Guidance for Industry

行业指南

Process Validation: General Principles and Practices

工艺验证：一般原则与规范

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Veterinary Medicine (CVM)
January 2011
Current Good Manufacturing Practices (CGMP)
Revision 1

美国卫生与人类服务部
食品药品管理局
药物评价和研究中心（CDER）
生物制品评价和研究中心（CBER）
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Guidance for Industry[1]
行业指南[1]

Process Validation: General Principles and Practices
工艺验证：一般原则与实施

I. INTRODUCTION

一. 简介

This guidance outlines the general principles and approaches that FDA considers appropriate elements of process validation for the manufacture of human and animal drug and biological products, including active pharmaceutical ingredients (APIs or drug substances), collectively referred to in this guidance as drugs or products. This guidance incorporates principles and approaches that all manufacturers can use to validate manufacturing processes.

本指南概述了 FDA 认为是包括原料药在内的人与动物用药和生物制品（在本指南中合称为药品或制品）生产工艺验证相应要素的一般原则和方法。该指南收编了所有生产商可用于验证生产工艺的多种原则和方法。

This guidance aligns process validation activities with a product lifecycle concept and with existing FDA guidance, including the FDA/International Conference on Harmonisation (ICH) guidances for industry, *Q8(R2) Pharmaceutical Development*, *Q9 Quality Risk Management*, and *Q10 Pharmaceutical Quality System*.[2] Although this guidance does not repeat the concepts and principles explained in those guidances, FDA encourages the use of modern pharmaceutical development concepts, quality risk management, and quality systems at all stages of the manufacturing process lifecycle.

本指南将工艺验证活动与产品生命周期概念和现有 FDA 指南进行了对齐，包括 FDA/人用药

[1] This guidance has been prepared by the Division of Manufacturing and Product Quality, Center for Drug Evaluation and Research (CDER), in cooperation with CDER's Office of Pharmaceutical Sciences, the Center for Biologics Evaluation and Research (CBER), the Office of Regulatory Affairs (ORA) and the Center for Veterinary Medicine (CVM) at the Food and Drug Administration.

[1].本指南由 FDA 制造与产品质量处、药物评价与研究中心（CDER）与 CDER 药物科学办公室、生物制品评价与研究中心（CBER）、监管事物办公室(ORA)和兽药中心（CVM）合作编制。

品注册技术规范国际协调会议(ICH)行业指南，*Q8(R2)《药品开发》*、*Q9《质量风险管理》*和*Q10《药品质量体系》*。[2] 尽管本指南不复述那些指南解释的概念或原则，但 FDA 鼓励在药物工艺生命周期所有阶段使用现代药物开发概念、质量风险管理和质量体系。

The lifecycle concept links product and process development, qualification of the *commercial manufacturing process*,[3] and maintenance of the process in a state of control during routine commercial production. This guidance supports process improvement and innovation through sound science.

生命周期概念衔接产品和工艺开发、商品化生产工艺确认[3]、以及日常商品化制造中处于受控状态的过程维护。本指南通过可靠的科学为工艺改进和创新提供支持。

This guidance covers the following categories of drugs:

- Human drugs
- Veterinary drugs
- Biological and biotechnology products
- Finished products and active pharmaceutical ingredients (APIs or drug substances)[4]
- The drug constituent of a combination (drug and medical device) product

本指南涵盖下列类别的药物：

- 人用药
- 兽用药
- 生物和生物技术制品
- 制剂产品和活性药物成分（原料药或药用物质）[4]
- 组合产品（药物和医疗器械）的药物组分

This guidance does not cover the following types of products:

- Type A medicated articles and medicated feed
- Medical devices5
- Dietary supplements
- Human tissues intended for transplantation regulated under section 361 of the Public Health Service

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[2]To make sure you have the most recent version of a guidance, check the CDER guidance page at www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm, the CBER guidance page at www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm, or the CVM guidance page at www.fda.gov/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/default.htm

[2.] 为确保您能得到指南的最新版本，请核对药物评价与研究中心（CDER）网页，网址为：www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm,, 生物制品评价与研究中心（CBER）指南网页，网址为：www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm, 或兽药中心指南网页，网址为：www.fda.gov/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/default.htm

[3] In this guidance, the term *commercial manufacturing process* refers to the manufacturing process resulting in *commercial product* (i.e., drug that is marketed, distributed, and sold or intended to be sold). For the purposes of this guidance, the term *commercial manufacturing process* does not include clinical trial or treatment IND material.

[3.] 本指南中，商品化生产工艺这一专业名词指生产出商品化产品的生产工艺（即用于经销、流通、出售或拟出售的药品）。就本指南而言，商品化生产工艺这一专业名词不包括临床试验或用于治疗的研究型药物（IND）材料。

[4]截止本指南发布之日，单独针对药物组分如有效药用成分(药用物质)和中间体的现行药品生产质量管理规范尚未公布，但这些组分受《联邦食品、药品和化妆品法》第501节(a)(2)(B) 法定cGMP要求约束。www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

《FDA/ICH行业指南 Q7活性药物成分良好生产规范指南（ICH）》对活性药物成分的工艺验证进行了讨论，可在下述网址获得，www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm 。ICH Q7 第十二部分详细描述了活性药物成分工艺验证的原则。

Act6

本指南不涵盖下列类型产品：

- A 类添加药物产品或添加药物饲料
- 医疗器械 [5]
- 膳食补充剂
- 受《公共卫生服务法》第 361 节监管的拟用于移植的人体组织 [6]

This guidance does not specify what information should be included as part of a regulatory submission. Interested persons can refer to the appropriate guidance or contact the appropriate Center in determining the type of information to include in a submission.

本指南没有详细说明哪些信息应该包括在监管提交文件部分中。有兴趣的人士可以参考相应指南或联系相应中心以确定应包括在提交文件中的信息类型。

This guidance also does not specifically discuss the validation of automated process control systems (i.e., computer hardware and software interfaces), which are commonly integrated into modern drug manufacturing equipment. This guidance is relevant, however, to the validation of processes that include automated equipment in processing.

本指南也没有具体讨论自动化工艺控制系统验证（即计算机硬件和软件界面），这些自动化控制系统通常集成在现代化药物生产设备中。然而，该指南与包括工艺过程自动设备在内的工艺验证有关。

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

FDA 的指南文件，包括本指南在内，没有规定依法强制执行责任。相反，除非引述具体的监管或法规要求，指南描述的是本机构目前对该主题的看法，应该仅仅被视为建议。在本机构指南中所使用的"应该"一词，指建议或推荐某事，并非必须的。

II. BACKGROUND

二. 背景

In the *Federal Register* of May 11, 1987 (52 FR 17638), FDA issued a notice announcing the availability of a guidance entitled *Guideline on General Principles of Process Validation* (the 1987 guidance).[7] Since then, we have obtained additional experience through our regulatory oversight that allows us to update our recommendations to industry on this topic. This revised guidance conveys FDA's current thinking on process validation and is consistent with basic principles first introduced in the 1987 guidance. The revised guidance also provides recommendations that reflect some of the goals of FDA's initiative entitled "Pharmaceutical

[5] Guidance on process validation for medical devices is provided in a separate document, Quality Management Systems – Process Validation, edition 2, available at www.ghtf.org/sg3/sg3-final.html. *See infra* note 6.

[5] 医疗仪器工艺验证指南以一个单独文件的形式提供，《质量管理体系——工艺验证》，第二版，可在 www.ghtf.org/sg3/sg3-final.html 获得。参见下文中的注释 6。

[6] See the FDA guidance for industry, *Validation of Procedures for Processing of Human Tissues Intended for Transplantation*, available on the Internet at *www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.*

[6] 参见 FDA 行业指南《拟用作移植的人体组织工艺流程验证》，可从以下网址获得：*www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm*

CGMPs for the 21st Century — A Risk-Based Approach," particularly with regard to the use of technological advances in pharmaceutical manufacturing, as well as implementation of modern risk management and quality system tools and concepts.[8] This revised guidance replaces the 1987 guidance.
1987 年 5 月 11 日，FDA 在*联邦公告* (52 FR 17638)上发布公告，宣布题为《工艺验证一般原则指导原则》的指南（1987 年版指南）面世。[7] 从那时起，通过监管监督，我们能够在此主题上更新对业界的建议，使我们获得了更多经验。该修订版指南传达了 FDA 目前对工艺验证的看法，并与 1987 年版指南首次提出的基本原则相一致。修订版指南还提出了一些反映 FDA"21 世纪制药行业现行药品生产管理规范——一种基于风险的方法"计划的若干目标的建议，特别是关于药品生产中技术进步的应用，以及对现代风险管理和质量体系的工具及概念的实施。[8] 该修订版指南取代 1987 年版指南。

FDA has the authority and responsibility to inspect and evaluate process validation performed by manufacturers. The CGMP regulations for validating pharmaceutical (drug) manufacturing require that drug products be produced with a high degree of assurance of meeting all the attributes they are intended to possess (21 CFR 211.100(a) and 211.110(a)).
FDA 有权力和责任对由生产商实施的工艺验证进行检查和评估。用于验证制药的 cGMP 法规要求药品在高度保证符合所有预期拥有属性的情况下生产(《联邦法规 21 编 122.100（a）和 211.110（a)》)。

A. Process Validation and Drug Quality

A. 工艺验证与药品质量

Effective process validation contributes significantly to assuring drug quality. The basic principle of quality assurance is that a drug should be produced that is fit for its intended use. This principle incorporates the understanding that the following conditions exist:

- Quality, safety, and efficacy are designed or built into the product.
- Quality cannot be adequately assured merely by in-process and finished-product inspection or testing.
- Each step of a manufacturing process is controlled to assure that the finished product meets all quality attributes including specifications.

有效的工艺验证对保证药品质量做出了重要贡献。质量保证的基本原则在于生产出来的药品符合其预定用途。该原则包括对存在下列情况的理解：

- 质量、安全性和功效被设计或构建于产品之中。

[7] The 1987 guidance was prepared by a working group that included representation from the Center for Devices and Radiological Health (CDRH). Since that time, CDRH elected to reference a process validation guidance prepared in cooperation with the Global Harmonization Task Force (GHTF). The principles and recommendations in that document, *Quality Management Systems – Process Validation,* edition 2 (available on the Internet at www.ghtf.org/sg3/sg3-final.html) are also useful to consider for drug manufacturing processes.
[7] 从那时以来， CDRH 选择与全球协调工作组（the Global Harmonization Task Force (GHTF)）合作编制的工艺验证指南作为参考。该文件的原则和建议，《质量管理体系—工艺验证》（第二版）（可从互联网上获得 www.ghtf.org/sg3/sg3-final.html），对考虑药物生产工艺也有用。
[8] *See* "Pharmaceutical cGMPS for the 21st Century — A Risk-Based Approach: Second Progress Report and Implementation Plan," available at www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/QuestionsandAnswersonCurrentGoodManufacturingPracticescGMPforDrugs/ucm071836.htm.
[8] 参见《21 世纪制药业现行药品生产规范––一种基于风险的方法：第二份进展报告实施计划》，可从以下网址获得：www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/QuestionsandAnswersonCurrentGoodManufacturingPracticescGMPforDrugs/ucm071836.htm。

- 质量不能仅通过生产中检查或检测以及成品检查或检测给予充分保证。
- 生产工艺的每一步均予以控制，确保成品符合包括规格在内所有质量属性。

B. Approach to Process Validation

B. 工艺验证方法

For purposes of this guidance, *process validation* is defined as the collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality product. Process validation involves a series of activities taking place over the lifecycle of the product and process. This guidance describes process validation activities in three stages.

就本指南而言，*工艺验证*被定义为从工艺设计阶段到商业生产的整个过程中，对数据进行收集和评价，建立能够使工艺能够始终如一地传递到优质产品中的科学证据。工艺验证涉及整个产品生命周期和生产中发生的一系列活动。本指南分三个阶段对工艺验证进行说明。

- Stage 1 – Process Design: The commercial manufacturing process is defined during this stage based on knowledge gained through development and scale-up activities.
- 第一阶段––工艺设计: 在开发和放大活动过程中获得的知识基础上，在此阶段对商品化制造工艺进行定义。

- Stage 2 – Process Qualification: During this stage, the process design is evaluated to determine if the process is capable of reproducible commercial manufacturing.
- 第二阶段––工艺确认: 在此阶段，对工艺设计进行评估，以确认工艺是否具备可重现的商品化制造能力。

- Stage 3 – Continued Process Verification: Ongoing assurance is gained during routine production that the process remains in a state of control.
- 第三阶段––持续工艺核实:在日常生产中获得工艺保持处于受控状态的持续和不断发展的保证。

This guidance describes activities typical of each stage, but in practice, some activities might occur in multiple stages.

本指南对每个阶段的典型活动进行了说明，但在实践中，有些活动可能发生于多个阶段。

Before any batch from the process is commercially distributed for use by consumers, a manufacturer should have gained a high degree of assurance in the performance of the manufacturing process such that it will consistently produce APIs and drug products meeting those attributes relating to identity, strength, quality, purity, and potency. The assurance should be obtained from objective information and data from laboratory-, pilot-, and/or commercial-scale studies. Information and data should demonstrate that the commercial manufacturing process is capable of consistently producing acceptable quality products within commercial manufacturing conditions.

经工艺生产出任何批次产品经过商业流通给消费者使用之前，生产商应在生产工艺性能方面取得高度保证，以始终如一地生产出满足与鉴别、含量、质量、纯度和效价相关的那些属性的原料药和药品。这些保证应该从来自于实验室小试、中试、和/或商品化大生产研究的客观信息或数据获得。信息和数据应该显示，商品化制造工艺应能在商品化制造条件下始终如

一地生产出合格的优质产品。

A successful validation program depends upon information and knowledge from product and process development. This knowledge and understanding is the basis for establishing an approach to control of the manufacturing process that results in products with the desired quality attributes. Manufacturers should:
一个成功的验证方案取决于来自产品和工艺开发的知识。这种知识和理解是建立能够生产出具备期望得到的质量属性产品生产工艺控制方法的基础。制造商应该：

- Understand the sources of variation
- 了解变异来源

- Detect the presence and degree of variation
- 探测变异存在和程度

- Understand the impact of variation on the process and ultimately on product attributes
- 了解变异对工艺和最终对产品属性的影响

- Control the variation in a manner commensurate with the risk it represents to the process and product
- 用与代表工艺与产品风险相称的方式控制变异。

Each manufacturer should judge whether it has gained sufficient understanding to provide a high degree of assurance in its manufacturing process to justify commercial distribution of the manufacturing process and associated variations may not lead to adequate assurance of quality. After establishing and confirming the process, manufacturers must maintain the process in a state of control over the life of the process, even as materials, equipment, production environment, personnel, and manufacturing procedures change.[9]
所有生产商均应判断是否已经对生产工艺提供高度保证获得足够理解，为产品商业流通提供保证。只是专注于确认努力，而忽略对生产工艺和相关变异的关注，不能导致对质量的充分保证。在建立和确认工艺之后，生产商必须保持工艺在工艺生命期内处于受控状态，即便是材料、设备、生产环境、人员和生产工序发生变更的情况下。[9]

Manufacturers should use ongoing programs to collect and analyze product and process data to evaluate the state of control of the process. These programs may identify process or product problems or opportunities for process improvements that can be evaluated and implemented through some of the activities described in Stages 1 and 2.
生产商应使用持续和不断发展的方案收集分析产品和工艺数据，对工艺受控状态进行评估。这些方案可以确定工艺或产品问题，或找出工艺改善的适当时机，这些时机可以通过在第一阶段和第二阶段中描述的一些活动进行评估和实施。

Manufacturers of legacy products can take advantage of the knowledge gained from the original process development and qualification work as well as manufacturing experience to continually improve their

[9] The statute and regulations described in section III of this guidance explain the requirement that the methods and facilities used for the manufacturing of drugs be operated and administered under control sufficient to assure that the identity, strength, purity, and quality of a drug are as they purport or are represented to possess.
[9] 本指南第三节描述的法规和章程，对处于控制之下的用于制药的方法与设施的操作及管理要求作出了说明，控制应足以保证其声称或据称具有的鉴别、含量、质量、纯度和效价。

processes. Implementation of the recommendations in this guidance for legacy products and processes would likely begin with the activities described in Stage 3.
传统产品生产商可利用从原先的工艺开发和确认工作、以及生产经验中获得的知识，不断改进工艺。本指南中对传统产品和工艺建议的实施，可能会始于第三阶段所描述的活动。

III. STATUTORY AND REGULATORY REQUIREMENTS FOR PROCESS VALIDATION

三. 对工艺验证的法规和监管要求

Process validation for drugs (finished pharmaceuticals and components) is a legally enforceable requirement under section 501(a)(2)(B) of the Act (21 U.S.C. 351(a)(2)(B)), which states the following:
根据法令（《美国联邦法典 U.S.C. 351(a)(2)(B), 21 编》）501(a)(2)(B)节，药物（药物成品与组分）工艺验证依法强制执行，其规定如下：

> A drug . . . shall be deemed to be adulterated . . . if . . . the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of this Act as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess.
> 一种药品……应当被视为掺假药品……如果……使用于制造、加工、包装或置放的方法或设施、控制装置不符合或没有遵照在安全性上保证药品符合本法令的规定，并保证符合其声称或据称的鉴别和含量、质量和纯度特征的现行药品生产质量管理规范操作和管理。

FDA regulations describing current good manufacturing practice (CGMP) for finished pharmaceuticals are provided in 21 CFR parts 210 and 211.
对用于成品的现行药品生产质量管理规范（CGMP）进行说明的 FDA 法规，见《美国联邦法规第 21 编》第 210 和 211 节。

The CGMP regulations require that manufacturing processes be designed and controlled to assure that in-process materials and the finished product meet predetermined quality requirements and do so consistently and reliably. Process validation is required, in both general and specific terms, by the CGMP regulations in parts 210 and 211. The foundation for process validation is provided in § 211.100(a), which states that "[t]here shall be written procedures for production and process control *designed to assure* that the drug products have the identity, strength, quality, and purity they purport or are represented to possess..." (emphasis added). This regulation requires manufacturers to design a process, including operations and controls, which results in a product meeting these attributes.
CGMP 法规要求对生产工艺进行设计与控制以保证在加工材料和成品符合预订的质量要求并始终如一和确实地这样做。按照 CGMP 第 210 和 211 节，在一般条款和具体条款中，工艺验证是必需的。在§ 211.100(a)中，规定了工艺验证的基础，其中规定"应当有用于保证药品具有其宣称或据称所有的鉴别、含量、质量、纯度的生产和工艺控制的书面程序……"（强调）。该法规要求生产商设计包括操作和控制在内的工艺，使产品符合这些属性。

Other CGMP regulations define the various aspects of validation. For example, § 211.110(a), *Sampling and testing of in-process materials and drug products*, requires that control procedures ". . . be established to monitor the output and *to validate* the performance of those manufacturing processes that may be

responsible for causing variability in the characteristics of in-process material and the drug product" (emphasis added). Under this regulation, even well-designed processes must include in-process control procedures to assure final product quality. In addition, the CGMP regulations regarding sampling set forth a number of requirements for validation: samples must represent the batch under analysis (§ 211.160(b)(3)); the sampling plan must result in statistical confidence (§ 211.165(c) and (d)); and the batch must meet its predetermined specifications (§ 211.165(a)).

其它的 CGMP 法规对验证的不同方面进行了定义。例如，§ 211.110(a)*在加工材料和药品的抽样和检测*，要求控制程序"……应被建立以监测产量和验证可能是引起在加工材料和药品特性变异原因的那些生产工艺进行验证。"（强调）。根据这一法规，即便设计周到的工艺也必须包括中间工艺控制程序以保证成品质量。此外，有关抽样的 CGMP 规定对验证提出若干要求：样品必须代表接受分析的批次(§ 211.160(b)(3));抽样方法必须产生统计学置信度(§ 211.165(c)和(d));批次必须符合其预设规格。

In addition to sampling requirements, the CGMP regulations also provide norms for establishing in-process specifications as an aspect of process validation. Section 211.110(b) establishes two principles to follow when establishing in-process specifications. The first principle is that ". . . in-process specifications for such characteristics [of in-process material and the drug product] shall be consistent with drug product final specifications . . ." Accordingly, in-process material should be controlled to assure that the final drug product will meet its quality requirements. The second principle in this regulation further requires that in-process specifications ". . . shall be derived from previous acceptable process average and process variability estimates where possible and determined by the application of suitable statistical procedures where appropriate." This requirement, in part, establishes the need for manufacturers to analyze process performance and control batch-to-batch variability.[10]

除抽样要求之外，作为工艺验证的一个方面，CGMP 法规也规定了建立中间工艺规范。211.110(b)节规定了建立中间工艺规范时的两个原则。第一个原则是，"……对这些（在加工材料和药品）特性的中间工艺规格，应当与药品成品规格一致。"因此，在加工材料应进行控制，以保证药品成品符合其质量要求。这份法规的第二个原则最中间工艺规范做了进一步要求"……应当源于之前认可的工艺均值和工艺变异性估计值。这项要求，部分地建立了生产商分析工艺性能和控制批间变异的需求。[10]

The CGMP regulations also describe and define activities connected with process design, development, and maintenance. Section 211.180(e) requires that information and data about product quality and manufacturing experience be periodically reviewed to determine whether any changes to the established process are warranted. Ongoing feedback about product quality and process performance is an essential feature of process maintenance.

CGMP 法规还说明和定义了与工艺设计、开发和维护有关的活动。211.180(e) 节要求对有关产品质量和制造经验的信息和数据进行定期审查，以决定对已建立工艺的所有变革是否合理和必要。对产品质量与工艺性能不间断的反馈是工艺维护的基本特征。

In addition, the CGMP regulations require that facilities in which drugs are manufactured be of suitable size,

[10] The Agency further explains this principle in the preamble to the final rule on "Current Good Manufacturing Practice in Manufacture, Processing, Packing, or Holding" (43 FR 45013 at 45052, September 29, 1978) (available on the Internet at www.fda.gov/cder/dmpq/preamble.txt).

[10] FDA 在《制造、加工、包装或置放的现行药品生产管理质量规范》（联邦公报：43 FR 45013 at 45052， 1978 年 9 月 29 日发布）最终规则序言中，对这一原则作了进一步解释。（可从以下网址获得：www.fda.gov/cder/dmpq/preamble.txt）

construction, and location to facilitate proper operations (§ 211.42). Equipment must be of appropriate design, adequate size, and suitably located to facilitate operations for its intended use (§ 211.63). Automated, mechanical, and electronic equipment must be calibrated, inspected, or checked according to a written program designed to assure proper performance (§ 211.68).
此外，CGMP 法规要求，生产药品的设施具有适当的规模、建筑和位置，以利于正确操作(§ 211.42)。设备必须拥有合理的设计、足够的尺寸、放置位置适当，以利于预期操作(§ 211.63)。自动化、机械和电子设备必须根据设计用来保证正确性能的书面计划校准、检查或核实(§ 211.68)。

In summary, the CGMP regulations require that manufacturing processes be designed and controlled to assure that in-process materials and the finished product meet predetermined quality requirements and do so consistently and reliably.
总之，CGMP 法规要求生产工艺应进行设计与控制，与保证在加工材料与成品符合预设的质量要求，并始终如一和确实地这样做。

IV. RECOMMENDATIONS

四. 建议

In the following sections, we describe general considerations for process validation, the recommended stages of process validation, and specific activities for each stage in the product lifecycle.
在下述部分中，我们对工艺验证的总体考虑、建议的工艺验证和产品生命周期内每一阶段的特殊活动进行说明。

A. General Considerations for Process Validation

A. 对工艺验证的总体考虑

In all stages of the product lifecycle, good project management and good archiving that capture scientific knowledge will make the process validation program more effective and efficient. The following practices should ensure uniform collection and assessment of information about the process and enhance the accessibility of such information later in the product lifecycle.
在产品生命周期的所有阶段，捕捉科学知识的良好项目管理和良好归档将使得工艺验证更为有效和更具效率。下述规范应保证与工艺有关的信息收集和评价一致性，并在其后的产品生命周期中，提高这些信息的可获得性。

- We recommend an integrated team approach[11] to process validation that includes expertise from a variety of disciplines (e.g., process engineering, industrial pharmacy, analytical chemistry, microbiology, statistics, manufacturing, and quality assurance). Project plans, along with the full support of senior management, are essential elements for success.
- 我们建议工艺验证采用包括来自多个学科专门知识的综合团队方法[11]（例如工艺学、制药工程、分析化学、微生物学、统计学、制造以及质量保证）。项目计划、以及高级管理团队的全力支持，是成功的基本要素。

[11]This concept is discussed in more detail in FDA's guidance for industry, *Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations*, available at www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.
[11]FDA行业指南《现行药品生产质量管理规范法规》对此概念进行了更为深入的讨论，该指南可从下述网站获得：www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

• Throughout the product lifecycle, various studies can be initiated to discover, observe, correlate, or confirm information about the product and process. All studies should be planned and conducted according to sound scientific principles, appropriately documented, and approved in accordance with the established procedure appropriate for the stage of the lifecycle.
• 在整个产品生命周期，可启动不同的研究，发现、观察、关联或确认有关产品和工艺的信息。所有的研究，应根据可靠的科学原则来计划和进行，妥善记录，并按照适用于生命周期阶段的既定程序予以批准

• The terms *attribute(s)* (e.g., quality, product, component) and *parameter(s)* (e.g., process, operating, and equipment) are not categorized with respect to *criticality* in this guidance. With a lifecycle approach to process validation that employs risk based decision making throughout that lifecycle, the perception of criticality as a continuum rather than a binary state is more useful. All attributes and parameters should be evaluated in terms of their roles in the process and impact on the product or in-process material, and reevaluated as new information becomes available. The degree of control over those attributes or parameters should be commensurate with their risk to the process and process output. In other words, a higher degree of control is appropriate for attributes or parameters that pose a higher risk. The Agency recognizes that terminology usage can vary and expects that each manufacturer will communicate the meaning and intent of its terminology and categorization to the Agency.
•专业名词*属性*（例如质量、产品、组分）和*参数*（例如工艺、操作和设备），在本指南中，不以其关键程度加以分类。在整个生命周期中，使用基于风险的决策的生命周期方法进行工艺验证，将关键程度视为连续态而不是非此即彼的二元态更为有用。所有的属性和参数，应该从它们在工艺中发挥作用和对产品或在加工材料发生影响的角度进行评估，并在新信息变得合用时重新进行评估。对这些属性或参数的控制程度，应该与其对工艺和工艺输出的风险相称。换句话说，对风险较高的属性或参数，更高程度的控制是恰当的。本机构认识到，专业名词的使用可能有差异，并希望所有生产商就其专业名词及归类的内涵和含义与本机构交流。

• Many products are single-source or involve complicated manufacturing processes. Homogeneity within a batch and consistency between batches are goals of process validation activities. Validation offers assurance that a process is reasonably protected against sources of variability that could affect production output, cause supply problems, and negatively affect public health.
•很多产品是单一来源或涉及复杂的生产工艺。一个批次内的均一性和批间一致性是工艺验证活动的目标。验证为一个工艺合理防止可能影响生产产出、引起供应问题、以及对公共健康造成负面影响的变异来源给予保证。

B. Stage 1 - Process Design

B. 第一阶段 - 工艺设计

Process design is the activity of defining the commercial manufacturing process that will be reflected in planned master production and control records. The goal of this stage is to design a process suitable for routine commercial manufacturing that can consistently deliver a product that meets its quality attributes.

工艺设计是界定商品化制造工艺的活动，将通过计划中的主生产和控制记录中反映。本阶段的目的在于，设计适合可以始终如一地产出符合其质量属性产品的日常商品化制造工艺。

1. Building and Capturing Process Knowledge and Understanding

1. 建立和捕获工艺知识与理解

Generally, early process design experiments do not need to be performed under the CGMP conditions required for drugs intended for commercial distribution that are manufactured during Stage 2 (process qualification) and Stage 3 (continued process verification). They should, however, be conducted in accordance with sound scientific methods and principles, including good documentation practices. This recommendation is consistent with ICH *Q10 Pharmaceutical Quality System*.[12] Decisions and justification of the controls should be sufficiently documented and internally reviewed to verify and preserve their value for use or adaptation later in the lifecycle of the process and product.

通常，早期工艺设计实验不需在 CGMP 条件下进行，CGMP 为拟用于商业流通的药品在第二阶段（工艺确认）和第三阶段（持续工艺核实所必需）。但是，早期工艺设计实验应该依照可靠的科学方法和原则进行，包括药品文件编制管理规范。该建议与 ICH Q10 *《药品质量体系》*一致。[12] 控制的决策和正当理由应有足够文件证明并经内部审核，以核实和维护决策及正当理由在随后的工艺和产品生命周期内的应用和改编价值。

Although often performed at small-scale laboratories, most viral inactivation and impurity clearance studies cannot be considered early process design experiments. Viral and impurity clearance studies intended to evaluate and estimate product quality at commercial scale should have a level of quality unit oversight that will ensure that the studies follow sound scientific methods and principles and the conclusions are supported by the data.

尽管经常在小型实验室中开展，绝大部分的病毒灭活和杂质清除研究不能被视为早期工艺设计实验。原打算用来与商品化大生产对产品质量进行评估和估计病毒和杂质清除研究应该具备质量部门监督水准，这样的监督水准将保证研究遵照可靠的科学方法和原则，并保证结论由数据支持。

Product development activities provide key inputs to the process design stage, such as the intended dosage form, the quality attributes, and a general manufacturing pathway. Process information available from product development activities can be leveraged in the process design stage. The functionality and limitations of commercial manufacturing equipment should be considered in the process design, as well as predicted contributions to variability posed by different component lots, production operators, environmental conditions, and measurement systems in the production setting. However, the full spectrum of input variability typical of commercial production is not generally known at this stage. Laboratory or pilot-scale models designed to be representative of the commercial process can be used to estimate variability.

产品开发活动为工艺设计阶段提供重要的数据输入，例如打算采用的剂型、质量属性和总的生产路径。从产品开发活动中获得的工艺信息可在工艺设计阶段应用。商品化制造设备的设计功能和局限应在工艺设计中予以考虑，生产环境的不同组成批、生产操作人员、环境条件和测量系统可能具有的对变异的预期贡献也应予以考虑。然而，一般在此阶段，商品化生产中典型的输入变异尚不知晓。设计来代表商品化工艺的实验室小试或中试模型可用来估计变异。

Designing an efficient process with an effective process control approach is dependent on the process

[12] Available at www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.
[12] 可从下述网址获得：www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

knowledge and understanding obtained. Design of Experiment (DOE) studies can help develop process knowledge by revealing relationships, including multivariate interactions, between the variable inputs (e.g., component characteristics [13] or process parameters) and the resulting outputs (e.g., in-process material, intermediates, or the final product). Risk analysis tools can be used to screen potential variables for DOE studies to minimize the total number of experiments conducted while maximizing knowledge gained. The results of DOE studies can provide justification for establishing ranges of incoming component quality, equipment parameters, and in-process material quality attributes. FDA does not generally expect manufacturers to develop and test the process until it fails.
设计具备有效的工艺控制方法的高效工艺，有赖于获得的工艺知识和理解。通过揭开关系，包括多种变异输入的多元相互作用（例如，组分特性[13]或工艺参数），以及结果输出（例如，在加工材料、中间体、或成品），实验设计（Design of Experiment (DOE) ）研究能有助于开发工艺知识。风险分析工具可用于甄选实验设计（DOE）研究的潜在变异以最大限度地减少开展的实验总数，以此同时使获得的知识最大化。实验设计（DOE）研究的结果能为建立即将来临的组分质量、设备参数和在加工材料质量属性范围提供正当理由。FDA 一般不希望生产商直至失败，还在对工艺进行开发和检测。

Other activities, such as experiments or demonstrations at laboratory or pilot scale, also assist in evaluation of certain conditions and prediction of performance of the commercial process. These activities also provide information that can be used to model or simulate the commercial process. Computer-based or virtual simulations of certain unit operations or dynamics can provide process understanding and help avoid problems at commercial scale. It is important to understand the degree to which models represent the commercial process, including any differences that might exist, as this may have an impact on the relevance of information derived from the models.
其它活动，例如实验室小试或中试期间的实验或演示，也能有助于某些条件评估和商品化工艺性能预测。这些活动还可提供可用于商品化工艺建模或模拟。对某些单元操作或动力学的基于计算机或虚拟模拟可提供工艺理解和帮助避免商品化大生产中的问题。了解模型表现商品化工艺的程度，包括可能存在的任何差异，具有重要性，原因在于这可能对源于模型的信息相关性有影响。

It is essential that activities and studies resulting in process understanding be documented. Documentation should reflect the basis for decisions made about the process. For example, manufacturers should document the variables studied for a unit operation and the rationale for those variables identified as significant. This information is useful during the process qualification and continued process verification stages, including when the design is revised or the strategy for control is refined or changed.
至关重要的是，用文件记录导致工艺理解的活动和研究。文件记录应反映工艺的决策基础。例如，生产商应该用文件记录单元操作研究的可变因素，以及这些变化因素被认为是有意义的理由。该信息在工艺确认和持续工艺核实阶段是有用的，包括设计修改或控制策略完善或变更的情况。

2. Establishing a Strategy for Process Control

2. 建立工艺控制策略

Process knowledge and understanding is the basis for establishing an approach to process control for each unit operation and the process overall. Strategies for process control can be designed to reduce input

[13] "*Component* means any ingredient [raw material] intended for use in the manufacture of a drug product, including those that may not appear in such drug product" (§ 210.3(b)(3)).
[13]"成分指用于药品生产的任何成分[原材料]，包括那些可能不出现在这些药品中的成分" (§ 210.3(b)(3))。

variation, adjust for input variation during manufacturing (and so reduce its impact on the output), or combine both approaches.
工艺知识和理解是对所有单元操作和工艺总体上建立工艺控制方法的基础。工艺控制策略可设计用来减少输入变异，在生产中调整输入变异（并因此降低对输出的影响），或将两种方法结合。

Process controls address variability to assure quality of the product. Controls can consist of material analysis and equipment monitoring at significant processing points (§ 211.110(c)). Decisions regarding the type and extent of process controls can be aided by earlier risk assessments, then enhanced and improved as process experience is gained.
工艺控制强调变异以保证产品质量。控制可由重要工艺控制点的物料分析与设备监控组成(§ 211.110(c))。与工艺控制类型和范围有关的决策可以借助于更早时候开展的风险评估，之后可随工艺经验的获得以加强和改进。

FDA expects controls to include both examination of material quality and equipment monitoring. Special attention to control the process through operational limits and in-process monitoring is essential in two possible scenarios:
FDA 希望控制包括物料质量检查和设备监控。对通过工作极限和中间工艺监控控制工艺的特别关注在两种可能的情况下是必不可少的：

1. When the product attribute is not readily measurable due to limitations of sampling or detectability (e.g., viral clearance or microbial contamination) or
1. 由于取样或可检测性限制（例如病毒清除或微生物污染），产品属性不容易测量的情况，或

2. When intermediates and products cannot be highly characterized and well-defined quality attributes cannot be identified.
2. 中间体和产物不能被高度表征,以及定义明确的质量属性不能被确认的情况。

These controls are established in the master production and control records (see § 211.186(a) and (b)(9)).
这些控制在主生产和控制记录中建立(参见 § 211.186(a)和 (b)(9))。

More advanced strategies, which may involve the use of process analytical technology (PAT), can include timely analysis and control loops to adjust the processing conditions so that the output remains constant. Manufacturing systems of this type can provide a higher degree of process control than non-PAT systems. In the case of a strategy using PAT, the approach to process qualification will differ from that used in other process designs. Further information on PAT processes can be found in FDA's guidance for industry on *PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance*.[14]
更为先进的策略，可能涉及过程分析技术（PAT）的应用，可能包括调整加工条件的及时分析和控制回路，以使输出保持恒定。该类型的生产体系能比非过程分析技术（PAT）体系提供更高程度的工艺控制。在使用过程分析技术（PAT）策略的情况下，工艺确认方法将有异于用于其它工艺设计中的方法。过程分析技术（PAT）工艺的进一步信息请参阅《FDA 行业指南：*过程分析技术—创新性药物开发、生产和质量保证》(PAT—A Framework for Innovative*

Pharmaceutical Development, Manufacturing, and Quality Assurance）.[14]

The planned commercial production and control records, which contain the operational limits and overall strategy for process control, should be carried forward to the next stage for confirmation.
计划中的商品化生产和控制记录，当中包含工艺控制的工作极限和总体策略，应转入下一阶段进行确认。

C. Stage 2 - Process Qualification

C. 第二阶段 - 工艺确认

During the process qualification (PQ) stage of process validation, the process design is evaluated to determine if it is capable of reproducible commercial manufacture. This stage has two elements: (1) design of the facility and qualification of the equipment and utilities and (2) process performance qualification (PPQ). During Stage 2, CGMP-compliant procedures must be followed. Successful completion of Stage 2 is necessary before commercial distribution.[15] Products manufactured during this stage, if acceptable, can be released for distribution.
在工艺验证的工艺确认（PQ）阶段，对工艺设计进行评估以确认在此阶段，对工艺设计进行评价，以确认工艺是否具备可重现的商品化生产能力。该阶段具有两个因素：(1)厂房设施设计以及设备和公用设施确认，以及（2）工艺性能确认（PPQ）。在第二阶段，必须遵照符合 CGMP 的程序。进入商业流通前，第二阶段的成功完成是必需的。[15] 在此阶段生产的产品，如果可以被接受，可以放行流通。

1. Design of a Facility and Qualification of Utilities and Equipment

1. 厂房设施设计以及公用设施与设备确认

Proper design of a manufacturing facility is required under part 211, subpart C, of the CGMP regulations on *Buildings and Facilities*. It is essential that activities performed to assure proper facility design and commissioning precede PPQ. Here, the term *qualification* refers to activities undertaken to demonstrate that utilities and equipment are suitable for their intended use and perform properly. These activities necessarily precede manufacturing products at the commercial scale.
根据 CGMP 法规 211 节 C 亚节对建筑和厂房设施的要求，生产厂房设施需要正确设计。至关重要的是，为保证适用的厂房设施设计和试运行而进行的活动应先于工艺性能确认（PPQ）。在这里，专业名词*确认*（*qualification*）指为显示公用设施及设备符合预期用途和运转正确而从事的活动。这些活动必需先于商品化大生产的产品生产。

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[14] Available at www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. Other references that may be useful include ASTM E2474-06 "Standard Practice for Pharmaceutical Process Design Utilizing Process Analytical Technology" and ASTM E2476-09 "Standard Guide for Risk Assessment and Risk Control as it Impacts the Design, Development, and Operation of PAT Processes for Pharmaceutical Manufacture."
[14]可从下述网址获得：www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. 其它可能有用的参考材料包括美国材料与检测协会（ASTM） E2474-06《利用过程分析技术的制药工艺设计标准规范》和美国材料与检测协会（ASTM）E2476-09《风险评价和风险控制标准指南及其对药品生产过程检测工艺设计、开发及操作的影响》。 ，

[15]As discussed in section III of this guidance, process validation (including process qualification) is legally enforceable under section 501(a)(2)(B) of the Act. FDA regulations require that process validation procedures be established and followed (§ 211.100) before a batch can be distributed (§§ 211.22 and 211.165).
[15]正如本指南第三部分讨论，根据法令（501(a)(2)(B)节，工艺验证（包括工艺确认）依法强制执行。FDA 法规要求，在批次进入流通前(§§ 211.22 and 211.165),应建立和遵守工艺验证程序（§ 211.100）。

Qualification of utilities and equipment generally includes the following activities:
公用设施和设备确认一般包括下述活动：

• Selecting utilities and equipment construction materials, operating principles, and performance characteristics based on whether they are appropriate for their specific uses.
• 选择公用设施和设备建筑材料、操作原则、以及性能特性是否以适用于其特定用途为基础。

• Verifying that utility systems and equipment are built and installed in compliance with the design specifications (e.g., built as designed with proper materials, capacity, and functions, and properly connected and calibrated).
• 核实公用设施体系和设备遵照设计规范建造与安装（例如，使用适当材料、产能、和功能按照设计建造，并正确连接和校准）。

• Verifying that utility systems and equipment operate in accordance with the process requirements in all anticipated operating ranges. This should include challenging the equipment or system functions while under load comparable to that expected during routine production. It should also include the performance of interventions, stoppage, and start-up as is expected during routine production. Operating ranges should be shown capable of being held as long as would be necessary during routine production.
• 按照工艺要求操作，在所有预见到的运行范围内，核实公用设施系统和设备。应包括在可与日常生产预期相比的负荷下考验设备或系统功能。还应包括预期的日常生产条件下的干预、停止和启动性能。运行范围应显示能够保持与日常生产需要一样尽可能长。

Qualification of utilities and equipment can be covered under individual plans or as part of an overall project plan. The plan should consider the requirements of use and can incorporate risk management to prioritize certain activities and to identify a level of effort in both the performance and documentation of qualification activities. The plan should identify the following items:
公用设施与设备确认可被个别计划覆盖，或作为一项整体项目计划的部分。计划应考虑使用需要，并融入风险管理，使某些活动得以优先进行，并从确认活动表现和文件记录两方面确认投入水平。计划应确定以下事项：

1. the studies or tests to use,
1. 使用的研究或检测；

2. the criteria appropriate to assess outcomes,
2. 适用于评价结果的标准；

3. the timing of qualification activities,
3. 确认活动的时机；

4. the responsibilities of relevant departments and the quality unit, and
4. 相关部门和质量部门的责任，以及

5. the procedures for documenting and approving the qualification.

5. 文件记录和批准确认程序。

The project plan should also include the firm's requirements for the evaluation of changes. Qualification activities should be documented and summarized in a report with conclusions that address criteria in the plan. The quality control unit must review and approve the qualification plan and report (§ 211.22).
项目计划应包括公司对变更评价的要求。确认活动应用文件记录，并用突出计划标准的结论的报告加以总结。质量控制部门必须审核和批准确认计划和报告(§ 211.22)。

2. Process Performance Qualification

2. 工艺性能确认

The process performance qualification (PPQ) is the second element of Stage 2, process qualification. The PPQ combines the actual facility, utilities, equipment (each now qualified), and the trained personnel with the commercial manufacturing process, 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.
工艺性能确认（PPQ）是第二阶段工艺确认的第二个要素。工艺性能确认（PPQ） 结合实际设施、公用设施、设备（现均确认）、以及在商品化制造工艺、控制程序、和生产商品批次组分方面接受过训练的人员。一项成功的工艺性能确认将对工艺设计给予确认，并显示商品化制造工艺性与预期一样。

Success at this stage signals an important milestone in the product lifecycle. A manufacturer must successfully complete PPQ before commencing commercial distribution of the drug product.16 The decision to begin commercial distribution should be supported by data from commercial-scale batches. Data from laboratory and pilot studies can provide additional assurance that the commercial manufacturing process performs as expected.
此阶段的成功，在产品生命周期中标志着一个重要的里程碑。生产商着手药品商业流通之前，必须成功完成工艺性能确认（PPQ）。[16] 开始商业流通的决策应有来自于商品化大生产批次的数据支持。来自于实验室小试和中试研究的数据能为商品化制造工艺表现达到预期。

The approach to PPQ should be based on sound science and the manufacturer's overall level of product and process understanding and demonstrable control. The cumulative data from all relevant studies (e.g., designed experiments; laboratory, pilot, and commercial batches) should be used to establish the manufacturing conditions in the PPQ. To understand the commercial process sufficiently, the manufacturer will need to consider the effects of scale. However, it is not typically necessary to explore the entire operating range at commercial scale if assurance can be provided by process design data. Previous credible experience with sufficiently similar products and processes can also be helpful. In addition, we strongly recommend firms employ objective measures (e.g., statistical metrics) wherever feasible and meaningful to achieve adequate assurance.
工艺性能确认方法应该以可靠的科学、以及生产商对产品和工艺的理解和可验证的控制的总体水平为基础。来自所有相关研究的累积数据（例如，经过设计的实验、实验室小试、中试、以及商品批次）应用于在工艺性能确认中建立生产条件。为充分理解商品化工艺，生产商需考虑规模效应。不过，如果有工艺设计数据提供保证，通常不需要在商品化大规模生产探索整个运行范围。之前就有足够类似商品和工艺的可靠经验也有帮助。此外，只要是可行和对

[16]See section III of this guidance, Statutory and Regulatory Requirements for Process Validation.
[16] 参见本指南第三节：对工艺验证的法定和监管要求。

取得足够保证有意义，我们强烈建议公司使用客观测量方法（例如统计度量）。

In most cases, PPQ will have a higher level of sampling, additional testing, and greater scrutiny of process performance than would be typical of routine commercial production. The level of monitoring and testing should be sufficient to confirm uniform product quality throughout the batch. The increased level of scrutiny, testing, and sampling should continue through the process verification stage as appropriate, to establish levels and frequency of routine sampling and monitoring for the particular product and process. Considerations for the duration of the heightened sampling and monitoring period could include, but are not limited to, volume of production, process complexity, level of process understanding, and experience with similar products and processes.
在绝大多数情况下，与典型的常规商品化生产相比，工艺性能确认将拥有较高的取样和额外检测水平，以及更仔细的工艺性能详查。监测和检测水平应足以在整个批次内确认始终如一的产品质量。在适当的情况下，审查、检测和取样程度增加应持续贯穿工艺核实阶段，以建立常规取样和对特定产品及工艺的监测水平和频率。考虑加强取样期限和监测期可能包括，但不局限于产量、工艺性复杂性、工艺理解水平和类似产品及工艺的经验。

The extent to which some materials, such as column resins or molecular filtration media, can be re-used without adversely affecting product quality can be assessed in relevant laboratory studies. The usable lifetimes of such materials should be confirmed by an ongoing PPQ protocol during commercial manufacture.
一些材料，例如柱填充树脂或分子过滤介质，在对产品质量没有不利影响的情况下可以再利用，再利用程度可在相关实验室研究中进行评价。这种材料的可用寿命应在商品化生产中通过正在进行的工艺性能确认确定。

A manufacturing process that uses PAT may warrant a different PPQ approach. PAT processes are designed to measure in real time the attributes of an in-process material and then adjust the process in a timely control loop so the process maintains the desired quality of the output material. The process design stage and the process qualification stage should focus on the measurement system and control loop for the measured attribute. Regardless, the goal of validating any manufacturing process is the same: to establish scientific evidence that the process is reproducible and will consistently deliver quality products.
使用过程分析检测（PAT）的生产工艺可能需要一种不同的工艺性能确认方法证明。过程分析检测（PAT）工艺被设计用来实时检测一种在加工材料的多种属性，并在随后通过实时控制环路对工艺进行调整，以使工艺保持输出材料的期望得到的产出材料质量。工艺设计阶段和工艺确认阶段应集中于待检测属性的检测系统和控制环。无论如何，验证任何生产工艺的目的只有一个：为工艺可重现和始终如一地产出优质产品建立科学证据。

3. PPQ Protocol

3. 工艺性能确认方案

A written protocol that specifies the manufacturing conditions, controls, testing, and expected outcomes is essential for this stage of process validation. We recommend that the protocol discuss the following elements:
规定了生产条件、控制、检测和预期结果的一份书面方案对质量验证的这一过程至关重要。我们建议方案讨论下述要素：

- The manufacturing conditions, including operating parameters, processing limits, and component (raw material) inputs.
- 生产条件，包括运行参数、工艺限度和组分（原材料）输入。

• The data to be collected and when and how it will be evaluated.
• 待收集数据以及何时和如何对其进行评估。

• Tests to be performed (in-process, release, characterization) and acceptance criteria for each significant processing step.
• 每一重要工艺步骤需开展的检测（过程、放行、鉴定）以及可接受标准。

• The sampling plan, including sampling points, number of samples, and the frequency of sampling for each unit operation and attribute. The number of samples should be adequate to provide sufficient statistical confidence of quality both within a batch and between batches. The confidence level selected can be based on risk analysis as it relates to the particular attribute under examination. Sampling during this stage should be more extensive than is typical during routine production.
• 取样方案，包括每一单元操作及属性的取样点、样品数和取样频率。样品数应该对批内和批间质量均足以提供统计学置信度。选定的置信水平可以考察中的特殊属性相关的风险分析为基础。此阶段取样应比日常生产中的典型取样更广泛。

• Criteria and process performance indicators that allow for a science- and risk-based decision about the ability of the process to consistently produce quality products. The criteria should include:
• 考虑到关于始终如一地生产优质产品能力的基于科学和风险的决策标准和工艺性能指标。这些标准应包括：

-a description of the statistical methods to be used in analyzing all collected data (e.g., statistical metrics defining both intra-batch and inter-batch variability).
-用于分析所有收集数据的统计学方法描述（例如：定义批内及批间变异的统计度量）。

-Provision for addressing deviations from expected conditions and handling of nonconforming data. Data should not be excluded from further consideration in terms of PPQ without a documented, science-based justification.[17]
-强调期望条件与非一致性数据处理间偏差的规定。就工艺性能确认而言，如果没有文件证明和基于科学的正当理由，数据不应被排除于进一步的考虑之外。[17]

• Design of facilities and the qualification of utilities and equipment, personnel training and qualification, and verification of material sources (components and container/closures), if not previously accomplished.
• 如果之前未完成，厂房设施设计和公用设施及设备确认、人员培训与确认、以及材料来源核实（组分和容器/密闭材料）。

• Status of the validation of analytical methods used in measuring the process, in-process materials, and the product.
• 用于工艺、在加工材料和产品测定的分析方法验证状态。

[17] For additional guidance regarding out-of-specification results, see FDA's Guidance for Industry, *Investigating Out-of-Specification (OOS)Test Results for Pharmaceutical Production*, available at www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070287.pdf.
[17]关于不合规格结果的额外指南，请参阅FDA行业指南《药品生产不合规格（OOS）检测结果审查》（FDA's Guidance for Industry, *Investigating Out-of-Specification (OOS)Test Results for Pharmaceutical Production*，）可从下述网址获得：www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070287.pdf.

• Review and approval of the protocol by appropriate departments and the quality unit.
• 相应部门及质量部门对方案的审核和批准。

4. PPQ Protocol Execution and Report

4. 工艺性能确认执行与报告

Execution of the PPQ protocol should not begin until the protocol has been reviewed and approved by all appropriate departments, including the quality unit. Any departures from the protocol must be made according to established procedure or provisions in the protocol. Such departures must be justified and approved by all appropriate departments and the quality unit before implementation (§ 211.100).
在相应部门、包括质量部门对方案已经审核和做出批准前，不应开始执行工艺性能确认方案。对方案的任何偏离，必须按照方案中已建立的程序或规定做出。这种偏离在实施前必须由所有相应部门和质量部门证明合理和批准。

The commercial manufacturing process and routine procedures must be followed during PPQ protocol execution (§§ 211.100(b) and 211.110(a)). The PPQ lots should be manufactured under normal conditions by the personnel routinely expected to perform each step of each unit operation in the process. Normal operating conditions should include the utility systems (e.g., air handling and water purification), material, personnel, environment, and manufacturing procedures.
在工艺性能确认期间，必须遵照商品化制造工艺和日常程序(§§ 211.100(b)和 211.110(a))。工艺性能确认批次应在正常条件下由日常要求进行工艺中每一单元操作中的每一步骤的人员生产。正常操作条件应包括公用设施系统（例如，空气处理和水纯化）、物料、人员、环境和制造工序。

A report documenting and assessing adherence to the written PPQ protocol should be prepared in a timely manner after the completion of the protocol. This report should:
方案完成之后，应编写报告，用文件记录和评价遵守书面工艺性能确认方案情况。该报告应：

• Discuss and cross-reference all aspects of the protocol.
• 讨论并相互参照方案的所有方面。

• Summarize data collected and analyze the data, as specified by the protocol.
• 按照方案规定，总结所收集的数据和对数据进行分析。

• Evaluate any unexpected observations and additional data not specified in the protocol.
•对任何意外的观察和方案中没有规定的额外数据进行评估。

• Summarize and discuss all manufacturing nonconformances such as deviations, aberrant test results, or other information that has bearing on the validity of the process.
•总结和讨论所有生产中的不符合项，例如偏差、异常检测结果或与工艺有效性有关的其它信息。

• Describe in sufficient detail any corrective actions or changes that should be made to existing procedures and controls.
•充分详细地说明应该对现行程序与控制采取的任何整改措施或变更。

• State a clear conclusion as to whether the data indicates the process met the conditions established in the protocol and whether the process is considered to be in a state of control. If not, the report should state what should be accomplished before such a conclusion can be reached. This conclusion should be based on a documented justification for the approval of the process, and release of lots produced by it to the market in consideration of the entire compilation of knowledge and information gained from the design stage through the process qualification stage.

• 对数据是否显示工艺符合方案建立的条件，和公式是否被认为处于受控状态，详述明确结论。如果不是，该报告应该声明，得到这样一个结论之前应该完成什么。该结论应基于对工艺批准，以及考虑从设计阶段到工艺确认阶段获得的所有知识和信息汇编条件下，放行按照该工艺生产批次进入市场的有文件证明的正当理由。

• Include all appropriate department and quality unit review and approvals.

• 包括所有相应部门和质量部门审核和批准。

D. Stage 3 - Continued Process Verification

D. 第三阶段 - 持续工艺验证

The goal of the third validation stage is continual assurance that the process remains in a state of control (the validated state) during commercial manufacture. A system or systems for detecting unplanned departures from the process as designed is essential to accomplish this goal. Adherence to the CGMP requirements, specifically, the collection and evaluation of information and data about the performance of the process, will allow detection of undesired process variability. Evaluating the performance of the process identifies problems and determines whether action must be taken to correct, anticipate, and prevent problems so that the process remains in control (§ 211.180(e)).

第三个验证阶段的目标,是在商品化生产期间持续保证工艺处于受控状态（已验证状态）。用于探测出计划之外从设计工艺偏离的一个或多个体系，对完成这一目标至关重要。遵守 CGMP 要求，特别是，收集和评估关于工艺性能的信息和数据，使探测出并非期望的工艺变异成为可能。评估工艺性能，发现问题和确定是否采取行动整改、提前预见和防止问题，从而使工艺保持受控 (§ 211.180(e))。

An ongoing program to collect and analyze product and process data that relate to product quality must be established (§ 211.180(e)). The data collected should include relevant process trends and quality of incoming materials or components, in-process material, and finished products. The data should be statistically trended and reviewed by trained personnel. The information collected should verify that the quality attributes are being appropriately controlled throughout the process.

必须建立一个持续和不断发展的程序,收集和分析与产品质量有关的产品和工艺数据(§ 211.180(e))。所搜集的数据,应包括相关的工艺趋势和引入物料或组分、在加工材料和成品。数据应进行统计学趋势分析,并由经过培训的人员审核。对所收集信息，应核实质量属性在整个工艺中正受到适当控制。

We recommend that a statistician or person with adequate training in statistical process control techniques develop the data collection plan and statistical methods and procedures used in measuring and evaluating process stability and process capability.[18] Procedures should describe how trending and calculations are to be performed and should guard against overreaction to individual events as well as against failure to detect unintended process variability. Production data should be collected to evaluate process stability and capability. The quality unit should review this information. If properly carried out, these efforts can identify

variability in the process and/or signal potential process improvements.
我们建议，由统计学家或是在统计学工艺控制技术方面受过充分训练的人员，开发用于测定和评估工艺稳定性和工艺能力的数据收集方案、统计学方法及程序。[18] 程序应说明如何进行趋势分析和计算，还应防止对个别事件的过度反应，以及防止不能探测到意外的工艺变异。应收集生产数据对工艺稳定性和工艺能力进行评估。质量部门应审核这类信息。如果正确实施，这些努力能够甄别出工艺变异和/或有潜力用于工艺改进的信号。

Good process design and development should anticipate significant sources of variability and establish appropriate detection, control, and/or mitigation strategies, as well as appropriate alert and action limits. However, a process is likely to encounter sources of variation that were not previously detected or to which the process was not previously exposed. Many tools and techniques, some statistical and others more qualitative, can be used to detect variation, characterize it, and determine the root cause. We recommend that the manufacturer use quantitative, statistical methods whenever appropriate and feasible. Scrutiny of intra-batch as well as inter-batch variation is part of a comprehensive continued process verification program under § 211.180(e).
良好的工艺设计和开发，应能提前预见变异的重要来源，建立适当的探测、控制和/或减轻策略，以及适当的报警和行动限制。然而，一项工艺可能会遇到之前没有探测到，或工艺没有在之前面临的多个变异来源。很多工具和技术，一些属于统计学的及更多属于定性的，能用来探测变异，表征其特征，以及确定根本原因。我们建议生产商在任何适当和可行的情况下，使用定量、统计学方法。详查批内以及批间变异，是§ 211.180(e)中全面持续工艺核查计划的部分。

We recommend continued monitoring and sampling of process parameters and quality attributes at the level established during the process qualification stage until sufficient data are available to generate significant variability estimates. These estimates can provide the basis for establishing levels and frequency of routine sampling and monitoring for the particular product and process. Monitoring can then be adjusted to a statistically appropriate and representative level. Process variability should be periodically assessed and monitoring adjusted accordingly.
我们建议，在拥有足够数据产生有意义的变异估计之前，在工艺确认阶段中，在已经建立的水平对工艺参数和质量属性进行持续检测和取样。这些估计能为特定产品和工艺建立日常取样和监测水平和频率提供基础。检测能因此调整到一个统计学上适当的、具有代表性的水平。工艺变异应定期进行评价，并相应地对监测做出调整。

Variation can also be detected by the timely assessment of defect complaints, out-of-specification findings, process deviation reports, process yield variations, batch records, incoming raw material records, and adverse event reports. Production line operators and quality unit staff should be encouraged to provide feedback on process performance. We recommend that the quality unit meet periodically with production staff to evaluate data, discuss possible trends or undesirable process variation, and coordinate any

[18] Some references that may be useful include the following: ASTM E2281-03 “Standard Practice for Process and Measurement Capability Indices,” ASTM E2500-07 “Standard Guide for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment,” and ASTM E2709-09 “Standard Practice for Demonstrating Capability to Comply with a Lot Acceptance Procedure.” This is not a complete list of all useful references on this topic. Many industry standards, books, and guides on these topics are available.
[18].包括下列在内的一些参考资料可能有用：美国材料与检测协会（ASTM）E2281-03 《工艺与量测能力指数标准规范》、美国材料与检测协会（ASTM）E2500-07 《制药与生物药生产系统及设备技术规格、设计与核实标准指南》，以及美国材料与检测协会（ASTM）E2709-09 《显示符合批次接受程序能力的标准规范》。此处所列并非该主题可用参考资料的完整列表。可以得到很多与这些主题有关的行业标准、书籍和指南。

correction or follow-up actions by production.
通过及时评价缺陷投诉、对不和规格的调查结果、工艺偏离报告、工艺产率差异、批报告、引入的原材料报告以及不良事件报告等，可以探测到变异。应鼓励生产线操作人员和质量部门员工提供对工艺性能的反馈。我们建议质量部门定期与生产部门人员开会，评估数据、讨论意料之外的工艺变异，并通过生产协调任何整改或后续行动。

Data gathered during this stage might suggest ways to improve and/or optimize the process by altering some aspect of the process or product, such as the operating conditions (ranges and set-points), process controls, component, or in-process material characteristics. A description of the planned change, a well-justified rationale for the change, an implementation plan, and quality unit approval before implementation must be documented (§ 211.100). Depending on how the proposed change might affect product quality, additional process design and process qualification activities could be warranted.[19]
本阶段收集到的数据，可能为通过改变工艺或产品的一些方面，例如操作条件（范围或设置点）、工艺控制、组分、或在加工材料特性对工艺进行改进和/或优化。计划中的变更、变更的充分正当理由、实施计划的说明，以及实施前质量部门的批准，必须以文件记录(§ 211.100)。取决于拟议中的变更可能对产品质量的影响，可能需要额外的工艺设计和工艺确认活动。[19]

Maintenance of the facility, utilities, and equipment is another important aspect of ensuring that a process remains in control. Once established, qualification status must be maintained through routine monitoring, maintenance, and calibration procedures and schedules (21 CFR part 211, subparts C and D). The equipment and facility qualification data should be assessed periodically to determine whether re-qualification should be performed and the extent of that re-qualification. Maintenance and calibration frequency should be adjusted based on feedback from these activities.
厂房设施、公用设施和设备的维护是确保一项工艺保持受控状态的另一个重要方面。一经建立，确认状态必须通过日常监测、维护、校准程序和日程进行维护（《联邦法规 21 编 211 节 C 和 D 亚节》。设备与厂房设施数据应进行定期评价，以确定是否应开展重新确认及重新确认的范围。维护和校准频率应基于这些活动的反馈予以调整。

V. CONCURRENT RELEASE OF PPQ BATCHES

五. 工艺性能确认批次的同时放行

In most cases, the PPQ study needs to be completed successfully and a high degree of assurance in the process achieved before commercial distribution of a product. In special situations, the PPQ protocol can be designed to release a PPQ batch for distribution before complete execution of the protocol steps and activities, i.e., concurrent release. FDA expects that concurrent release will be used rarely.
在绝大多数情况下，在产品商业流通之前，工艺性能确认研究需要成功完成，并实现工艺的高度保证。特殊情况下，可以设计工艺性能确认方案，在完全执行方案步骤和活动之前放行工艺性能确认批次，即同时放行。FDA 希望很少使用同时放行。

Concurrent release might be appropriate for processes used infrequently for various reasons, such as to manufacture drugs for which there is limited demand (e.g., orphan drugs, minor use and minor species

[19] Certain manufacturing changes may call for formal notification to the Agency before implementation, as directed by existing regulations (see, e.g., 21 CFR 314.70 and 601.12).
[19] 按现行法规的规定(参见《联邦法规 21 编 314.70 和 601.1221》，某些生产变更可能需要在实施前需要正式通知 FDA。

veterinary drugs) or which have short half lives (e.g., radiopharmaceuticals, including positron emission tomography drugs). Concurrent release might also be appropriate for drugs that are medically necessary and are being manufactured in coordination with the Agency to alleviate a short supply.
同时放行可能适用于由于多种原因不经常使用的工艺，例如生产需求有限的药品（例如罕见病用药，较少使用及次要物种用兽药），或半衰期短的药品（例如放射性药品，包括正电子发射断层扫描术用药）。同时放行可能也适用于医学上需要或与本机构协调生产，用来减缓供应短缺的药品。

Conclusions about a commercial manufacturing process can only be made after the PPQ protocol is fully executed and the data are fully evaluated. If Stage 2 qualification is not successful (i.e., does not demonstrate that the process as designed is capable of reproducible performance at commercial scale), then additional design studies and qualification may be necessary. The new product and process understanding obtained from the unsuccessful qualification study(ies) can have negative implications if any lot was already distributed. Full execution of Stages 1 and 2 of process validation is intended to preclude or minimize that outcome.
只有在工艺性能确认方案完全实施，以及和对数据进行完全评估之后，才能就商品化制造工艺做出结论。如果第二阶段确认未获成功（即未能显示按照设计的工艺在商品化大规模生产中具有可重现的性能），那么可能需要额外的设计研究和确认。如果有任何批次进入流通，从不成功的确认研究中获得的新产品和工艺理解，会具有负面的可能影响。充分实施第一和第二阶段工艺验证旨在排除或最大程度地减少这种结果。

Circumstances and rationale for concurrent release should be fully described in the PPQ protocol. Even when process performance assessment based on the PPQ protocol is still outstanding, any lot released concurrently must comply with all CGMPs, regulatory approval requirements, and PPQ protocol lot release criteria. Lot release under a PPQ protocol is based upon meeting confidence levels appropriate for each quality attribute of the drug.
应在工艺确认方案中,对同时放行的客观环境和理由给予充分说明。即便基于工艺性能确认方案的工艺性能评价依然是出色的，任何同时放行的批次必须符合 CGMPs、监管批准要求和工艺性能确认批次放行要求。按照工艺性能确认草案的批次放行以符合适用于药品所有质量属性的置信度水平为基础。

When warranted and used, concurrent release should be accompanied by a system for careful oversight of the distributed batch to facilitate rapid customer feedback. For example, customer complaints and defect reports should be rapidly assessed to determine root cause and whether the process should be improved or changed. Concurrently released lots must also be assessed in light of any negative PPQ study finding or conclusions and appropriate corrective action must be taken (§§ 211.100(a), 211.180(e), and 211.192). We recommend that each batch in a concurrent release program be evaluated for inclusion in the stability program. It is important that stability test data be promptly evaluated to ensure rapid detection and correction of any problems.
需要和使用时，同时放行应伴以对流通批次进行仔细监督，以促进快捷的顾客反馈。例如，顾客投诉和缺陷报告应进行迅速评价，以确定根本原因和工艺是否应改进或变更。考虑到任何的负面工艺性能确认研究结果或结论，必须采取适当的整改措施，同时放行批次也必须进行评价(§§ 211.100(a), 211.180(e), 和 211.192)。我们建议，同时放行计划中的每一批次评价纳入稳定性程序中进行评估。重要的是，对稳定性检测数据迅速做出评估，以保证快速探测到和

纠正任何问题。

VI. DOCUMENTATION

六. 文件记录

Documentation at each stage of the process validation lifecycle is essential for effective communication in complex, lengthy, and multidisciplinary projects. Documentation is important so that knowledge gained about a product and process is accessible and comprehensible to others involved in each stage of the lifecycle. Information transparency and accessibility are fundamental tenets of the scientific method. They are also essential to enabling organizational units responsible and accountable for the process to make informed, science-based decisions that ultimately support the release of a product to commerce.
在工艺验证生命周期的所有阶段，文件记录对复杂、漫长和多学科项目的有效沟通至关重要。文件记录非常重要，从有关产品和工艺获得的知识，可供生命周期每一阶段涉及的其他人获得和领会。信息透明和可获得性是科学方法的基本信条。它们对促使对此工艺负责和负有被问责义务的企业中各管理部门做出有资料根据的、基于科学的最终使产品成为商品的决策。

The degree and type of documentation required by CGMP vary during the validation lifecycle. Documentation requirements are greatest during Stage 2, process qualification, and Stage 3, continued process verification. Studies during these stages must conform to CGMPs and must be approved by the quality unit in accordance with the regulations (see §§ 211.22 and 211.100). Viral and impurity clearance studies, even when performed at small scale, also require quality unit oversight.
在验证生命周期中，CGMP 要求的文件记录的程度和类型各不相同。在第二阶段工艺确认和第三阶段持续工艺核实，对文件记录的要求最大。这些阶段的研究必须符合 CGMPs，并且必须由质量部门依据法规（参见§§ 211.22 和 211.100)给予批准。病毒和杂质清除研究，即便是在小规模水平上开展，也要求质量部门监督。

CGMP documents for commercial manufacturing (i.e., the initial commercial master batch production and control record (§ 211.186) and supporting procedures) are key outputs of Stage 1, process design. We recommend that firms diagram the process flow for the full-scale process. Process flow diagrams should describe each unit operation, its placement in the overall process, monitoring and control points, and the component, as well as other processing material inputs (e.g., processing aids) and expected outputs (i.e., in-process materials and finished product). It is also useful to generate and preserve process flow diagrams of the various scales as the process design progresses to facilitate comparison and decision making about their comparability.
用于商品化制造的 CGMP 文件记录（即最初的商品化主批次生产、控制记录(§ 211.186)和支持程序），是第一阶段工艺设计的关键产品。我们建议公司绘制完整的工艺流程。工艺流程图应说明每一个单元操作，以及其它加工材料输入（例如加工助剂）和预期输出（即在加工材料和成品）。随工艺设计进展，利于比较和就其可比性做出决策，生成和保存不同规模的工艺流程图也是有用的。

VII. ANALYTICAL METHODOLOGY

七. 分析方法

Process knowledge depends on accurate and precise measuring techniques used to test and examine the quality of drug components, in-process materials, and finished products. Validated analytical methods are not necessarily required during product- and process-development activities or when used in characterization

studies. Nevertheless, analytical methods should be scientifically sound (e.g., specific, sensitive, and accurate) and provide results that are reliable. There should be assurance of proper equipment function for laboratory experiments. Procedures for analytical method and equipment maintenance, documentation practices, and calibration practices supporting process-development efforts should be documented or described. New analytical technology and modifications to existing technology are continually being developed and can be used to characterize the process or the product. Use of these methods is particularly appropriate when they reduce risk by providing greater understanding or control of product quality. However, analytical methods supporting commercial batch release must follow CGMPs in parts 210 and 211. Clinical supply production should follow the CGMPs appropriate for the particular phase of clinical studies.

工艺知识有赖于用于药品组分质量、在加工材料以及成品质量检测和检查的准确和精密的测定技术。经过验证的分析方法，在产品开发和工艺开发活动中或使用于鉴定研究中不一定需要。然而，分析方法应科学合理（例如特异、敏感和准确）和提供可靠结果。应为实验室实验保证正确的仪器功能。支持工艺开发努力的分析方法和仪器维护、文件记录规范、校准规范应以文件记录和说明。新的分析技术对现有技术的修改处于持续发展中，并能用于鉴定工艺或产品。在这些方法通过提供对产品质量更多的理解或控制降低风险的情况下，这些方法的使用尤其适合。但是，支持商品化批放行的分析方法必须遵照 CGMPs201 和 211 节。临床供应生产应遵照适合于临床研究特定阶段的 CGMPs。

GLOSSARY

术语表

Capability of a process: Ability of a process to produce a product that will fulfill the requirements of that product. The concept of process capability can also be defined in statistical terms. (ISO 9000:2005)
工艺能力：一种工艺生产满足产品需求的产品的能力。工艺能力概念也能以统计学术语定义。(ISO 9000:2005)

Commercial manufacturing process: The manufacturing process resulting in commercial product (i.e., drug that is marketed, distributed, and sold or intended to be sold). For the purposes of this guidance, the term *commercial manufacturing process* does not include clinical trial or treatment IND material.
商品化制造工艺:生产出商品化产品的生产工艺（即用于经销、流通、出售或拟出售的药品）。就本指南而言，商业生产工艺这一专业名词不包括临床试验或用于治疗的研究型药物（IND）材料。

Concurrent release: Releasing for distribution a lot of finished product, manufactured following a qualification protocol, that meets the lot release criteria established in the protocol, but before the entire study protocol has been executed.
同时放行：一个批次的成品流通的放行，遵照确认方案生产，符合方案中建立的批放行标准，但在整个研究方案已获执行之前。

Continued process verification: Assuring that during routine production the process remains in a state of control.
连续工艺核实:保证日常生产中工艺处于受控状态。

Performance indicators: Measurable values used to quantify quality objectives to reflect the performance of an organization, process or system, also known as *performance metrics* in some regions. (ICH Q10)
性能指标:用于量化质量目标以反映一个组织、工艺或系统性能，在一些地区也被称为性能度量。(ICH Q10)

Process design: Defining the commercial manufacturing process based on knowledge gained through development and scale-up activities.
工艺设计:基于通过开发或放大活动获得的知识定义商品化制造工艺。

Process qualification: Confirming that the manufacturing process as designed is capable of reproducible commercial manufacturing.
工艺确认:确认按照设计的生产能够可重现商品化制造。

Process validation: The collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality products.
工艺验证：从工艺设计阶段到商品化生产，收集和评估数据，建立工艺能够始终如一地产出优质产品的科学证据。

Quality: The degree to which a set of inherent properties of a product, system, or process fulfils

requirements. (ICH Q9)
质量:一个产品、系统、或工艺的一组内在特性满足需求的程度。(ICH Q9)

State of control: A condition in which the set of controls consistently provides assurance of continued process performance and product quality. (ICH Q10)
受控状态: 一组其中的控制始终如一地提供持续工艺性能和产品质量的状况。(ICH Q10)

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