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Committee for Medicinal Products for Human Use (CHMP)

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

EMA和FDA关于优先药品/突破性疗法申请在质量和GMP方面的联合问答

Introduction 简介

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.

欧洲药品管理局（EMA）的"优先发展新药"（PRIME）计划和美国食品及药物管理局（FDA）的"突破性疗法"（BT）指定计划旨在帮助加速开发满足未满足医疗需求的创新产品。对于列入这些加速开发计划的产品，其上市申请仍应需包括所有临床、非临床以及化学、生产和质量控制 (CMC) 信息，以满足审批标准。由于在更紧凑的时间内生成 CMC 信息会给公司带来挑战，EMA 和 FDA 一直在与行业利益相关者进行公开

[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.

对话，以探索在不降低患者对药品期望标准的前提下加快这些产品开发和审批的方法。为此，2018 年 11 月 26 日，EMA 和 FDA 组织了一次利益相关者研讨会，探讨 PRIME 和突破性疗法等早期准入方法中的质量发展问题。此次研讨会重点关注解决与加速产品开发相关的挑战的潜在科学和监管方法，以便提交可靠的质量和生产数据包，从而实现患者及时获得药物，同时确保产品的安全性、有效性和质量不受影响。

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.

研讨会期间，通过结合来自行业的真实案例研究（涵盖化学分子、生物制剂和先进治疗药物产品 (ATMP)）以及监管机构的观点和小组讨论，探讨了面临的挑战和解决方案

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, 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.

根据优先药品/突破性疗法计划的经验，监管机构和业界选择了以下领域进行讨论：工艺验证、控制策略、符合现行药品生产质量管理规范 (GMP) 要求、可比性、稳定性和监管工具。研讨会的讨论和主要结论，包括已有的科学要素和监管工具、研讨会的讨论情况和主要结论，包括科学要素和监管工具，这些要素和工具已经存在，或将从探索中受益，以帮助应对开发挑战。在研讨会期间，FDA 和 EMA 还反思了可从以下方面获益的领域控制策略、创新工艺验证方法、稳定性数据以及从临床生产现场或与研究用医药产品批次一起投放市场。

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.

此外，还认识到，在某些情况下，如果申请符合批准标准，则有可能通过在批准后提交数据来降低某些风险。

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

如 ICH Q12 所详述，这包括使用：

- Post-approval change management protocols to support changes anticipated during the lifecycle of the product.

  批准后的变更管理协议，以支持产品生命周期内的预期变更。

- 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.

  CMC承诺将制定一项计划，概述在批准后将收集哪些开发数据，并定义如何分析、评估这些数据并向监管机构报告。

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.

自 2018 年的研讨会以来，EMA 和 FDA 的药物评价与研究中心 (CDER) 一直在就这些主题开展进一步讨论，分享他们在 PRIME/BT 申请方面的经验和监管期望。作为这些讨论的成果，我们编写了这四份共识问答 (Q&A) 文件，以汇编 EMA 和FDA/CDER 现有指导文件中反映的当前思路。如同现有指导文件中所反映的那样。这些被作为附件呈现在原始研讨会报告中。

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.

对于EMA而言，这些问答（Q&As）适用于人类使用的化学和生物医药产品，包括复杂的生物制品（如ATMPs），除非另有说明。对于FDA，这些额外的讨论及其产生的附件仅适用于CDER管辖的产品。因此，附件中提到的所有生物产品都是指仅限CDER管辖的生物人类药品产品。生物制品评价和研究中心（CBER）管辖的产品，例如先进治疗药品（ATMPs），不在这些文件的范围内。

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.

这些文件仅旨在提供一般信息，并不构成监管指导。有意采用这些问答文件中描述的方法的申请者应在提交市场申请之前，与相关监管机构讨论其特定产品所需的策略。

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

附件1. 针对PRIME/BT申请的控制策略考虑的问答

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

附件2. 针对PRIME/BT申请的工艺验证方法的问答

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

附件3. 针对PRIME/BT申请的重新测试期限或保质期确定的替代方案的问答

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

附件4. 针对PRIME/BT申请的GMP考虑事项的问答

Glossary of Terms 术语表

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.

评估设施的替代工具：这些是监管机构可能用来评估设施的替代工具。包括请求来自其他受信任外国监管伙伴的现有检查报告，向申请者请求信息，直接向设施和其他受检实体请求记录及其他信息，以及进行远程交互式评估。

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).

剂型：一种含有药物成分的药品类型（例如，片剂、胶囊、溶液、乳膏），通常与辅料（根据ICH Q1A）结合，但不一定非结合不可。

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

药物制剂（DP）：打算上市的最终即时包装中的剂型（根据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).

药物物质（DS）：未配制的药物物质，可能随后与辅料一起配制以产生剂型（根据ICH Q1(A)）。对于生物技术产品，DS可以包括所需的产品、与产品相关的物质、与产品和工艺相关的杂质。它还可能包含辅料，包括诸如缓冲剂之类的其他成分（按照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).

有效期：放置在药品产品容器标签上的日期，指定在此日期之前，如果按规定条件存储，产品批次预期将保持在批准的保质期规格内，此日期之后则不应使用（根据ICH Q1A）

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

检查：就本文件而言，'检查'包括一般的GMP检查以及批准前/许可前的检查。

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].

市场许可：在这些附件的背景下：

- 市场许可资料夹（或资料夹）与市场申请同义。
- 市场许可与"批准的申请"同义。对于CDER来说，这包括那些获得突破性产品指定并根据《食品药品化妆品法》第505节批准的新药申请（NDAs）或根据《公共卫生服务法》第351节获得许可的生物制品许可申请（BLAs）

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).

批准后变更管理协议（PACMP）：一份描述申请人打算在产品生命周期的商业阶段实施的CMC变更的协议，包括如何准备和验证变更，包括评估拟议变更的影响，以及建议的报告类别，以符合区域法规和指南（根据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.

批准后CMC承诺：在批准时，持有市场许可的公司（MAH）和监管机构之间商定的特定CMC开发活动（例如，特定的过程监控、额外测试），应在商业阶段进行并被记录下来

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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)

注册/申报批次：用于正式稳定性研究的药物物质或药品产品的批次，从中提交稳定性数据到注册申请

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.

工艺性能确认（PPQ）：一种针对生产过程的正式验证活动，其中使用来自足够数量批次的全面生产数据来证明商业过程处于受控状态。PPQ结合了实际设施、公用设施、设备、控制程序和组件来生产商业批次。成功的PPQ将确认过程设计，并证明商业生产过程按预期执行。为了证明过程处于验证状态所需的批次数量，通常被称为PPQ批次，这取决于过程的可变性、过程/产品的复杂性、在开发过程中获得的过程知识、商业规模的支持数据，以及生产商对类似产品和过程的整体经验。

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.

PPQ方案/工艺验证方案：一份书面的前瞻性协议，概述了将在生产规模批次上进行的正式过程验证研究，指定了生产条件、控制、测试、取样计划和接受标准。实际的过程验证数据应随相关产品的提交一起提供，或在许可后由监管机构进行核实。这可以包括针对过程验证之外的活动的资质协议（例如，引入未来的参考标准或细胞库）；这些协议规定了将在批准后收集哪些数据，以及如何分析这些数据，以及是否将其提交给监管机构。

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.

工艺设计/工艺表征：基于通过开发和放大活动获得的知识来定义商业生产过程。其目标是设计一个适合常规商业生产的过程，能够始终如一地交付符合其质量属性的药品。

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.

工艺评价：在小规模和/或商业规模上进行的研究，以提供证据表明完整的生产过程以及每个步骤/操作单元已被适当设计，以定义生产过程的完整操作范围。

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.

工艺验证（PV）：从工艺设计阶段到商业生产的过程中，对数据的记录收集和评估，以此证明在既定参数内操作的工艺能够持续地交付符合预定规格和质量属性的高质量产品。

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).

复检期：原料药在此期间内预期将保持符合其规格，因此可以用于特定药品的生产，前提是该原料药已按定义的条件储存。经过此期限后，用于药品生产的原料药批次应重新检验以符合规格，然后立即使用。一个原料药批次可以多次重新检验，每次重新检验后都可以使用该批次的不同部分，只要它继续符合规格。对于大多数已知不稳定的生物技术/生物物质，建立保质期比重新检验期限更为合适。对于某些抗生素（根据ICH Q1A），同样也适用。

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)

保质期（也称为有效期）：药品产品预期保持在批准的保质期规格内的时间长度，前提是其按照容器标签上定义的条件储存（根据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).

质量标准：质量标准被定义为一系列测试、分析程序的参考以及适当的接受标准，这些标准是测试所描述的数值限制、范围或其他标准（ICH Q6A/Q6B）

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

附录 1. 针对优先药品/突破性疗法申请的控制策略考虑问题与答案

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

1. 对于PRIME/BT项目，如何建立质量标准？

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.

PRIME/BT项目在上市前可能生产的开发和商业批次比传统项目少，因此，与各种批次的临床经验和由此产生的产品质量知识用于设定规格可能有限，与传统项目相比。因此，在建立和证明这些产品的规格的临床相关性时，可能需要额外的考虑。这对于在开发早期相对较早获得PRIME/BT指定的项目尤其如此。

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?

2. 在临床经验有限的情况下，可以使用哪些额外考虑来建立规格及其接受标准？接受标准比临床批次报告的测试结果更宽松是否可接受？如果可以，应如何证明其合理性？

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]

可能可以建立比临床研究中使用的批次的实际测试结果更宽松的质量标准。在这种情况下，这些限制仍应就临床影响（即，与安全性和有效性相关的产品知识）合理地进行证明。重要的是，除了临床经验之外，总是可以考虑其他信息来源，按照适用的法律和规章，在为任何产品（不仅仅是PRIME/BT产品）建立规格

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及其接受标准时。控制策略的灵活性量取决于产品和过程理解的总体情况（例如，经验知识、开发研究），并结合ICH Q9质量风险管理原则。

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.

然而，人们认识到，比临床经验更宽松地设定规格接受标准通常是PRIME/BT项目的特定需求。这些额外的信息来源可以包括但不限于：体外数据、动物数据、已发表的信息、特定于开发平台的经验知识，以及潜在关键质量属性（CQA）从相关开发项目的影响。在使用来自其他产品的信息时，应提供产品之间的比较，并对任何差异进行合理化说明。这种比较可以包括例如使用背景（例如，剂型、给药方案、给药途径和持续时间、临床适应症以及预期的患者人群）、化学特性、作用机制、分析测试、生产过程、配方和容器封闭系统。对CQAs的规格接受标准的合理化应与临床表现相关联，而不仅仅是从统计方法（如容忍区间）中推导出来的。对有限批次的统计分析可能导致接受标准过宽，临床上无法证明。

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)?

3. 如果确定有必要，修订批准后规格的最合适方法是什么？修订规格的计划是否可以在批准后变更管理协议（PACMP）中记录？

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:

虽然提出的控制策略可能适用于初始批准，但在获得更多信息后，可能需要在批准后修订规格。例如:

- Revising acceptance criteria using information gained from additional manufactured batches, with a justification based on clinical relevance;

  使用从额外生产的批次获得的信息来修订接受标准，并基于临床相关性进行理由说明。

- 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;

  基于更多临床经验、质量属性的额外特性数据的可用性或提交的额外研究，重新评估接受标准。

- Adding an orthogonal or replacement method that was under development at the time of approval.

  添加一个在批准时正在开发中的正交或替代方法。

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.

未来修订规格的策略理想情况下应提前规划，并在初始批准时与监管机构沟通。在这种情况下，使用批准后变更管理协议（PACMP），按照ICH Q12指南，是一个可能使用的工具

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?

4.申请人如何调整其控制策略，以抵消由于加速开发而导致的产品和过程知识水平的降低？控制策略的哪些元素可以进行调整？

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.

调整控制策略可能是一种可接受的方法，特别是对于加速开发项目，因为这些项目可能有限的生产和临床经验和/或相对有限的产品和过程理解。这种方法可能会考虑例如对给定工艺参数（PP）提出更窄的范围，识别额外的CQAs/CPPs，以及包括额外的过程控制或规格中的额外属性。

For example, when there is uncertainty about :

例如，当存在不确定性时

- whether an attribute is a CQA,

  是否某个属性是关键质量属性（CQA）

- the level of risk associated with a CQA,

  与关键质量属性（CQA）相关联的风险程度

- the ability to measure a CQA, or

  关键质量属性（CQA）的测量能力，或

- the control of a CQA by the manufacturing process,

  通过生产过程控制CQA

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

控制策略将需要解决这些不确定性带来的风险。

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)

当采用调整后的控制策略来支持初始批准时，控制策略可以在批准后进行修订，以提供更大的灵活性（见问题3和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?

5. 在批准后进行额外的工艺开发研究之前，工艺参数是否应默认为关键？是否可以提前在PACMP中同意一项旨在降低工艺参数关键性和扩大范围的预期策略？

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.

由于生产经验有限或工艺开发/工艺特性研究有限，可能对参数及其对生产过程的关键性理解不足。在这种情况下，默认将工艺参数定义为关键（即CPP）可能是适当的，其目的是在批准后重新评估参数的关键

性和相关的接受标准，随着从生产控制策略的实际操作和产品的临床使用中获得更多信息（也参见问题4）。在PACMP中提出修订计划的建议是有可能的。

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]

6. 如何将经验知识整合到PRIME/BT产品的控制策略中？可以提交哪些类型的信息？经验知识是否可用于确定工艺参数、范围和规格？

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).

经验知识的使用不限于PRIME/BT项目，并且任何时候只要能够适当地证明其合理性，就被认为是合适的。例如，经验知识可以用来支持对属性关键性、工艺参数关键性、工艺参数范围或工序控制或规格限制的理由。在这些情况下，应清楚地解释从其他产品获取的信息如何与所讨论的产品相关（见问题2）。对于具有特别加速开发时间线的项目，如PRIME/BT，经验知识可能很有用。选择经验知识的适当性取决于申请人支持其预期用途的能力。除了对药品产品和过程的平台理解外，还应包括对任何分子功能、作用机制和/或生物活性的理解，这些是特定于药物的，或关于使用背景的具体信息（例如，可能影响免疫原性的CQA在不同的使用背景下可能会有不同的看法，如免疫抑制人群）

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

7. PRIME/突破产品的分析方法验证有哪些期望？

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-

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approval. Alternative approaches to analytical method validation would typically require discussion with the regulatory authority.

PRIME/BT项目对分析方法的验证预期并无不同。应该应用ICH Q2指南中关于分析程序验证的原则。申请人还可以参考ICH Q14草案指南关于分析程序开发。此外，PRIME/BT状态并不一定支持在提交时减少产品特定分析验证数据的预期。在相对罕见的情况下，可能接受一些在批准后补充的方法验证数据。与监管机构讨论分析方法验证的替代方法通常是必需的。

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

附件2：关于PRIME/BT申请的工艺验证方法问答

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

1.化学药品和生物药品成品工艺验证要求有何不同？

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.

在欧盟，对于使用标准工艺生产的化学药品，在监管提交时，不需要在市场许可档案中提供生产规模的工艺验证数据。对于这些产品，档案中应提交一份工艺验证方案（3.2.R），概述将在生产规模批次上进行的正式工艺验证研究。商业规模工艺的正式验证应在市场上投放批次之前完成。工艺验证研究的信息应供监督机构在许可后核查。对于生物产品和使用非标准工艺生产的化学产品，在批准前应在档案中提供生产规模连续批次的预先指定数量的工艺验证数据。EMA关于工艺验证的建议可以在现有指导文件中找到，例如《成品工艺验证 - 在申报资料中应提供的信息和数据 - 科学指南 | 欧洲药品管理局 (europa.eu)》、《生物类似物生产的工艺验证和申报资料中应提供的数据 - 科学指南 | 欧洲药品管理局 (europa.eu)》、《欧盟良好生产实践指南附件15：资质确认和验证》以及《欧盟高级治疗药物良好生产实践特定指南》。

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,

对于FDA，根据FD&C法案第501(a)(2)(B)节，药品的工艺验证在商业分销前需要成功完成。21 CFR第210和211部分的CGMP法规对工艺验证既有一般要求也有具体要求。尽管尚未颁布针对药品成分（如活性药物成分和中间体）的单独cGMP法规，但这些成分仍受FD&C法案第501(a)(2)(B)节的法定cGMP要求约束。FDA关于工艺验证的更多建议可以在现有指导文件中找到，例如行业指南《工艺验证：一般原则和实践（2011年1月）》和《Q7良好生产实践（2016年9月）》，其中包括关于不同类型和阶段工艺验证的信息。

- 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]
- 此外，对于化学（即新药申请或NDA）产品，工艺验证的第一阶段（即开发和放大活动，以定义商业生产过程）应包含在申请中。工艺验证的第二阶段（即工艺性能确认或PPQ，评估商业过程以证明其可重复性）必须在商业分销前完成，但信息无需提交给申请。第二阶段可以在检查时审查。然而，完整的无菌保证验证数据应提交在申请中。

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]

相比之下，对于由CDER监管的生物产品（即生物制品许可申请（BLA）产品），PPQ（即第二阶段工艺验证）信息通常被认为是申请中必要的，以确保该工艺始终能够生产出安全、纯净且有效的产品。

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]

BLA通常包括来自第一阶段和第二阶段验证的数据和信息以支持批准，包括第二阶段验证协议和报告。

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

2. 何时可以使用并行验证/并行许可PPQ批次的方法？

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]

当对患者有很强的收益风险比时，可以使用这种方法。并行方法的使用是基于具体情况的，可能会考虑用于市场上需求有限的药品（例如，孤儿药物）、用于治疗威胁生命或严重削弱健康的疾病、具有短半衰期的产品（例如，放射性药物），或在紧急需求情况下（例如，在像COVID-19这样的大流行病情况下）。

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

鼓励公司与欧洲药品管理局（EMA）或美国食品药品监督管理局（FDA）尽早沟通，讨论并行验证/并行许可的提议。

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

3. 并行验证方案/PPQ方案中应包含哪些信息以支持并行批准？

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.

对于所有产品，方案应包括验证活动的预期范围、批次数量、预期测试和接受标准。规定的信息应包括许可规格、所有相关的过程控制、过程参数以及作为工艺验证活动一部分的任何额外监测和评估。所有测试

的拟议接受标准应适当地进行理由说明。拟议的控制策略应确保只有符合每个监管司法管辖区适用法律和法规要求的批次才能供应。PPQ批次应放置在稳定性研究中。

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.

对于市场许可申请，其中PPQ信息通常提交在市场许可档案中（见问题1），并行方法的验证协议仍应随市场申请提供，且并行验证方法应在药品质量体系（PQS）的验证总计划中描述。并行工艺验证批次/并行许可批次的任何可用释放和稳定性数据一旦可用，应包含在档案中。将PPQ批次放置在稳定性研究中的承诺应反映在申请中的稳定性方案中。

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

4. 可以提交哪些类型的数据以支持并行验证方案/PPQ方案？

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.

在使用并行验证/许可的情况下，可用数据应支持该过程处于受控状态，并且能够一贯地生产出符合预定规格的高质量产品。支持并行验证/许可方法的信息可以包括过程开发研究、经验知识、平台知识、小规模模型的支持数据，以及使用商业生产过程生产的PPQ/PV之前的批次数据（包括临床批次）。这些信息应在申请中提供。所有相关设备和测试方法应在开始并行工艺验证之前适当地进行资格认证和验证。

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

并行批次的许可还应由强有力的风险评估支持。总体而言，应有足够的数据支持结论，即任何给定批次的产品都是均匀的，并符合定义的接受标准。这应正式记录并在批次放行前可用。

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?

5. 并行验证批次的数据应如何提交给监管机构？批次是否可以在未经事先批准的情况下投放市场？

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.

通常情况下，在市场申请获得批准之后，根据适用的法律法规，已按照批准条件生产的新批次（例如，按照并行验证协议的条款）通常在许可前不需要监管批准。

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.

对于通常会提交PPQ数据的市场申请，申请人应在获批后向监管机构提交并行工艺验证数据。

- 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.

  在欧盟，存在多种机制向EMA提供此类数据，例如推荐、附件II条件或特定义务。最合适的机制将根据具体情况决定，并取决于整体数据包和风险水平。

- 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).

  在美国，对于通常会提交PPQ数据的市场申请（即生物制品许可申请），在适当的监管灵活性范围内，公司应在获批后向FDA提交此类数据，并以预先同意的分类形式提交（例如，在CBE30补充文件中）。

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

6. 如果并行过程验证活动和结果不在已同意的协议范围内，应采取哪些措施？

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.

在这种情况下，公司应进行深入的根本原因调查，包括适当的风险评估，以确定对产品质量的影响，是否需要对流程和控制策略进行修改，以及任何修改的程度是否需要更新已批准的申请（例如，向监管机构提交CMC补充/变更，支持产品质量变化的临床或非临床数据）。公司应该在决定将未能达到验证协议的任何批次投放市场之前，联系监管机构，讨论失败的性质、调查的结果以及对产品质量的影响。

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

7. 使用并行验证/许可方法对GMP的影响是什么？

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.

将批次并行生产/许可到市场可能会影响GMP（良好生产规范）检查的时机和范围（例如，在某些情况下，可能需要在检查中观察正在生产的PPQ/PV批次）。因此，应尽早与相关监管机构和GMP检查机构讨论提案。

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.

申请者应遵循现有的关于并行验证/并行许可PPQ/PV批次的监管指南，因为这种方法并不意味着改变遵守GMP的任何期望。质量体系仍然必须确保一个批次已经满足其质量规格，并在GMP下生产，以支持其许可到市场。

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

8. 可以利用经验的知识来支持过程验证活动吗？

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.

是的，在适用法律和法规允许的范围内，可以利用经验的知识来支持过程验证活动。在某些情况下，如果有足够的经验知识，这可能证明简化PPQ/PV方法是合理的，影响确认流程合格所需的批次数量，并且可能支持将某些过程验证研究推迟到批准后阶段。

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

9. 能否将药物物质和药物产品的过程验证活动分离？

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.

是的，虽然通常过程验证涉及使用药物活性物质PPQ/PV（过程性能确认/过程验证）批次来生产药物产品PPQ/PV批次，但使用临床或开发阶段药物活性物质的GMP（良好生产规范）批次生产药物产品PPQ/PV批次可能是可以接受的。采用这种方法的适当性取决于证明用于药物制剂验证的药物活性物质批次代表了预期商业药物活性物质（例如，一个代表性的生产过程产生预期质量的药物活性物质）。这种方法不限于PRIME/突破性项目中的产品，在有限的情况下，也可能适用于其他情况。对于希望采用这种方法的人来说，建议事先与监管机构讨论。

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

10. 当从临床试验药品生产设施启动时，对过程验证活动有什么影响？

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).

当从临床试验药品生产设施启动时，预期生产过程应完全经过验证。上述提到的早期进入工具和并行验证/并行许可验证批次的方法，也可能适用于从临床试验药品生产设施启动。在批准前所需的过程验证数据的程度应与相关监管机构根据具体情况协商确定（见附件4的Q4）

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

附件3：关于确定PRIME/BT申请的复检期或有效期的替代方案的问答

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

A. 对于小分子/化学实体和特性良好的生物技术产品

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

1. 我可以提交一个销售申请，其中的稳定性数据与ICH推荐的不同吗？

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.

虽然预期销售申请将包含符合ICH建议的数据，但在某些情况下，主要数据的数量可能会有一定的灵活性。应基于对所提供所有信息的整体利益-风险评估进行科学合理的论证。

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.

根据所提供的信息，销售申请可能会与ICH Q1A (R2) 新药物质和产品的稳定性测试以及ICH Q5C 生物技术/生物产品的质量测试的建议不同，例如，

- 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.

  提交少于ICH建议的稳定性数据，如在提交时仅提交6个月的实时初期稳定性数据和加速数据，并同意在销售申请审核期间提交额外的稳定性数据。

- Batch sizes (used for stability data) that vary from the normal ICH recommendations.

  用于稳定性数据的批次大小与常规ICH建议的不同。

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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.

这种方法的可接受性将取决于提供的其他信息，以解决没有ICH指南中描述的数据的风险。除了整体产品和流程知识外，这还可以包括来自支持批次的稳定性数据（例如，药物活性物质（DS）或药物制品（DP）的临床和开发批次）和其他产品的经验知识。

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.

这些话题将在下面更详细地描述。如果建立重新检测期或保质期的具体方法与ICH建议不同，应事先与相关监管机构协商确定。

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?

2. 当主要批次的实时稳定性数据有限时，我可以依靠支持性实时稳定性数据来确定复检期或有效期吗？

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.

是的。如果申请人从主要批次中获得的实时数据有限（例如，少于12个月的实时数据），可能可以使用来自药物活性物质（DS）或药物制剂（DP）的支持性批次的稳定性数据，只要使用这些支持性批次（参见对Q1的回应）是科学合理的。在这种情况下，支持性批次应该与即将上市的产品相当或代表性，任何差异应解释并合理化。如果证明了主要批次和支持性稳定性批次之间的可比性，那么这些支持性稳定性批次的DS或DP的实时数据可以用来确定重新检测期或保质期。

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).

如果对产品稳定性存在不确定性（例如，有限的支持性稳定性数据，类似化学实体的稳定性问题），可能需要更严格的重新检测期或保质期，至少在批准时（例如，仅基于主要稳定性批次的实时数据确定的重新检测期或保质期）。

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

与ICH Q1A一致，批准后，申请人应使用批准的稳定性协议继续稳定性研究，以确认重新检测/保质期，并根据地区要求提交数据。此外，应根据与相关监管机构达成的任何协议提交稳定性数据。

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?

3. 当主要批次的实时稳定性数据有限时，我可以使用来自其他产品的经验知识来确定复验期或有效期吗？

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.

是的，在适用法律和法规允许的情况下，经验的知识可以有助于建立重新检测期和保质期所需的全部信息。为了依赖经验的知识，应提供足够的信息来证明依赖于那些其他产品的具体数据的科学相关性。

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

例如，这可能包括对产品之间的比较，并对任何差异进行解释和合理化，包括：

- physical and chemical characteristics of the API,

  原料药的物理和化学性质

- susceptibility to environmental conditions (e.g., pH and moisture).

  对环境条件的敏感性（例如，pH值和湿度）

- formulations,

  制剂

- manufacturing processes,

  生产工艺

- analytical testing,

分析测试方法

- container closure systems

容器密封系统

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.

采用这种方法可能允许复检期或有效期长于仅基于现有实时主要稳定性数据的ICH推荐时间跨度。

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.

与ICH Q1A一致，批准后，申请人应使用批准的稳定性协议继续稳定性研究，以确认复检期/有效期，并根据地区要求提交数据。此外，应根据与相关监管机构达成的任何协议提交稳定性数据。

B. For Small Molecules/Chemical Entity Products

B. 小分子/化学实体产品

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?

1. 如果原始批次的实时稳定性数据有限，而我想依靠支持性稳定性批次来确定复验期和/或有效期，我是否可以使用稳定性建模？

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.

是的，产品的稳定性建模可用于支持主要和辅助稳定性批次的可比性。例如，稳定性建模可用于支持临床研究后，在提交上市申请前发生的 CMC 变更。在这种情况下，作为可比性评估的一部分，可使用临床和商业产品的加速稳定性研究数据建模，以支持在确定待上市产品的复验期和/或有效期时使用研究用药批次的长期稳定性数据

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.

如果新的 CQA 以前未在模型中评估过（即未在该产品或相关产品的模型中使用过），则应重新考虑模型的使用，应根据新的 CQA 对模型进行重新验证。

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

2. 需要提交哪些信息来支持使用预测稳定性模型？

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.

申请人应提供所有数据和信息，以证明模型的可靠性和拟议模型对估计特定产品的复验期和有效期的适用性。支持预测模型的证据可包括，除另有规定外，特定产品或类似产品使用模型的数据，以及模型捕捉所有相关稳定性因素（如温度、湿度、光照条件等）的能力。提交的信息还应支持模型适用于产品的说法--包括模型验证数据，例如：证明模型中的动力学假设是适当的，模型适用于商业容器封闭系统。此外，还应提供相关信息，说明在哪些情况下模型不适用。

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.

DS 或 DP 中最能体现稳定性的属性（如用于设定复验期或保存期/失效期的属性） 应证明与所建议的模型相适应。例如，如果模型专门针对显示阿伦尼斯降解 （如化学降解）的属性，那么如果非阿伦尼斯控制的 CQA 行为（如物理变化）可能与确定复验期或保存期有关，则不应使用该模型。

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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.

例如，溶出度（口服固体药物生理（吸收）行为的体外指标）可能不适合某些稳定性预测模型。因此，应仔细考虑特定模型中包含的每项 CQA。

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

3.我应该何时提交使用稳定性建模来估算复验期（DS）或保质期（DP）的建议？

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.

在提交上市申请之前，应与相关监管机构讨论在上市申请中使用稳定性模型确定复验期或有效期的建议。

- 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.

  FDA要求：FDA希望尽快讨论这种方法。FDA建议在首次指定突破后的 B 类会议或随后的 CMC 特定 C 类会议上讨论稳定性模型。最迟应将使用稳定性建模的建议作为 CMC 议题纳入预国家药品证书（NDA）会议包。

- 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.

  对于 EMA：该机构建议尽快就这类方法展开讨论，在 PRIME 启动会议上提及这些方法，并提出科学建议请求作为后续行动。

C. For Well-Characterized Biotechnology Products

C. 特性明确的生物技术产品

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

1. 预测稳定性模型是否可用于支持生物制品的有效期？

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

目前，FDA/CDER 一般不建议对生物制品使用预测模型，但如果有充分的理由，可以考虑使用。有关 EMA 建议对生物制品使用预测性稳定性模型的信息，以及有关在化学/小分子产品中使用建模的更多信息，请参阅 "工具箱 "中有关科学要素和监管工具的指南，以支持 PRIME 上市许可申请的高质量数据包。

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

附件 4. PRIME/BT 应用的 GMP 注意事项问答

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

1. 在哪种情况下可以接受使用研究用药产品的生产工艺和设施进行初始商业生产？

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.

一般来说，商业生产应从预定的商业生产设施开始，采用商业生产工艺。从研究用医药产品生产机构进行上市的情况预计极为罕见，应仅限于商业生产机构无法及时提供产品以满足患者需求的情况。使用研究用医药产品生产设施需要得到监管机构的同意。

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

2. 研究用药产品的生产工艺和设施应满足哪些条件才能被接受进行初始商业生产？

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

研究用药产品的生产工艺和设施至少应满足以下条件，才能被接受开始商业生产：

- The facility should be GMP compliant.

  设施应符合 GMP 标准

- 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.

应全面评估研究产品生产设施与商业产品生产设施在 GMP 控制方法上的任何差异，并利用风险管理原则确定、控制和减轻这些差异对产品质量的潜在影响。申请人和生产设施应向监管机构说明这些方法的合理性。

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.

申请人应提供一份详细计划，说明在预定的商业生产设施开发和过渡到全面商业化生产工艺的情况，包括证明用于上市的工艺与预定的商业化工艺之间的可比性（例如，作为批准后变更管理协议（PACMP））。此外，还应作出上市后 CMC 承诺，说明何时将全面建立商业生产。

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

3. 在研究用医药产品生产设施开始商业生产之前，是否需要重新检查该设施？

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.

GMP 适用于任何供人类使用的药物制备的管理，包括仍处于研究阶段的药物。然而，要达到适当的产品质量，所需的生产控制程度是分阶段的，早期临床生产和商业生产之间也存在差异。例如，在生产规模、固定程序、验证和清洁方法以及经验/知识方面可能存在差异。因此，在准备商业化生产时，需要对所采用的生产控制措施和设施是否符合 GMP 以及商业化医药产品生产的 GMP 原则和指南进行评估。

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.

如果建议将研究用医药产品生产设施用于商业化上市，则应在上市申请中将该设施指定为特定产品的商业化生产商。相关监管机构将对相关生产基地的 GMP 合规性进行评估，以支持上市批准。

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.

对于 FDA 来说，是否需要对在研医药产品生产设施进行批准前检查或许可前检查是以风险为基础的，并取决于多种因素，包括正在生产的分子的性质、生产工艺和控制策略的性质，以及生产场所的检查和合规历史。

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).

就欧盟而言，如果研究用医药产品的生产设施尚未因生产相应的商业剂型而接受检查/获得许可，则需要更新 MIA（生产和进口许可）或 GMP 证书，这通常需要监管机构进行基于风险的设施评估。(例如，批准前/批准后检查、桌面评估）。

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

4. 从研究用医药产品生产设施投产时有哪些验证要求？

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.

在考虑将研究用药产品生产设施作为产品上市的初始商业生产基地时，必须证明其符合商业上市产品生产的 GMP 要求。资格确认和验证方法的范围和程度应基于对设施、设备、公用设施和工艺进行的合理且有记录的风险评估。生产工艺验证方法应合理，以确保生产工艺能始终如一地生产出具有适当质量的产品，并应考虑临床产品生产的经验水平，以及在研发和临床阶段对工艺所做任何更改的程度。应确定所有被认为对确保生产操作和产品质量的验证状态十分重要的质量属性和工艺参数都能通过工艺始终如一地得到满

足。如果生产工艺与在研药品生产工艺相比发生了变化，可能需要提供可比性数据，并评估是否需要开展进一步的验证活动。投放市场的产品应由经过全面验证的工艺生产。

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

5. 如何在加速评估程序中适当安排检查申请的时间？

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.

与 PRIME/突破计划的许多方面一样，与监管机构的沟通至关重要。及时提交相关信息并及早通知监管机构，有助于充分规划设施评估（如检查、 使用替代工具评估设施），而不会延误申请评估程序，特别是对于以前未就上市许可申请中描述的操作对设施进行过检查的情况。在申请评估程序中，可能需要进行检查，以评估设施的 GMP合规性和生产准备情况。申请人必须提供药物和药物产品生产供应链中所有生产场所的信息。应提交有关这些生产设施的 GMP 符合情况的信息。在审查了有关生产设施GMP符合情况的所有可用信息后，相关监管机构将评估并决定是否需要进行现场检查（或使用替代工具）。此外，在评估上市申请期间提出的具体问题和疑问也可能触发检查请求。

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

6. 质量审查和检查的一致性是否有助于尽早获得服务？

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 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

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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.

在加快时限期间，尤其重要的是确保质量审查和检查活动保持一致，以便评估人员和检查人员及时共享适当的信息。这种信息共享可使各方了解生产建议，以支持早期准入，并允许开展风险评估和缓解活动。生产厂家或申请人，以支持特殊方法（例如，从研究用医药产品生产厂家推出）在欧盟，对于某些产品，检查和评估小组可能属于同一机构，而对于其他产品，检查和评估可能由两个不同的机构进行。对于检查小组和评估小组不属于同一机构的产品，尽早与检查小组联系可能有助于与质量审查保持良好的一致。

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

7.在研究环境中生产的生物起始材料能否用于商业生产？

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.

是的，在特殊情况下，如果得到监管机构的同意，可以接受使用在适当水平的 GMP下为研究用医药产品生产的起始材料（如主细胞库）。在这种情况下，应提供足够的文件来确认可追溯性和防止污染，包括与开发过程中使用的对产品安全有潜在影响的成分有关的信息，以及已进行的广泛特征描述和测试。应进行记录在案的风险评估，以确定必要的检测要求，确保初始材料和药用产品的质量。应提供有关起始材料生产的充分文件，包括成品生产商的审计结果，以核实供应商的材料是否符合商定的规格，以及材料是否适合其预期用途。在适用情况下，应针对特定的起始原料进行符合 GMP 的全面病毒安全性研究。

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

8.为临床研究生产的批次的现有库存能否用于初始商业供应？

In exceptional circumstances, it may be possible to commercialise/market the existing inventory of batches which

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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.

在特殊情况下，有可能将已生产的用于关键临床研究的批次的现有库存进行商业化/销售。在这种情况下，申请人应尽早与相关监管机构联系，事先征得同意。在这种情况下，生产即将进行商业销售的临床批件的工厂应通知监管机构。生产临床批件的设施应被列为商业生产设施。关于检查的必要性，请参阅问题 3。应提供资料证明这些批次是按照 GMP 生产的，并证明用临床和商业生产工艺生产的产品具有可比性。此外，任何批次的商业销售都必须符合批准的标签和预定的商业控制策略。如果在上市申请审查期间规格发生变化，则已生产的关键临床批次在上市时必须符合更新后的规格。