproval Changes to the Chemistry, Manufacturing, and Controls Information in an NDA, ANDA, or BLA* (October 2022)

9. Guidance for industry *Benefit-Risk Assessment for New Drug and Biological Products* (October 2023)

10. Guidance for industry *Pre-Launch Activities Importation Requests (PLAIR)* (March 2022)

ICH Guidances for Industry

1. ICH guidance for industry *Q5C Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products* (July 1996)

2. ICH guidance for industry *Q1A(R2) Stability Testing of New Drug Substances and Products* (November 2003)

3. ICH guidance for industry, *Q1E Evaluation of Stability Data* (June 2004)

4. ICH guidance for industry *Q9(R1) Quality Risk Management* (January 2023)

5. ICH guidance for industry *Q10 Pharmaceutical Quality System* (April 2009)

6. ICH guidance for industry *Q8(R2) Pharmaceutical Development* (November 2009)

7. ICH guidance for industry *Process Validation: General Principles and Practices* (January 2011)

8. ICH guidance for industry *Q11 Development and Manufacture of Drug Substances* (November 2012)

9. ICH guidance for industry *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients* (September 2016)

10. ICH guidance for industry *Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management* (May 2021)

Manuals of Policies and Procedures

1. MAPP 6025.7 Rev. 1 *Good Review Practice: Review of Marketing Applications for Breakthrough Therapy-Designated Drugs and Biologics That Are Receiving an Expedited Review* (February 2024)

EFFECTIVE DATE

- This MAPP is effective upon date of publication.

CHANGE CONTROL TABLE

Effective Date	Revision Number	Revisions
12/7/2022	Initial	N/A
2/14/2025	Rev. 1	Revised to make administrative changes to reflect OPQ reorganization and updated references
7/31/2025	N/A	Corrected one typo. Moved from internal to public MAPPs site.