December 2023

Committee for Medicinal Products for Human Use (CHMP)

EMA–FDA joint Q&As on Quality and GMP aspects of PRIME/Breakthrough therapy applications

Introduction

EMA's PRIority MEdicines (PRIME) scheme[1] and FDA's breakthrough therapy (BT) designation program[2] are designed to help speed development of innovative products which address unmet medical needs. For products included in these expedited development programs, the marketing application is still expected to include all the clinical, non-clinical, and chemistry, manufacturing, and control (CMC) information to meet approval standards. Because generating CMC information on more compressed timelines can present challenges for companies, EMA and FDA have been engaging in open dialogue with industry stakeholders in order to explore approaches to expedite the development and approval of these products without lowering the standards that patients have come to expect in a medicine. To this end, on 26 November 2018, EMA and FDA organized a stakeholder workshop on quality development in early access approaches, such as PRIME and Breakthrough Therapies. This workshop focused on potential scientific and regulatory approaches to address challenges associated with expedited product development, so that robust quality and manufacturing data packages will be submitted to enable timely access to medicines for patients whilst assuring that product safety, efficacy, and quality will not be compromised.

During the workshop, challenges and solutions were explored by a combination of real case studies from industry [covering chemical molecules, biologicals, and advanced therapy medicinal products (ATMPs)] and regulators' perspectives and panel discussions.

Based on the experience with PRIME and BT programs, regulators and industry selected the following areas for discussion: process validation, control strategy, compliance with Current Good Manufacturing Practice (GMP) requirements, comparability, stability and regulatory tools. The discussions and main conclusions from the workshop, including scientific elements and regulatory tools which already exist,

[1] For detailed information on the PRIME scheme please refer to: *PRIME: priority medicines | European Medicines Agency (europa.eu)*. From an EMA perspective, this document complements the *EMA* Toolbox guidance on scientific elements and regulatory tools to support quality data packages for PRIME and certain marketing authorisation applications targeting an unmet medical need - Scientific guideline | European Medicines Agency (europa.eu)

[2] From an FDA/CDER perspective, this document provides information on the use of regulatory flexibilities contemplated in 21 CFR 314.105 (c) and as interpreted in publicly available guidance and the Center for Drugs Evaluation and Research MAPP 5015.13 *Quality Assessment for Products in Expedited Programs*. See also 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). FDA updates 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. In addition, see the draft guidance for industry *Benefit-Risk Considerations for Product Quality Assessments Guidance for Industry* (May 2022). When final, this guidance will represent the FDA's current thinking on this topic.

See websites for contact details

European Medicines Agency www.ema.europa.eu
U.S. Food and Drug Administration www.fda.gov

An agency of the European Union

or which would benefit from exploration, to help address development challenges, were captured in a meeting report. During the workshop, FDA and EMA also reflected on areas that would benefit from further discussion between both regions and identified the following topics: control strategy, innovative process validation approaches, stability data, and launching from the clinical manufacturing site or with investigational medicinal product batches.

In addition, it was recognized that, in certain cases, where an application otherwise meets the standards of approval, it may be possible to mitigate certain risks through the submission of data post-approval.

As detailed in ICH Q12, this includes the use of:

- Post-approval change management protocols to support changes anticipated during the lifecycle of the product.
- CMC commitments to outline a plan of which certain development data will be gathered post-approval and to define how these data will be analysed, assessed, and reported to the regulatory authority

Since the workshop in 2018, EMA and FDA's Center for Drugs Evaluation and Research (CDER) have been engaging in further discussions on these topics, sharing their experiences and regulatory expectations in the context of PRIME/BT applications. As an outcome of these discussions, these four consensus Questions and Answers (Q&A) documents have been prepared to compile EMA and FDA/CDER current thinking as reflected in existing guidance documents. These are presented as annexes to the original workshop report.

For EMA, these Q&As are applicable to chemical and biological medicinal products for human use, including complex biologicals (such as ATMPs), unless stated otherwise. For FDA, these additional discussions and the resulting annexes are only applicable to *CDER-regulated* products. Therefore, all references in the annexes to biological products are intended to refer to CDER-regulated biological human drug products only. Center for Biologics Evaluation and Research (CBER) -regulated products, such as advanced therapy medicinal products (ATMPs), are **not** in the scope of these documents.

These documents are only intended to provide general information and do not constitute regulatory guidance. Applicants interested in pursuing the approaches described in these Q&A documents should discuss the strategy required for their specific product with the relevant regulatory authority ahead of their marketing submission.

Annex 1. Q&A on Control strategy considerations for PRIME/BT applications

Annex 2. Q&A on Process validation approaches for PRIME/BT applications

Annex 3. Q&A on Alternatives for determination of re-test period or shelf-life for PRIME/BT applications

Annex 4. Q&A on GMP considerations for PRIME/BT applications

Glossary of Terms

Alternative tools to evaluate facilities: These are the alternative tools to inspections that a regulatory authority may use to evaluate facilities. This includes requesting existing inspection reports from other trusted foreign regulatory partners, requesting information from applicants, requesting records and other information directly from facilities and other inspected entities, and conducting remote interactive evaluations.

Dosage form: a pharmaceutical product type (e.g., tablet, capsule, solution, cream) that contains a drug substance generally, but not necessarily, in association with excipients (as per ICH Q1A).

Drug product (DP): the dosage form in the final immediate packaging intended for marketing (as per ICH Q1A).

Drug substance (DS): the unformulated drug substance that may subsequently be formulated with excipients to produce the dosage form (as per ICH Q1(A)). For biotechnology products, DS can be composed of the desired product, product-related substances, and product- and process-related impurities. It may also contain excipients including other components such as buffers (per ICH Q6B).

Expiration date: the date placed on the container label of a drug product designating the time prior to which a batch of the product is expected to remain within the approved shelf-life specification, if stored under defined conditions, and after which it should not be used (per ICH Q1A).

Inspection: for the purposes of this document, "inspection" covers general GMP inspection as well as preapproval/pre-licensing inspections.

Marketing Authorisation: in the context of these annexes,

- Marketing authorisation dossier (or dossier) is used synonymously with marketing application
- Marketing authorisation is used synonymously with "approved applications". For CDER, this includes products with Breakthrough Product Designation that are New Drug applications (NDAs) approved under Section 505 of the Food Drug and Cosmetic Act or Biologics License Applications (BLAs) licensed under section 351 of the PHS Act.[3]

Post Approval Change Management Protocol[4] **(PACMP)**: A protocol describing a CMC change that an applicant intends to implement during the commercial phase of a product lifecycle, how the change would be prepared and verified, including assessment of the impact of the proposed change, and the suggested reporting category in line with regional regulations and guidance (per ICH Q12).

Post-approval CMC commitments[5,6]: specified CMC development activities, agreed between the MAH and regulatory authority at the time of approval (e.g., specific process monitoring, additional testing) that will be performed during the commercial phase should be documented.

Primary batch: a batch of a drug substance or drug product used in a formal stability study, from which stability data are submitted in a registration application for the purpose of establishing a retest period or shelf life, as applicable (per ICH Q1A)

[3] In this document, 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.
[4] In the US, post approval change management protocols are the same as comparability protocols as provided in 21 CFR 314.70(e) and 601.12(e).
[5] **In EU these are named Post- Authorisation Measures (PAMs)**
[6] The FDA 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.

Process performance qualification (PPQ): A formal validation activity for the manufacturing process where comprehensive manufacturing data from a sufficient number of batches is used to demonstrate that the commercial process is in a state of control. PPQ combines the actual facility, utilities, equipment, control procedures, and components to produce commercial batches. A successful PPQ will confirm the process design and demonstrate that the commercial manufacturing process performs as expected. The number of batches, often referred to as PPQ batches, required to demonstrate that the process is in a validated state depends on the variability of the process, the complexity of the process / product, process knowledge gained during development, supportive data at commercial scale, and the overall experience of the manufacturer with similar products and processes.

PPQ protocol/ Process validation scheme: a written prospective protocol that outlines the formal process validation studies to be conducted on production scale batches, specifying the manufacturing conditions, controls, testing, sampling plans and acceptance criteria. The actual process validation data generated should be provided with the submission for relevant products or available for verification post-authorisation by the regulatory authority. This can include qualification protocols for activities other than process validation (e.g., for introduction of future reference standards or cell banks); such protocols specify what data will be gathered post-approval and how it will be analysed and how/if it will be submitted to the regulatory authority.

Process design/ **process characterisation**: defining the commercial manufacturing process based on knowledge gained through development and scale-up activities. The goal is to design a process suitable for routine commercial manufacturing that can consistently deliver a medicinal product that meets its quality attributes.

Process evaluation: studies performed at small and/or commercial scale, to provide evidence that the complete manufacturing process and each step/operating unit have been appropriately designed to define the full operating ranges of the manufacturing process.

Process validation (PV): the documented collection and evaluation of data, from the process design stage through commercial production, which provides evidence that the process, operated within established parameters, is capable of consistently delivering quality product meeting its predetermined specifications and quality attributes.

Retest period: the period of time during which the drug substance is expected to remain 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. After this period, a batch of drug substance destined for use in the manufacture of a drug product should be retested for compliance with the specification and then used immediately. A batch of drug substance can be retested multiple times and a different portion of the batch used after each retest, as long as it continues to comply with the specification. For most biotechnological/biological substances known to be labile, it is more appropriate to establish a shelf life than a retest period. The same may be true for certain antibiotics (as per ICH Q1A).

Shelf-life (also referred to as expiration dating period): the length of time during which a drug product is expected to remain within the approved shelf-life specification, provided that it is stored under the conditions defined on the container label (as per ICH Q1A)

Specification: A specification is defined as a list of tests, references to analytical procedures, and appropriate acceptance criteria which are numerical limits, ranges, or other criteria for the tests described (ICH Q6A/Q6B).

Annex 1. Q&A on Control strategy considerations for PRIME/BT applications

1. How does the establishment of specifications differ for PRIME/BT programs?

PRIME/BT programs may have fewer development and commercial batches produced prior to marketing compared to traditional programs, and consequently, clinical experience with various batches and resultant product quality knowledge to set specifications may be limited, compared to traditional programs. For this reason, additional considerations may be necessary when establishing and justifying the clinical relevance of specifications for these products. This is particularly true for programs that acquired a PRIME/BT designation relatively early in development.

2. What additional considerations can be used to establish specifications and their acceptance criteria where there is limited clinical experience? Is it acceptable to have acceptance criteria wider than the test results reported for clinical batches? If so, how should they be justified?

It may be possible to establish specification acceptance criteria wider than the actual test results of the batches used in clinical studies. In this case, the limits should still be appropriately justified in terms of clinical impact (i.e., product knowledge as it relates to safety and effectiveness). Importantly, additional sources of information beyond clinical experience, can always be considered, as permitted by applicable laws and regulations, when establishing specifications and their acceptance criteria for any product, not just PRIME/BT products. 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 ICH Q9 Quality Risk Management.[7] However, it is recognised that setting specification acceptance criteria wider than clinical experience is frequently a need specifically for PRIME/BT programs.

Such additional sources of information could include but are not limited to: in vitro data, animal data, published information, prior knowledge specific to a development platform, and the impact of a potential critical quality attribute (CQA) from related development programs. In using information from other products, a comparison, and justification for any differences between products should be provided. This comparison can include, for example, context of use (e.g., dosage forms, dosing regimens, route and duration of drug administration, clinical indications, and the intended patient populations), chemical characteristics, mechanism of action, analytical testing, manufacturing processes, formulations, and container closure systems.

The justification of specification acceptance criteria for CQAs should be linked to clinical performance rather than solely derived from statistical methods such as tolerance intervals. Statistical analysis on a limited number of batches could result in acceptance criteria which are too broad and cannot be justified clinically.

3. What is the most appropriate approach for revising the specifications post-approval if it is determined to be necessary? Could a plan for revision of specifications be documented in a Post Approval Change Management Protocol (PACMP)?

While a proposed control strategy may be acceptable for initial approval, there may be a need to revise specifications post-approval when additional information becomes available. For example:

[7] Also see control strategy information in the ICH *Q8(R2) Pharmaceutical Development* (November 2009) and *Q11 Development and Manufacture of Drug Substances* (November 2012).

- Revising acceptance criteria using information gained from additional manufactured batches, with a justification based on clinical relevance;
- Re-evaluating acceptance criteria based on additional clinical experience, the availability of additional characterization data for a quality attribute, or the submission of additional studies;
- Adding an orthogonal or replacement method that was under development at the time of approval.

The strategy for future revision of specifications should ideally be planned in advance and communicated to the regulator at the time of initial approval. In this context, the use of a post approval change management protocol (PACMP), as per ICH Q12 guideline, is a possible tool that could be used.

4. ***How might an applicant adapt their control strategy to offset the reduced level of knowledge on the product and process due to expedited development? What elements of the control strategy could be adapted?***

Adapting the control strategy may be an acceptable approach, in particular for expedited development programs where there may be limited manufacturing and clinical experience and/or relatively limited product and process understanding. Such an approach may consider, for example, narrower ranges proposed for a given process parameter (PP), identification of additional CQAs/CPPs, and the inclusion of additional in-process controls or additional attributes in the specification.

For example, when there is uncertainty about:

- whether an attribute is a CQA,
- the level of risk associated with a CQA,
- the ability to measure a CQA, or
- the control of a CQA by the manufacturing process,

the control strategy will need to address the risk associated with these uncertainties.

When an adapted control strategy is used to support an initial approval, the control strategy can be revised post-approval to provide for increased flexibility (see question 3 and 6)

5. ***Should process parameters default to critical until additional process development studies are conducted post-approval? Could an intended strategy for reducing the criticality of process parameters and widening ranges be agreed in advance in a PACMP?***

Due to limited manufacturing experience or process development/process characterisation studies, there may be limited understanding of a parameter and its corresponding criticality for the manufacturing process. In such cases, a default to define process parameters as critical (i.e. CPP) may be appropriate with an intention to re-assess parameter criticality and the associated acceptance criteria post approval, as more information is obtained from practical operation of the manufacturing control strategy and clinical use of the product (see also question 4). Submission of a plan for revision could potentially be proposed in a PACMP.

6. ***How can one integrate Prior Knowledge into the control strategy for PRIME/BT Products? What types of information can be submitted? Can Prior Knowledge be used for establishing process parameters, ranges, and specifications?***[8]

[8] Any use of prior knowledge in an application should be consistent with applicable legal and regulatory constraints.

The use of Prior Knowledge is not limited to PRIME/BT programs and is considered suitable anytime it can be appropriately justified. Prior Knowledge can, for example, be used to support the justification for attribute criticality, process parameter criticality, ranges of process parameters, or limits for in-process controls or specifications. In such cases, it should be clearly explained how the information leveraged from other product(s) is relevant for the product in question (see question 2). Prior Knowledge can be useful for programs that have a particularly expedited development timeline, such as PRIME/BT. The appropriateness of the Prior Knowledge selected is dependent on the ability of an applicant to support its intended use. In addition to platform understanding of drug products and processes, understanding, as applicable on, any molecular functions, mechanism of action(s) and/or biological activity(ies) unique to the drug, or specific information regarding the context of use should also be included (e.g., a CQA that may influence immunogenicity could be viewed differently depending on the context of use, such as an immunosuppressed population).

7. What are the expectations for analytical method validation for PRIME/Breakthrough products?

The validation expectations for analytical methods are no different for PRIME/BT programs. The principles in ICH Q2 guideline on Validation of Analytical Procedures should be applied. Applicants may also refer to the draft ICH Q14 guideline on Analytical Procedure Development. Moreover, a PRIME/BT status would not necessarily support a reduced expectation for product specific analytical validation data to be included at the time of submission.

In a relatively rare instance, it may be possible to accept some supplemental method validation data post-approval. Alternative approaches to analytical method validation would typically require discussion with the regulatory authority.

Annex 2. Q&A on Process validation approaches for PRIME/BT applications

1. What are the differences in requirements for finished product process validation between chemical and biological medicinal products?

In the EU, for chemical medicinal products which are manufactured using a standard process, it is not necessary to provide production scale process validation data in the marketing authorisation dossier at the time of regulatory submission. For these products, a process validation scheme should be submitted in the dossier (3.2.R) outlining the formal process validation studies to be conducted on production scale batches. Formal validation of the commercial scale process should be completed prior to placing batches on the market. The information from the process validation studies should be available for verification post authorisation by the supervisory authority. For biological products, and chemical products manufactured using non-standard processes, process validation data should be provided in the dossier on a pre-specified number of consecutive batches at production scale prior to approval. EMA recommendations on process validation can be found in existing guidance documents, such as Process validation for finished products – information and data to be provided in regulatory submissions – Scientific guideline | European Medicines Agency (europa.eu),Process validation for the manufacture of biotechnology-derived active substances and data to be provided in the regulatory submission - Scientific guideline | European Medicines Agency (europa.eu),EU Guidelines for Good Manufacturing Practice Annex 15: Qualification and validation and EU Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products.

For FDA, 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. Process validation is required in both general and specific terms by CGMP regulations at 21 CFR parts 210 and 211. Although 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. 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) and *Q7 Good Manufacturing Practice* (September 2016) which includes information on the different types and stages of process validation. In addition,

- For chemical (i.e., new drug application or NDA) products, 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 performance qualification or PPQ, where the commercial process is evaluated to demonstrate reproducibility) must be completed before commercial distribution,[9] but the information does not need to be submitted to the application. Stage 2 can be reviewed during inspections.[10] However, complete sterility assurance validation data should be submitted in the application.[11]

In contrast, for biological products regulated by CDER (i.e., biologics license application (BLA) products) PPQ (i.e., 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.[12]

[9] Section 501(a)(2)(B) of the FD&C Act.

[10] See compliance policy guide *CPG Sec. 490.100 – Process Validation Requirements for Drug Products and Active Pharmaceutical Ingredients Subject to Pre-market Approval*. Compliance policy guides can be found at https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/compliance-manuals/manual-compliance-policy-guides.

[11] 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).

[12] 42 U.S.C. 262(a)(2)(C)); see also 21 CFR 601.2(a) and 601.20(c).

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.[13]

2. When can a concurrent validation / concurrent release of PPQ batches approach be used?

This approach can be used where there is a strong benefit-risk ratio for the patient. The use of a concurrent approach is on a case-by-case basis and might be considered for marketing medicinal products for which there is limited demand (e.g., orphan drugs), for a life threatening or severely debilitating condition, for products which have short half-lives (e.g., radiopharmaceuticals), or situations when there is an urgent demand (e.g., in case of a pandemic like COVID-19).[14]

Companies are encouraged to engage early with EMA or FDA to discuss proposals for concurrent validation/concurrent release.

3. What information should be included in a concurrent validation protocol / PPQ protocol to support concurrent release?

For all products, the protocol should include the intended scope of the validation activities, the number of batches, and the intended tests and acceptance criteria. The information specified should include the release specifications, all relevant in-process controls, process parameters, and any additional monitoring and evaluation intended as a part of the process validation activities. The proposed acceptance criteria for all tests should be appropriately justified. The proposed control strategy should ensure that only batches that meet the requirements under each regulatory jurisdiction's applicable laws and regulations be released for supply. The PPQ lots should be placed on stability.

For marketing authorisation applications where the PPQ information is normally submitted in the marketing authorisation dossier (see question 1), the validation protocol for the concurrent approach should still be provided with the marketing application and the concurrent validation approach should be described within the Pharmaceutical Quality System (PQS) in the Validation Master Plan. Any available release and stability data from the concurrent process validation batches / concurrently released batches should be included in the dossier as soon as they become available. A commitment to place the PPQ lots on stability should be reflected in the stability protocol in the application.

4. What type of data can be submitted in support of a concurrent validation protocol / PPQ protocol?

Where a concurrent validation/release is used, available data should support that the process is in a state of control and is capable of consistently delivering quality product adhering to predetermined specifications. Information to support the concurrent validation/release approach can include process development studies, prior knowledge, platform knowledge, supportive data from small scale models, and data from batches manufactured prior to PPQ/PV (including clinical batches) using the commercial manufacturing process. This information should be provided in the application. All related equipment and testing methods should be appropriately qualified and validated prior to commencing concurrent process validation.

The release of concurrent batches should also be supported by a robust risk assessment. Overall, there should be sufficient data to support a conclusion that any given batch of product is uniform and meets

[13] For information on validation of biological drug substances, see ICH

Q11 Development and Manufacture of Drug Substances (November 2012).

[14] In the EU, it can also be considered for those autologous products where the PPQ batches can only be manufactured using patient material.

In the US, these Q&A are only applicable to FDA *CDER-regulated* products, and therefore do not apply to CBER -regulated products, such as ATMPs.

the defined acceptance criteria. This should be formally documented and available prior to batch release.

5. How should the data from concurrent validation batches be submitted to the regulatory agency? Can batches be released to the market without prior approval?

In general, following the approval of a marketing application, under applicable laws and regulations, the release and distribution of new batches that have been manufactured under approved conditions (e.g., in accordance with the terms of the concurrent validation protocol) will generally not be subject to regulatory approval prior to release.

For marketing applications where PPQ data would have normally been submitted, the applicant should submit the concurrent process validation data to the regulatory authority post-approval.

- In the EU, several mechanisms exist for providing such data to the EMA, for example a Recommendation, Annex II condition or Specific Obligation. The most appropriate mechanism will be decided on a case-by-case basis and will depend on the overall data package and level of risk.
- In the US, for marketing applications where PPQ data would have normally been submitted (i.e., a Biologic License Application), to the extent regulatory flexibility is appropriate, the company should submit such data to FDA post-approval in a submission of a pre-agreed upon classification (e.g., in a CBE30 supplement).

6. What actions should be taken if the concurrent process validation activities and results do not fall within the scope of the agreed protocol?

In this situation, the company should conduct an in-depth root cause investigation, including an appropriate risk assessment to determine the impact to product quality, whether modifications to the process and control strategy are needed, and if the degree of any modifications requires updates to the approved application (e.g., submission of a CMC supplement/variation to the regulators, clinical or nonclinical data to support any changes in product quality). The company should contact the regulatory agency to discuss the nature of the failure, the outcome of investigations, and impact to product quality prior to a decision to release to the market of any batches that failed to meet the validation protocol.

7. What are the GMP implications of using a concurrent validation/release approach?

The concurrent manufacture/release of batches to the market may have implications for the timing and scope of GMP inspections (e.g., in some cases, it may be necessary to observe a PPQ/PV batch being manufactured on an inspection). Proposals should therefore be discussed as early as possible with the relevant regulatory authority and GMP inspection authority.

Applicants should follow existing regulatory guidance on concurrent validation/ concurrent release of PPQ/PV batches as this approach is not meant to alter any expectation for compliance with GMP. The quality system must still ensure that a batch has met its quality specifications and was manufactured under GMP in order to support release to the market.

8. Can prior knowledge be leveraged to support process validation activities?

Yes, prior knowledge can be used to support process validation activities, to the extent permitted under applicable laws and regulations. In certain cases, where there is sufficient prior knowledge, this may justify streamlined approaches to PPQ/PV, influence the number of batches required to confirm the process is qualified, and may support deferral of certain process validation studies to the post-approval phase.

9. Is it possible to decouple drug substance and drug product process validation activities?

Yes, while normally process validation involves the use of drug substance PPQ/PV batches in manufacturing drug product PPQ/PV batches, it may be acceptable to manufacture drug product PPQ/PV batches using clinical or development drug substance GMP batches. The appropriateness of this approach depends on a demonstration that the drug substance batches used for drug product validation are representative of the intended commercial drug substance (e.g., a representative manufacturing process that produces a drug substance of the intended quality). This approach is not limited to products in the PRIME/Breakthrough programs, and may be suitable in other cases, under limited circumstances. For those seeking to employ this approach, prior discussion with the regulatory authority is recommended.

10. What are the implications for process validation activities when launching from an investigational medicinal product manufacturing facility?

When launching from an investigational medicinal product manufacturing facility it is expected that the manufacturing process is fully validated. The early access tools and approaches to concurrent validation / concurrent release of validation batches discussed above may also be applicable when launching from an investigational medicinal product manufacturing facility. The extent of process validation data required prior to approval should be agreed with the relevant regulatory authority on a case-by-case basis (see Q4 of Annex 4).

Annex 3. Q&A on Alternatives for determination of re-test period or shelf-life for PRIME/BT applications

A. For Small Molecules/Chemical Entities and Well-Characterized Biotechnology Products[15]

1. Can I submit a marketing application with stability data that differs from what is recommended by ICH?

Although the expectation is that marketing applications will contain data as per ICH recommendations, in some scenarios, some flexibility in the amount of primary data may be allowed. This should be scientifically justified based upon a holistic benefit-risk assessment of all the information provided.

Depending upon the information provided, a marketing application could differ from what is recommended by ICH Q1A (R2) *Stability Testing if New Drug Substances and Products and ICH Q5C Quality Testing of Biotechnological/Biological Products*, for example

- Submission of less than the recommended stability data per ICH, such as 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.
- Batch sizes (used for stability data) that vary from the normal ICH recommendations.

The acceptability of the approach will depend upon the other information provided to address the risks of not having the data described in ICH guidelines. In addition to overall product and process knowledge, this can include, for example, stability data from supportive batches (e.g., clinical and development batches of the drug substance (DS) or drug product (DP)) and prior knowledge from other products. These topics are described in more detail below.

The specific approach to establishing the retest period or shelf-life, if it differs from the ICH recommendations, should be agreed upon in advance with the relevant regulatory authority.

2. When there is limited real-time stability data available from the primary batches, can I rely on supportive real-time stability data to establish a retest period or shelf-life?

Yes. If the applicant has limited real-time data from primary batches (e.g., less than 12 months of real time data), it may be possible to use stability data from supportive batches of the DS or DP, as long as the use of the supportive batches (see response to Q1) is scientifically justified. In this situation, supportive batches should be comparable or representative of the to-be-marketed product, with any differences explained and justified. If comparability between the primary and supportive stability batches is demonstrated, the real time data from these supportive stability batches of DS or DP can be considered in establishing the retest period or shelf-life.

If there is uncertainty about the stability of the product (e.g., limited supportive stability data, stability issues with similar chemical entities), a more restrictive retest period or shelf-life may be warranted, at least at the time of approval (e.g., retest period or shelf-life based only on real-time data from the primary stability batches).

Consistent with ICH Q1A, after approval, applicants should, using the approved stability protocol(s), continue stability studies to confirm the re-test/shell-life, and submit the data according to regional

[15] As indicated in the glossary, retest periods are not applicable for well characterized biotechnology drug substances where shelf lives instead are established.

requirements. In addition, stability data should be submitted in alignment with any agreements that were reached with the relevant regulatory authority.

3. ***Where there is limited real time stability data from the primary batches, can I use prior knowledge from other products in establishing a retest period or shelf-life?***

Yes, prior knowledge can, where appropriate under applicable laws and regulations, contribute to the totality of the information available to establish retest periods and shelf-lives. In order to rely upon prior knowledge, sufficient information should be provided to justify the scientific relevance of the specific data being relied upon from those other products.

This could include, for example, a comparison, and justification for any differences between products in terms of:

- physical and chemical characteristics of the API,
- susceptibility to environmental conditions (e.g., pH and moisture).
- formulations,
- manufacturing processes,
- analytical testing,
- container closure systems

Such an approach could allow for a retest period or shelf-life longer than what would be the ICH recommended timespan based solely on available real-time, primary stability data.

Consistent with ICH Q1A, after approval, applicants should, using the approved stability protocol(s), continue stability studies to confirm the re-test/shelf-life, and submit the data according to regional requirements. In addition, stability data should be submitted in alignment with any agreements that were reached with the relevant regulatory authority.

B. For Small Molecules/Chemical Entity Products

1. ***Where there is limited real time stability data from primary batches, and I want to rely on supportive stability batches to establish the re-test period and/or shelf-life, could I use stability modelling?***

Yes, stability modelling for a product may be used to support comparability of primary and supportive stability batches. For example, stability modelling could be used to support CMC changes that occur after clinical studies, but prior to submission of a marketing application. In this scenario, modelling on data from accelerated stability studies from both clinical and commercial product could be used, as part of a comparability assessment, to support the use of long-term stability data from the investigational medicinal product batches in establishing the re-test period and/or shelf-life of the to-be-marketed product.

However, if new critical quality attributes (CQAs), such as new impurities, are identified for the post-change product, and where the new CQAs were not previously assessed in the model (i.e., not used in the model for this or related products), the use of the model should be reconsidered, or the model should be requalified with the newly identified CQAs.

2. What information would need to be submitted to support the use of predictive stability models?

The applicant should include all data and information that justifies the reliability of the model and applicability of the proposed model to estimate the retest period and shelf-life of the particular product. The evidence supporting a proposed predictive model could include, among other things, data on the use of the model for the particular product or similar products as well as the capability of the model to capture all relevant stability factors (e.g., temperature, humidity, light conditions, etc.). The information submitted should also support the claim that the model is appropriate for application to your product – including model validation data, for example demonstrating that kinetic assumptions in the model are appropriate and that the model is applicable to the commercial container closure system. Information identifying situations when the model would not be appropriate should also be provided.

The most stability indicating attribute(s) of the DS or DP (e.g., the attributes that will be used to set the retest period or shelf-life/expiration period) should be shown to be amenable to the model proposed. For example, if the model is specific for attributes that demonstrate Arrhenius degradation[16] (e.g., chemical degradation), it should not be used if the behaviour of a non-Arrhenius-governed CQA (e.g., physical changes) could be relevant to defining the retest period or shelf-life.

Some CQAs may be more challenging to include in predictive stability models. For example, dissolution (an in vitro indicator of the physiological (absorption) behaviour of solid oral drugs) may not be amenable to certain stability prediction models. Careful consideration should, therefore, be given to each CQA that is included in a given model.

3. When should I submit a proposal for using stability modelling to estimate the retest period (DS) or shelf-life (DP)?

The proposal to use stability modelling to establish the retest period or shelf-life in a marketing application should be discussed with the relevant regulatory authority prior to submission of the marketing application.

- For FDA: The Agency prefers such an approach be discussed as soon as possible. We recommend that stability modelling be discussed at the Type B meeting following the initial Breakthrough designation or at a subsequent CMC-specific Type C meeting. At the very latest, the proposal for using stability modelling should be included as a CMC topic in the pre-NDA meeting package.
- For EMA: The Agency recommends starting discussions on this type of approaches as soon possible, mentioning them in the PRIME kick-off meeting, and following up with a Scientific Advice request.

C. For Well-Characterized Biotechnology Products

1. Can predictive stability models be used to support the shelf life of biological products?

Currently FDA/CDER does not generally recommend predictive modeling for biological products, but it can be considered if sufficiently justified. For information on EMA's recommendations for the use of predictive stability models for biologics, and for more information on the use of modeling for

[16] 2003 ICH guideline "Q1A(R2) Stability Testing of New Drug Substances and Products."

chemical/small molecule products, see the *Toolbox guidance on scientific elements and regulatory tools to support quality data packages for PRIME marketing authorisation applications*.

Annex 4. Q&A on GMP considerations for PRIME/BT applications

1. In which situation would launching initial commercial manufacturing with an** investigational medicinal product **manufacturing process and facility be acceptable?

As a general rule, commercial manufacturing is expected to start from the intended commercial manufacturing facility using the commercial manufacturing process. Launching from an investigational medicinal product manufacturing facility is expected to be extremely rare and should be reserved for those situations where commercial manufacturing facilities cannot provide product for launch in a timely manner considering patient needs. Agreement by the regulatory authority is needed to utilize an investigational medicinal product manufacturing facility.

2. Which conditions should an** investigational medicinal product **manufacturing process and facility meet to be acceptable for initial commercial manufacturing?

An investigational medicinal product manufacturing process and facility should meet at least the following conditions to be acceptable to start commercial manufacturing from:

- The facility should be GMP compliant.
- The manufacturing process should be fully validated using robust Quality Risk Management.

Any differences in the approach to GMP controls at the investigational product manufacturing facility compared to the commercial product manufacturing facilities, should be fully assessed and their potential impact on product quality should be identified, controlled, and mitigated utilizing risk management principles. The applicant and manufacturing facility should justify these approaches to the regulator.

The applicant, should provide a detailed plan for the development and transition to a full commercial manufacturing process at the intended commercial manufacturing facility, including demonstration of comparability between the process used for launching and the intended commercial process (e.g. as a Post-Approval Change Management Protocol (PACMP)). Additionally, there should be a post-marketing CMC commitment specifying when the commercial manufacturing will be fully established.

3. Does the facility need to be re-inspected prior to commencing commercial manufacturing from the investigational medicinal product manufacturing facility?

GMP applies to the preparation of any drug for administration to humans, including those still in investigational stages. However, the extent of manufacturing controls needed to achieve appropriate product quality are phase appropriate and differs between early phase clinical and commercial manufacturing. For example, there can be differences in manufacturing scale, fixed routines, validation and cleaning approaches, and experience/knowledge. Therefore, an evaluation of employed manufacturing controls and the facility's compliance to GMP, and GMP principles and guidelines for manufacturing commercial medicinal products is required in preparation for commercial manufacturing.

When it is proposed that an investigational medicinal product manufacturing facility be used for commercial launch, the facility should be designated in the marketing application as a commercial manufacturer for the specific product. The relevant regulatory agency will evaluate the concerned site for GMP compliance in support of the marketing authorisation.

For the FDA, the need for a Pre-Approval Inspection or Pre-License Inspection of the investigational medicinal product manufacturing facility is risk based and would depend on a number of factors, including the nature of the molecule being manufactured, the nature of the manufacturing process and control strategy, as well as the inspection and compliance history of the site.

For EU, if the investigational medicinal product manufacturing facility has not already been inspected/authorized for the manufacture of the corresponding commercial dosage form, the MIA (Manufacturing and Importation Authorisation) or the GMP certificate needs to be updated, and this normally requires a risk-based facility assessment by a regulatory authority. (e.g., pre/post-approval inspection, desktop assessment).

4. What are the validation requirements when launching from an investigational medicinal product manufacturing facility?

When considering use of the investigational medicinal product manufacturing facility as the initial commercial manufacturing site to launch the product, the compliance to GMP for the manufacture of commercially marketed products must be demonstrated. The scope and extent of the qualification and validation approach should be based on a justified and documented risk assessment of the facility, equipment, utilities, and processes. The manufacturing process validation approach should be justified to ensure a manufacturing process that consistently results in product with appropriate quality, and should consider the level of experience with the clinical product manufacturing, as well as the extent of any changes made to the process during the development and the clinical phase. It should be established that all quality attributes and process parameters considered important for ensuring the validated state of the manufacturing operations and product quality are consistently met by the process. If manufacturing changes are implemented compared to the investigational medicinal product manufacturing process, comparability data may be required, as well as an assessment of need for further validation activities. Product for launch should be manufactured from a fully validated process.

5. How could a request for inspection be appropriately timed in an accelerated assessment procedure?

As with many aspects of PRIME/Breakthrough programs, communication with the regulatory authorities is critical. Timely submission of the relevant information and early notification to the regulatory authorities can help to adequately plan the facility assessment (e.g., inspection, use of alternative tools to assess facilities) without causing delays to the application assessment procedure, in particular for facilities that have not been inspected previously for the operations described in the marketing authorisation application.[17] During the application assessment procedure, an inspection could be required in order to assess the GMP compliance and the readiness of a facility for manufacture. Applicants are required to provide information on all sites in the manufacturing supply chain for the drug substance and the drug product. Information on the GMP compliance status of these manufacturing facilities should be submitted. Following the review of all of the available information on the GMP status of the manufacturing facilities, the need for an on-site inspection (or use of alternative tools) will be evaluated and decided by the relevant regulatory authority/authorities. In addition, an inspection request may be triggered by specific issues and questions raised during the assessment of the marketing application.

6. Does alignment of quality review and inspection contribute to early access?

During accelerated timelines, it is particularly important to ensure that quality review and inspection activities are aligned to allow appropriate information sharing between assessors and inspectors in a timely manner. Such information sharing allows for parties to understand manufacturing proposals to support early access, as well as allowing risk assessment and mitigation activities undertaken by

[17] In the US, commercial facility information may be submitted as an amendment to the investigational new drug (IND) application prior to submission of the marketing application. If the commercial facility information has not been submitted by the time of the pre-NDA (new drug application)/BLA (biologics license application) meeting, for rolling NDA/BLA submissions, Form FDA 356h can be submitted with any complete module as long as changes in the commercial facilities are not anticipated before submission of the CMC module.

manufacturing sites or applicants to support exceptional approaches (e.g., launching from an investigational medicinal product manufacturing facility). In the EU, for some products the inspection and the assessment teams may be part of the same agency and for others the inspection and assessment may be carried out by two different agencies. For those products where the inspectorate and assessment teams are not part of the same agency, early contact with the inspectorate may facilitate a good alignment with the quality review.

7. Can a biological starting material that has been manufactured in a research environment be used for commercial manufacture?

Yes, exceptionally, if agreed by the regulatory authorities, it could be acceptable to use starting material (e.g., master cell bank) that has been manufactured under an appropriate level of GMP[18] for investigational medicinal products. In this case, adequate documentation should be available to confirm traceability, and prevention of contamination, including information related to components used during development with potential impact on product safety, and that extensive characterisation and testing has been performed. A documented risk assessment should be conducted to identify the testing requirements necessary to ensure the quality of the starting material and the medicinal product. Adequate documentation should be available on the production of the starting material, including finished product manufacturer audit results to verify compliance of the supplier's materials with the agreed specifications and that the materials are suitable for their intended use. A comprehensive viral safety study complying with GMP should be performed, as applicable, for the specific starting material.

8. Can existing inventory of batches produced for clinical studies be used for initial commercial supply?

In exceptional circumstances, it may be possible to commercialise/market the existing inventory of batches which have already been manufactured for use in pivotal clinical studies. In such cases, applicants should engage as early as possible with the relevant regulatory authority to seek prior agreement. In this scenario, it is expected that the facility manufacturing the to be commercially distributed clinical batches is communicated to the regulatory authority. The facility manufacturing the clinical batches should be listed as a commercial manufacturing facility. With regard to the need for inspection, please refer to question 3. Information should be provided to support that the batches were manufactured under GMP and that comparability of product manufactured with the clinical and commercial manufacturing processes has been established. In addition, any batches distributed commercially will need to comply with the approved labelling and the intended commercial control strategy. If there are changes to specifications during the review of the marketing application, the already manufactured pivotal clinical batches that will be marketed will need to meet those updated specifications.

[18] EU: refer to Eudralex volume 4, Annex 2 and Part IV, Guidelines on GMP specific to ATMPs. FDA: refer to ICH Q7.