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1.0 Introduction
前言

1.1 Purpose and Scope
目的和范围

This Technical Report (TR) is intended to provide practical guidance on the implementation of a lifecycle approach to pharmaceutical process validation (PV). It contains information that enables manufacturers to implement globally-compliant PV programs consistent with the principles of recent lifecycle-based PV guidance documents and current expectations for Pharmaceutical Quality Systems ***(1-4).*** In pharmaceutical manufacturing, "process validation" is the collection and evaluation of data -from the process design stage through commercial production that establishes scientific evidence that a process is capable of consistently delivering quality product ***(3).*** The U.S. FDA and EMA consider PV a requirement in both general and specific terms in current Good Manufacturing Practice (cGMP) guidelines and an essential element in the assurance of drug quality ***(2,3,5).***

本技术报告（Technical Report,TR）旨在为制药工艺验证（PV）生命周期方法的实施提供实用指南。它包含的信息能够使生产厂家实施全球认可的工艺验证程序，该程序与最近的基于生命周期的工艺验证指导文件和现行对药品质量系统期望相一致（1-4）。在医药生产中，"工艺验证"是收集和评价工艺设计阶段的数据，通过商业化生产的方式确定科学的证据，证明一个工艺能够持续地提供高质量的产品（3）。美国 FDA 和欧洲药监局认定 PV 在现行 GMP 指南的综述和具体条框中都是必要条件和药品质量保证的必需元素（2,3,5）。

The PV lifecycle concept links product and process development, the qualification of the commercial manufacturing processes, and maintenance of the commercial production process in a coordinated effort ***(3).*** When based on sound process understanding and used with quality risk management principles, the lifecycle approach allows manufacturers to use continuous process verification (enhanced approach) in addition to, or instead of, traditional PV ***(1,2,6).***

工艺验证生命周期概念连接产品和工艺开发、商业化生产确认和协同努力下商业化生产过程的维持（3）。当基于良好的工艺理解和使用质量风险管理时，生命周期法可考虑生产者在使用传统的工艺验证外，再使用连续工艺确证（增强的方式），或者直接由后者代替前者（1,2,6）。

The information in this TR applies to the manufacturing processes for drug substances and drug products, including:

在本 TR 中应用于药物和药品生产过程的信息，包括：

- Pharmaceuticals, sterile and non-sterile
  无菌和非无菌药物
- Biotechnological/biological products, including vaccines
  生物技术/生物产品，包含疫苗
- Active Pharmaceutical Ingredients (APIs)
  原料药（APIs）
- Radiopharmaceuticals
  放射性药物
- Veterinary drugs
  兽药

• Drug constituents of combination products (e.g., a combination drug and medical device)
组合产品的药物成分（如，复方抗菌药和医疗器械）

This report is prepared for global use and applies to new and existing (i.e., legacy) commercial manufacturing processes. Its scope does not include manufacturing processes for:
这份报告是为全球使用和应用到新的和现有的（即遗留的）商业生产过程做准备。它的范围不包括生产的生产过程如下：

• Medical devices
医疗器械
• Dietary supplements
膳食补充剂
• Medicated feed
药用物料
• Human tissues
人体组织

Although these product categories are outside the scope of this TR, its recommendations are based on modern quality concepts, ICH Quality Guidelines, and recent regulatory authority guidance documents. As such, it may be a useful reference in the development of PV lifecycle approaches for other product categories. The validation of ancillary supporting operations used in pharmaceutical manufacturing processes is not discussed in the report. Many PDA TRs already provide specific guidance for such procedures; for example, cleaning**,** aseptic process simulation**,** moist heat sterilization and dry heat sterilization ***(7-10).***
尽管这些产品分类超出了这份 TR 的范围，但它的建议是基于现代质量思想的/ICH 质量指南和最近的监管机构权威指导性文件。因此，它可能在其他产品类别的工艺验证生命周期法的开发中是有用的参考文献。药物生产过程中的辅助操作的验证在这个报告中不做讨论。一些 FDA 的技术报告已经提供了此类操作规程的具体指导性文件；如：清洁、无菌过程模拟、湿热灭菌和干热灭菌（7-10）。

1.2 Background
背景

The lifecycle concept includes all phases in the life of a product from initial development through commercial production and product discontinuation ***(4,11).*** The use of a lifecycle approach to pharmaceutical product quality is widely thought to facilitate innovation and continual improvement as well as strengthen the link between pharmaceutical development and manufacturing (ICH Q10). The lifecycle philosophy is fundamental in the ICH guidance documents for Pharmaceutical Development (ICH Q8 (R2)), Quality Risk Management (ICH Q9) ***(12),*** Pharmaceutical Quality Systems (ICH Q10), and Development and Manufacture of Drug Substances (ICH Q11). The principles they contain provide the product lifecycle framework and quality system enablers that have been used in recent pharmaceutical process validation guidance documents. A central concept in these documents is that PV is not a one-time event, but rather, an activity that spans the product lifecycle, linking process development, validation of the commercial manufacturing process, and its maintenance during routine commercial production.
生命周期概念包括从起始开发到工业生产直至产品退市的所有阶段（4，11）。生命周期在药品质量上的使用被普遍认为能促进创新和持续改进，也增强了医药开发和生产之间的联系（ICH Q10）。在 ICH 对药物开发（ICH Q8(R2)）、质量风险管理（ICH Q9）（12）、制药质量体系（ICH Q10）和药品

的开发和生产（ICH Q11）,的指导文件中，生命周期哲学是基本原则。这些原则包含提供产品生命周期框架和在最近制药工艺验证指导文件中使用这些原则的质量体系推动者。这些文件的核心理念是工艺验证不是一次性的事，更确切的说，是一项跨越了产品整个生命周期的活动，链接了工艺开发、商品化生产过程的验证和常规商业生产时期的维护等。

The ICH Q8 (R2) guidance document for pharmaceutical development defines procedures for linking product and process development planning to the final commercial process control strategy and quality system. It describes an enhanced scientific and risk-based approach to product and process development that emphasizes statistical analysis, formal experimental design, and the incorporation of knowledge gained from similar products and processes. Manufacturing capabilities and the quality system must be integrated into the process development plan to ensure effective and compliant commercial operations. The functionality and limitations of commercial manufacturing equipment are a primary consideration in the process design.
ICH Q8（R2）对药物开发的指导文件定义了连接产品和工艺开发计划直至最终的商品化过程控制策略和质量体系的程序。它采用了增强的科学的和基于风险的方法去生产和工艺开发，强调统计学分析、正规实验设计和从相似产品和工艺上获取知识等。生产能力和质量体系必须结合到工艺开发计划中去，确保有效作用和商业化操作的兼容性。商业化生产设备的功能性和局限性是工艺设计首先要考虑的问题。

The ICH Quality Risk Management guidance document (ICH Q9) describes the use of a risk-based approach to pharmaceutical development and manufacturing quality. These approaches identify and prioritize those process parameters and product quality attributes with the greatest potential to affect product quality. Specific guidance on the application of the ICH Q9 concepts can be found in *PDA Technical Report 54: Implementation of Quality Risk Management for Pharmaceutical and Biotechnology Manufacturing Operations* and *PDA Technical Report 59: Utilization of Statistical Methods for Production and Business Processes* ***(13,14).*** The FDA process validation guidance document stresses a risk-based approach to develop criteria and process performance indicators, and improve the design and execution of other validation-related activities, such as developing confidence levels and sampling plans ***(3).***
ICH 质量风险管理指导文件（ICH Q9）叙述了使用基于风险的方法指导药品开发和生产质量。这些方法识别和优先考虑那些对产品质量有这最大潜在影响的工艺参数和产品质量属性。应用 ICH Q9 的思想的明确的指导见于 PDA 技术报告 54：*质量风险管理在药物和生物技术生产操作上的实施和 PDA 技术报告 59：统计学方法在生产和商业化流程上的使用（13,14）*。FDA 工艺验证指导文件强调了基于风险方式的开发标准和工艺性能指标和增强了设计和其他验证相关活动的执行，如提高置信水平和取样计划（3）。

Both the FDA and EMA process validation guidance documents aim to integrate PV activities into the pharmaceutical quality system. To achieve the goals outlined in ICH Q10, it is essential to integrate the process design stage into the quality system. Throughout the development effort, product and process development input and alignment from the Quality Unit are required to ensure compatibility with the quality system. Key considerations in product and process design include the commercial control strategy and use of modern quality risk management procedures. Quality and Regulatory organizational components should be part of the cross-functional product team from the beginning of the process validation study design. Their participation is essential to ensure that the study design is compatible with the firm’s quality system, and that submissions will meet regulatory agency expectations.

美国 FDA 和欧洲药监局（EMA）工艺验证指导文件的目标是整合工艺验证活动到药品质量体系中。为了达到 ICH 10 概述中的目标，整合工艺设计阶段到质量体系中是必不可少的。整个研发计划，为了确保质量系统的兼容性，要求产品和工艺的开发投入和质量部平等对接。产品和工艺设计关键考虑的问题包括商业控制策略和使用现代化的质量风险管理程序。从工艺验证研究设计开始，质量和监管组织部门应当是部门功能交叉的产品团队。他们的参与是确保研究设计与公司质量体系相适应的必不可少的条件，并且他们提交的意见书将能满足监管部门的期望。

The Quality Unit should provide appropriate oversight and approval of process validation studies required under GMPs. Although not all process validation activities are performed under GMPs (for example, some Stage 1 – Process Design studies) ***(4),*** it is wise to include the Quality and Regulatory representatives on the cross-functional team. The degree and type of documentation required varies during the validation lifecycle, but documentation is an important element of all stages of process validation. Documentation requirements are greatest during the process qualification and verification stages. Studies during these stages should conform to GMPs and be approved by the Quality Unit.
质量部应当提供适当的审核和并批准 GMP 要求的工艺验证研究。。尽管不是所有的工艺验证活动是在 GMP 框架下执行（例如，某些阶段 1 工艺设计研究）（4），但是在交叉职能的团队中包含有质量和法规部门的代表是明智的。文件的级别和类型在验证生命周期中是需要变化的，但是文件是工艺验证所有阶段的一个重要元素。工艺确认和确证期间文件需求是最大的。这期间的研究应当遵守 GMP 法规和得到质量部门的审批。

The Process Validation Master Plan (PVMP) should describe the rationale, overall validation strategy, and list of specific studies. It should reside within the firm's quality documentation system ***(15).*** A successful validation program is one that is initiated early in the product lifecycle and is not completed until the process or product reaches the end of that lifecycle. A comprehensive corporate policy that defines the expectations and commitment to process validation lifecycle principles is the foundation of a successful validation program. This policy should define the quality management philosophy, components of validation, periodic review or requalification time frames, documentation requirements (including a process validation master plan), validation protocols and reports, and responsibilities of key stakeholders within the organization ***(16).***
工艺验证主计划（PVMP）应当叙述基本原理、全部的验证策略和具体研究清单。它应当归属于公司质量文件系统（15）。成功的验证规程是在产品生命周期的前期就开始了，并且一直持续到工艺或者产品走到生命周期的尽头之前。一个全面的公司政策规定对工艺验证生命周期原则的期望和投入是验证规程成功的基础。公司政策应当规定质量管理理念、验证的组件、定期检查或再确认时间周期、文件需求（包括工艺验证主计划）、验证方案和报告和组织内相关关键人员的责任（16）。

This TR follows the principles and general recommendations presented in current regulatory process validation guidance documents. Of particular note, is that the TR uses the traditional/nontraditional (enhanced) process validation terminology employed by EMA ***(1).*** In this context, nontraditional or enhanced process validation may use Continuous Process Verification as an alternative approach to traditional PV. In the enhanced approach, manufacturing process performance is continuously monitored and evaluated. It is a science and risk-based real-time approach to verify and demonstrate that a process operates within specified parameters and consistently produces material that meets quality and process performance requirements.
本技术报告遵守的原则和基本建议出现在当前法规性的工艺验证指导文件中。特别注意的是，技术

报告使用的传统/非传统（增强的）工艺验证术语来源于欧洲药监局（EMA）(1)。由于这个原因，非传统或增强的工艺验证可使用持续工艺确证作为传统工艺验证的替代方法。在增强版的方法中，连续监控和评估生产工艺性能。这是一个科学的和基于风险的实时方法，它验证和证明了按照规定的参数进行工艺操作，可持续生产出满足质量和工艺性能要求的材料。

The FDA three-stage process validation lifecycle nomenclature (Stage 1-Process Design, Stage 2– Process Qualification, and Stage 3–Continued Process Verification) is used in this TR. Implementation of these stages is discussed in detail in **Sections 3–5.** It should be noted that Continued Process Verification and Continuous Process Verification are distinct terms and have different meanings. Continuous Process Verification refers to validating manufacturing processes that utilize advanced manufacturing and analytical technologies (e.g., PAT systems). FDA uses the term Continued Process Verification generally to mean those activities which maintain the process in a state of control and encompasses all manufacturing scenarios, i.e., traditional manufacturing, manufacturing employing advanced technologies of any kind or any combination thereof.

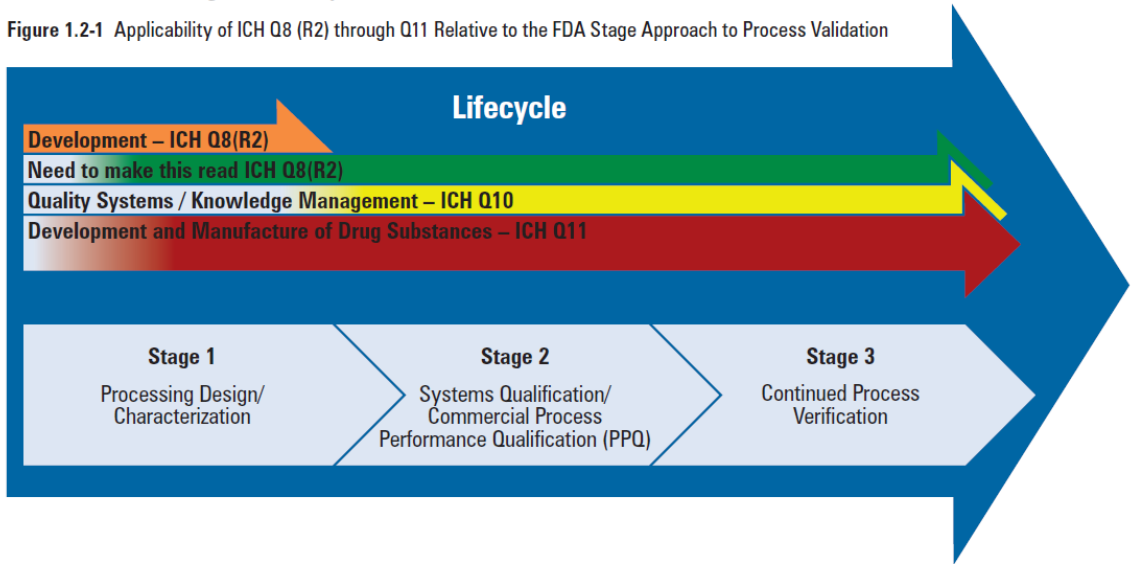
本技术报告中使用 FDA 的三阶段工艺验证生命周期命名法（第一阶段工艺设计，第二阶段工艺确认和第三阶段持续工艺确证）。这些阶段的实施细节在 3-5 进行讨论。应当指出持续工艺验证和连续工艺验证是不同的专业术语，有着不同的含义。连续工艺验证指的是验证利用先进生产和分析技术的生产工艺（如，过程分析技术（PAT）系统）。FDA 用的术语持续工艺验证通常是指那些维持工艺在可控状态的活动，包含所有的生产场景，如传统生产和采取任何类型任何组合先进技术的生产。

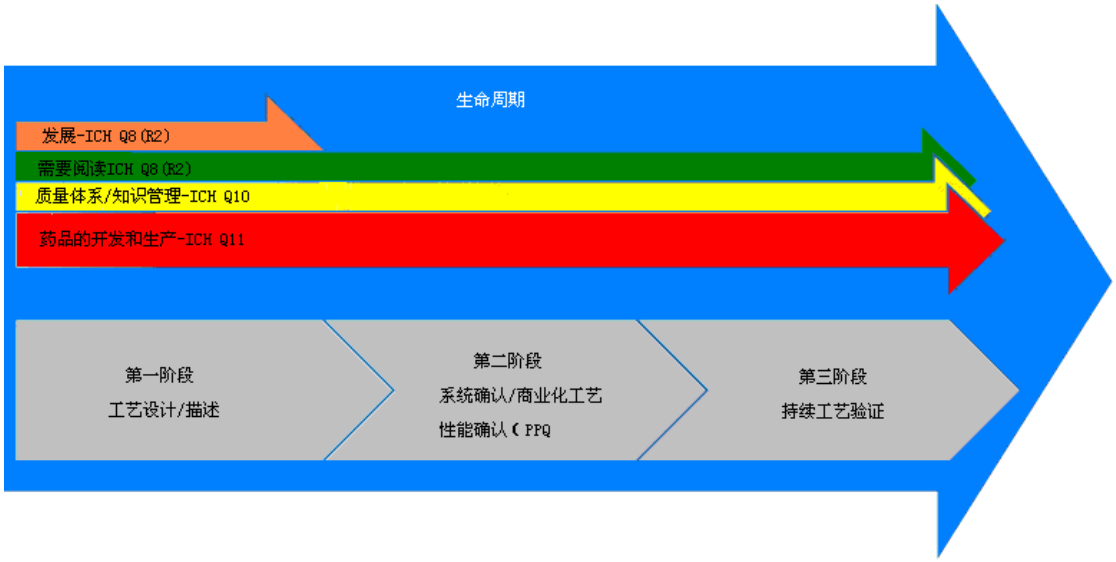
These are defined in **Section 2.0** and are also discussed later in this TR. **Figure 1.2-1** shows the relationship between the relevant ICH guidance documents and the FDA stage approach to process validation across the product lifecycle.

这些在 2.0 章进行了定义并在技术报告的后面部分进行了讨论。表格 1.2-1 表明了相关 ICH 指导文件和 FDA 分阶段方式两者之间在对整个产品生命周期进行工艺验证的关系。

Figure 1.2-1 Applicability of ICH Q8 (R2) through Q11 Relative to the FDA Stage Approach to Process Validation

表 1.2-1 ICH Q8(R2)通过 Q11 相对于 FDA 分阶段方式对工艺验证的适用性





This TR is based on the experiences and knowledge of the Task Force on Process Validation: A Lifecycle Approach. It represents a cross-section of industry professionals covering products within its scope (e.g., large and small molecules, and sterile and non-sterile products), and presents approaches to best practices that are scientifically sound, good business practices, and designed to meet current regulatory expectations. The document does not include isolated responses to individual inspection or review issues. These are most often case-by-case requirements particular to specific organizational needs.
本技术报告是基于工艺验证专业小组的经验和知识：生命周期法。它代表了这个领域内涉及到的产品（如，大分子和小分子、无菌和非无菌产品）的产业化专家们的思想，并且提出的最好的实践方法是科学合理的、良好的商业实践和设计，并且它的设计能满足当前监管的期望。文件不包括个别的单独检查和审查的回复。这些都是对于特定组织需要的最常见的个性需求。

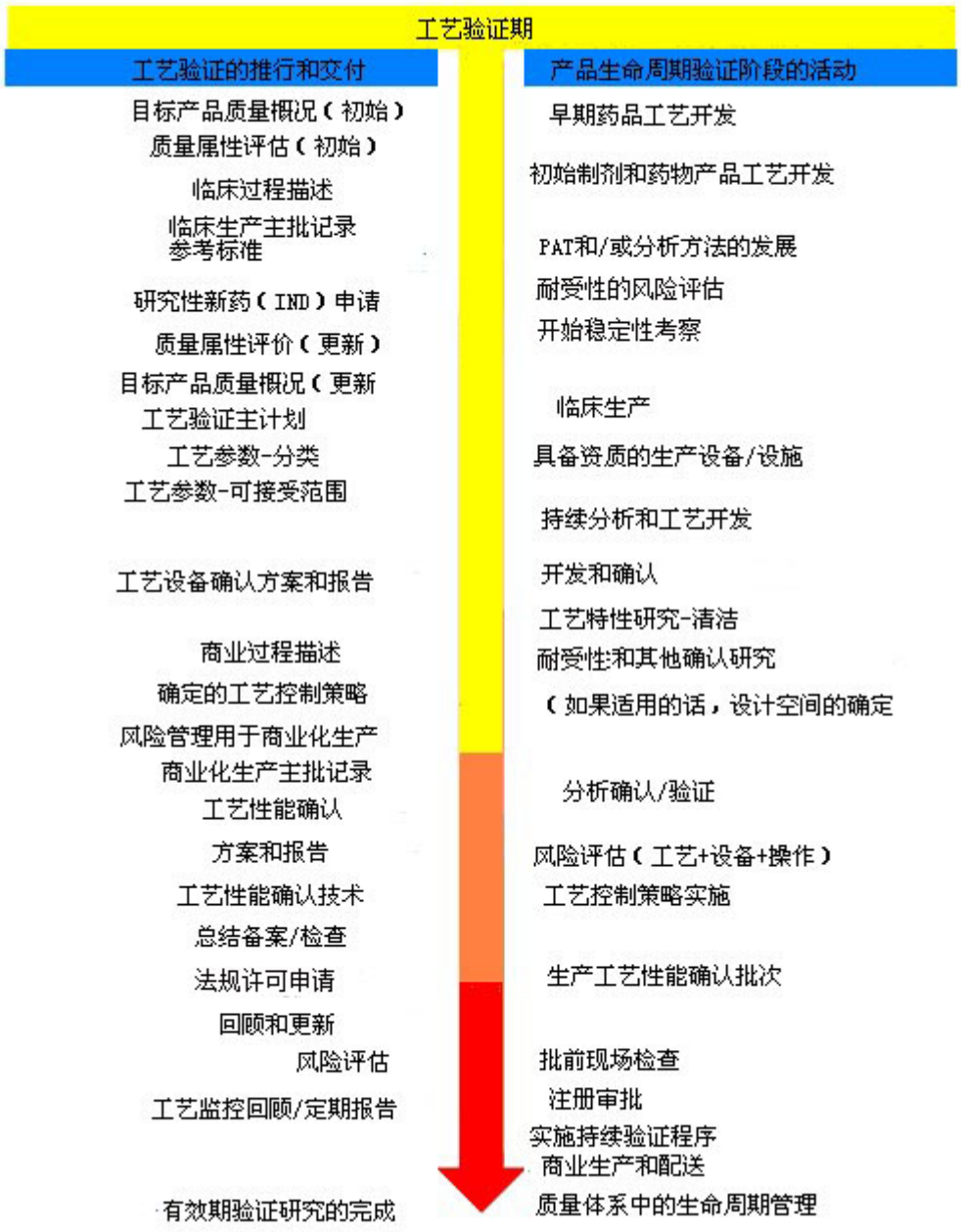
The intent of this TR is not to establish mandatory standards, but rather to be a single-source overview that complements existing regulatory authority guidance documents. References throughout the document provide greater detail on various topics. It is always advisable to consult with the appropriate regulatory authorities for agreement on the strategies employed for product development and lifecycle management strategies.
这个技术报告的目的不是建立法定标准，而是对目前的监管机构的指导文件进行单一的概述补充。整个文件的参考文献对各种主题提供了更广泛的细节。采取与监管部门进行适当沟通协商的策略用于产品的开发和生命周期管理，这总是明智的。

Figure 1.2-2 illustrates the progression of typical process validation enablers or deliverables relative to validation activities that are conducted throughout the product lifecycle. The figure represents stages and validation studies as single “point in time” events. However, in practice, the exact timing of product development activities or validation studies may vary with the specific product development strategy. For example, the enablers for Stage 1 process validation activities will be much less extensive for a production formulation change than for development of a new molecular entity. Thus, the figure presents an overall sequence of activities and their approximate correlation to the stages of process validation.
表 1.2-2 说明典型的工艺验证推行和交付资料的发展相对于整个生命周期进行的验证的关系。图表代表的阶段和验证研究作为单一的“时间点”事件。然而在实施中，产品开发活动或者验证研究的准确时间可能随着具体产品的开发策略而变化。例如，对于生产配方的改变和新的分子实体的开发而

言，第一阶段工艺验证活动的推动力，前者就比后者弱得多。因此，本表格显示了工艺验证阶段的整个活动的顺序和他们之间的大概关系。

Figure 1.2-2 Common Timing of Process Validation Enablers and Deliverables to Validation Stage Activities

表 1.2-2 验证阶段活动工艺验证推行和交付常规时间



Tools used throughout the lifecycle (e.g., risk management, statistical analysis, Process Analytical Technology [PAT], technology transfer, documentation, and knowledge management) are described in **Section 6.0.** Examples of the lifecycle approach for a large and small molecule are described in **Section 7.0.**

整个生命周期中试用的工具（如，风险管理、统计分析、过程分析技术（PAT）、技术转移、文件和知识产权管理）在章节 6.0 进行叙述。大分子和小分子使用生命周期法的例子见章节 7.0。

2.0 Glossary of Terms
术语表

Terminology usage may differ by company, at individual companies and some terms may be subject to change over time. Those terms used in a validation program should be clearly defined, documented, and well-understood. Terminology definitions that are widely recognized by the industry should be considered when establishing internal definitions. These can be found in regulatory guidance documents. Definitions of company-specific terminology should also be included in the validation documents to provide clarity and context. This Technical Report uses the terms below, which are accompanied by their definitions, synonyms, and references where applicable:
术语的用法因公司而异，在独立的公司或者某些团队可能主题会随着时间的推移而改变。那些用到验证项目上的术语应当定义明确、有文件记录和容易理解。当建立内部定义时，应当考虑术语的定义要被行业内广泛接受。这些可能会在法规性指导文件中发现。包括验证文件中的公司特定术语的定义也应当清晰和提供上下文环境。以下是本技术报告使用的术语及他们的定义、同义词和此处引用的参考文献：

Active Pharmaceutical Ingredient (API; Equivalent to Drug Substance for large molecules)
Any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product and that, when used in the production of drug, becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body ***(17).***
药物活性成分（Active Pharmaceutical Ingredient，API；相当于大分子的药物性质）：
准备用于制造药物（药用）产品任何物质或物质的混合物，当用于药物生产时，就成为药品的活性成分。这些物质将提供药理活性或者说直接影响诊断、治疗、缓解、治疗或者预防疾病或影响身体的结构和功能（17）。

Active Pharmaceutical Ingredient (API) Starting Material
A raw material, intermediate, or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. An API Starting Material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or produced in-house. API Starting Materials normally have defined chemical properties and structures ***(17).***
原料药（API）起始原料
原料、中间体或药物活性成分用于原料药生产和作为重要结构段结合到原料药结构中去。原料药的起始原料可能是一件商业物品、通过合同或商业协议从一个或多个供应商处购买材料或者内部生产。API 起始原料一般定义了化学性能和结构（17）。

Attributes
Critical Quality Attribute (CQA)
A physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality ***(11).***
属性
关键质量属性（Critical Quality Attribute，CQA）
物理、化学、生物或者微生物性能或特征应当在适当的限度、范围或分布，确保得到期望的产品质量（11）。

Process Performance Attribute (Synonym- Process Performance Parameter)

An output variable or outcome that cannot be directly controlled, but is an indicator that the process performed as expected ***(15).***

工艺性能属性（同义词，过程性能参数）

不能直接控制的输出变量或结果，但它是期望的工艺性能的一个指示（15）。

Quality Attribute

A molecular or product characteristic that is selected for its ability to indicate the quality of the product. Collectively, the quality attributes define identity, purity, potency and stability of the product, and safety with respect to adventitious agents. Specifications measure a selected subset of the quality attributes ***(18).***

质量属性

分子或产品的特性，因为它们能够显示产品的质量而被选中。共同点是质量属性定义一致性、纯度、产品的效价和稳定性和相关外来代理商的安全性。标准可以衡量经选择的一部分质量属性。（18）。

Attribute

A physical, chemical, or microbiological property or characteristic of an input or output material ***(19).***

属性

投入或产出原材料的物理、化学或微生物性能或特征（19）。

Continued Process Verification (CPV)

Assuring that during routine production the process remains in a state of control ***(3).***

持续工艺确证

保证在常规生产过程中保持一个可控的状态（3）。

Continuous Process Verification

An alternative approach to process validation in which manufacturing process performance is continuously monitored and evaluated ***(11).***

连续性工艺验证

连续性监控和评估生产工艺性能的工艺验证方法的替代方式（11）。

Continuum of Criticality

As Used for Parameters

A non-discrete scale where parameters or attributes are evaluated relative to their impact on drug substance and drug product quality ***(3).***

关键性的连续

用于参数

非离散型数值范围的参数或属性相对于药物和药品质量的影响（3）。

As Used for Attributes

Following comprehensive assessments of scientific evidence and risk, quality attributes are ranked according to the degree of criticality. The continuum, as opposed to binary classifications of Critical and Non-Critical, is thought to “more accurately reflect complexity of structure-function relationships and the reality that there is some uncertainty around attribute classification” ***(20).***

用于属性

遵循科学依据和风险的综合评估，质量属性可根据关键程度进行排名。对照二元的关键性和非关键性分类，连续性被认为“能更精确的反映结构功能关系的复杂性和围绕属性分类存在不确定性的事实”（20）。

Control Strategy

A planned set of controls, derived from current product and process understanding, which ensures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control ***(4).***

控制策略

来源于当前产品和工艺理解的一套有计划的控制，确保工艺性能和产品质量。这些控制可能包括与药物和药品原料和组份有关的参数和属性、设施和设备的运行条件、过程控制、完成的产品规格和相关方法及监控和控制的频率（4）。

Design Space

The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality. Working within the design space is not considered a change. Movement out of the design space is considered to be a change, and would normally initiate a regulatory post-approval change process. Design space is proposed by the applicant and is subject to regulatory assessment and approval ***(11).***

设计范围

输入变量（例如材料属性）的多维组合和相互作用和被证明了的提供质量保证的工艺参数。在这个设计范围内工作不认为是改变。超出这个设计范围认为是一种变化，监管部门会认为是批后改变工艺。

Drug Product (DP)

The dosage form in the final immediate packaging intended for marketing ***(17).***

药品（DP）

最后直接包装用于市场销售的剂型（17）。

Drug Substance (DS; Equivalent to Active Pharmaceutical Ingredient for small molecules)

The material which is subsequently formulated with excipients to produce the drug product. It can be composed of the desired product, product-related substances, and product- and processrelated impurities. It may also contain excipients including other components such as buffers ***(21).***

药物（DS，相当于药物活性成分中的小分子）

随后与辅料按配方生产药品的原料。它可能由所需的产品、产品相关物质、产品和工艺相关杂质。也包括含有其他组分（如缓冲剂）的辅料（21）。

Formal Experimental Design (Synonym-Design of Experiments)

A structured, organized method for determining the relationship between factors affecting a process and the output of that process ***(11).***

正规实验设计（同义词-实验设计）

用来测定影响工艺因素和工艺输出结果之间关系的规范有序的方法（11）。

Good Engineering Practice (GEP)

Those established engineering methods and standards that are applied throughout the lifecycle to deliver appropriate and cost-effective solutions ***(22).***

良好工程规范（GEP）

那些应用于提供适合的和符合成本效益的解决方案的整个生命周期的已确定的工程方法和标准（22）。

Intermediate (or In-Process Material)

A material produced during the steps of the processing of an API that undergo further molecular change or purification before it becomes an API. Intermediates may or may not be isolated ***(17).***

中间体（或 过程产物）

一个原料在成为原料药之前经历了进一步的分子量变化或纯化的加工步骤，期间的原料产品就是中间体。中间体可以是经过分离的，也可以是未经分离的（17）。

Lifecycle

All phases in the life of a product, from the initial development through marketing until the product's discontinuation ***(11).***

生命周期

从产品最初的开发到上市直至产品停产退市的所有阶段（11）。

Normal Operating Range (NOR)

A defined range, within (or equal to) the Proven Acceptable Range, specified in the manufacturing instructions as the target and range at which a process parameter is controlled, while producing unit operation material or final product meeting release criteria and CQAs ***(23).***

正常操作范围（NOR）

定义一个范围，在可接受范围内，按照受控的工艺参数范围和目标制定生产指令，加工单元可使操作材料和最终产品满足公布的标准和关键质量属性（CQAs）（23）。

Parameters

Critical Process Parameter (CPP; Synonym - Critical Operational Parameter)

A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality ***(11).***

参数

关键工艺参数（CPP，同义词-关键操作参数）

工艺参数的变化对关键质量属性会有影响，因此应当监控和控制工艺参数确保加工的产品达到想要的质量（11）。

Key Process Parameter (KPP; Synonym -Key Operational Parameter)

An input process parameter that should be carefully controlled within a narrow range and is essential for process performance. A key process parameter does not affect product quality attributes. If the acceptable range is exceeded, it may affect the process (e.g. yield, duration) but not product quality ***(15).***

重要工艺参数（KPP，同义词-重要操作参数）

输入工艺参数应当在很窄的范围内仔细控制，并且其对加工性能是必不可少的。关键工艺参数不影响产品质量属性。如果超出可接受的范围，它将影响工艺（如产率、持续时间），但不影响产品质量（15）

Non-Key Process Parameter (Non-KPP; Synonym – Non-key Operational Parameter)

An input parameter that has been demonstrated to be easily controlled or has a wide acceptable limit. Non-key operational parameters may have an impact on quality or process performance if acceptable limits are exceeded ***(15).***

非重要工艺参数（Non-KPP；同义词-非重要操作参数）

输入参数已被证明易操作控制或者有着很宽泛的接受限度。如果可接受限度超出，非关键性操作参数可能会对质量或工艺性能产生影响。（15）

Process Parameter (Synonym –Operational Parameter)

An input variable or condition of the manufacturing process that can be directly controlled in the process. Typically, these parameters are physical or chemical (e.g. temperature, process time, column flow rate, column wash volume, reagent concentration, or buffer pH) ***(15).***

工艺参数（同义词-操作参数）

输入变量和工艺中可直接控制的生产工艺条件。通常，这些参数是物理或者化学的（如，温度、工艺时间、柱流速、柱冲刷体积、试剂浓度或缓冲液 pH 值）（15）。

Platform Manufacturing

Development of a production strategy for a new drug starting from manufacturing processes similar to those used to manufacture other drugs of the same type (the production for which there already exists considerable experience) ***(6).***

平台化生产

一种生产方式的开发，用于新药从哪些以前应用的类似的生产工艺开始到使用该生产过程生产其他相同类型的药物（这种生产过程已经存在了相当多的经验）（6）。

Process Analytical Technology (PAT)

A system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality (***11).***

过程分析技术（PAT）

设计、分析、并通过对关键质量标准、原料的性能属性、过程中材料和工艺的实时测量（如加工处理期间）来控制生产，目的是确保最终产品质量的一套系统（11）。

Process Performance Qualification (PPQ)

The second element of the Process Qualification. It includes a combination of the actual facility, utilities, equipment, 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. Batches prepared are also called Conformance batches or PPQ batches (***3).***

工艺性能确认（PPQ）

工艺确认的第二个组成部分。它包括实际设施、工具、设备、商业化生产的个人培训、控制程序和生产商业化批次的组份等的综合。一个成功的 PPQ 可以确定工艺设计和证明商业化生产工艺是按照预期执行的。这些制备的批次也叫做一致性批次或者 PPQ 批次（3）。

Process Qualification

Confirming that the manufacturing process, as designed, is capable of reproducible commercial manufacturing (***3).***

工艺确认

明确按照设计的生产工艺，能够可重复的进行商业化生产（3）。

Process Robustness

Ability of a process to tolerate variability of materials and changes of the process and equipment without negative impact on quality (***11).***

工艺耐受性

一个工艺，可以承受原料的变化、工艺和设备的改变而不对质量造成负面影响的能力（11）。

Process Validation

US FDA

The collection and evaluation of data from the process design stage to commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality products ***(3)..***

工艺验证

美国食品药品监督管理局（US FDA）

收集和评估从工艺设计阶段到商业化生产的数据，根据数据制定科学的证据，证明某个工艺能够持续稳定的生产出优质产品（3）。

EMA

The documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce a medicinal product meeting its predetermined specifications and quality attributes ***(2).***

欧洲药品管理局（EMA）

文件证明这个过程在确定的参数下操作就能有效的执行和可重复地生产满足预定标准和质量属性的药品（2）。

Process Validation Master Plan (Synonym – Validation Master Plan)

A document that defines the process validation scope and rationale and that contains the list of process validation studies to be performed (***15).***

工艺验证主计划（同义词-验证主计划）

定义了工艺验证范围、基本原理和包含了执行工艺验证研究列表的文件（15）。

Proven Acceptable Range (PAR)

A characterized range of a process parameter for which operation within this range, while keeping other parameters constant, will result in producing a material meeting relevant quality criteria (***11).***

可接受范围（PAR）

工艺参数的表征范围，在这个范围内操作，保持其他参数不变的情况下，可以生产出满足相关质量标准的材料（11）

Quality

The suitability of either a drug substance or drug product for its intended use. This term includes such attributes as the identity, strength and purity (***24).***

质量

药物或者药品的使用目的适合性。这个术语包含如一致性、强度和纯度等属性（24）。

Quality by Design (QbD)

A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management ***(11).***

质量源于设计（QbD）

系统的开发方法，基于健全科学和质量风险管理，从预先确定的目标开始，强调产品、工艺了解和过程控制。

Quality Target Product Profile (QTPP)

A prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product (***11).***

目标产品质量概况（QTPP）

药物产品质量特征的预期总结，理想情况应当是确保达到期望的质量、重视安全性和药品疗效（11）

Target Product Profile (TPP)

A format for a summary of a drug development program described in terms of labeling concepts to facilitate communication regarding a particular drug development program ***(25).***

目标产品概况（TPP）

用于药物开发项目总结的一种格式，记录了依据标记的概念促进关于一个特定药物开发项目的沟通（25）。

Validation Master Plan

See Process Validation Master Plan.

验证主计划

见工艺验证主计划。

Verification

A systematic approach to verify that manufacturing systems, acting alone or in combination, are fit for intended use, have been properly installed, and are operating correctly. This is an umbrella term that encompasses types of approaches to ensure the systems are fit for such as qualification, commissioning and qualification, verification, system validation, or other ***(26).***

确证

用于证明生产体系（独立的方面或者综合方面）是适合预期用途、已被正确安装和准确操作运行的系统化方法。这是个总括的术语，包含确保体系适合于如确认、运行和确认、验证、系统验证或其他的各种类型的方法（26）。

Worst Case

A set of conditions encompassing upper and lower processing limits and circumstances, including those within standard operating procedures, that pose the greatest chance of process or product failure (when compared to ideal conditions). Such conditions do not necessarily induce product or process failure ***(8).***

最差条件

工艺限度范围上限和下限和环境周围情况的一系列条件，包括标准操作规程、造成工艺或产品失败的最大机会（当与理想情况比较时）。这样的情况未必引起产品或工艺失败（8）。

2.1 Acronyms

缩略语

简称	英文全拼	中文
API	Active Pharmaceutical Ingredient	药物活性成分
CMA	Critical Material Attribute	关键物料属性
CPP	Critical Process Parameter	关键工艺参数
CPV	Continued Process Verification	连续工艺确证
CQA	Critical Quality Attribute	关键质量属性
DoE	Design of Experiments	实验设计
DP	Drug Product	制剂药品
DS	Drug Substance	药品
FMEA	Failure Mode Effects Analysis	失败模式影响分析
HCP	Host Cell Protein	宿主细胞蛋白
ICH	International Conference Harmonization	国际协调会
KPP	Key Process Parameter	关键工艺参数
NOR	Normal Operating Range	正常运转范围
PAR	Proven Acceptable Range	已证明可接受范围
PAT	Process Analytical Technology	过程分析技术
PPQ	Process Performance Qualification	工艺性能确认
PTT	Product Technical Team	产品技术团队
PVMP	Process Validation Master Plan	工艺验证主计划
QbD	Quality by Design	质量源于设计
QTPP	Quality Target Product Profile	目标产品质量概况
TPP	Target Pruduct Profile	目标产品概况
TT	Technology Transfer	技术转移

3.0 Building and Capturing Process Knowledge (Stage 1 — Process Design)

工艺知识的建立和获取（第一步-工艺设计）

This section focuses on approaches used during development to implement robust manufacturing processes. It addresses the first Stage of process validation in which process and product knowledge are explored to establish the control strategy. Risk assessment and management are used to focus the development effort. Process and product knowledge evolve through the course of the pharmaceutical development program. Designing a comprehensive and efficient program for a lifecycle approach to process validation compels thoughtful planning very early in development. Early planning facilitates appropriate data gathering in Stage 1, with the objective of enhancing the effectiveness and success of Stage 2 Commercial Process Qualification. It also establishes a foundation for continued process verification in Stage 3.

本节集中于开发过程中所用的方法以实现具耐受性的生产工艺，它解决了工艺验证第一阶段中工艺和产品知识被开发以建立控制策略。风险评估和管理被使用以集中于研发工作。工艺和产品知识通过药物研发方案逐步形成。为对工艺验证用生命周期方法而设计一个综合的、有效的程序/方案强迫在研发非常早期考虑规划。早期规划便于在阶段 1 收集恰当数据，加强阶段 2 商业工艺确认的有效性和成功的目标，它也为阶段 3 持续工艺确证建立一个基础。

Sources of knowledge available prior to (and that may be used during) Stage 1 of the Process Validation lifecycle, include:

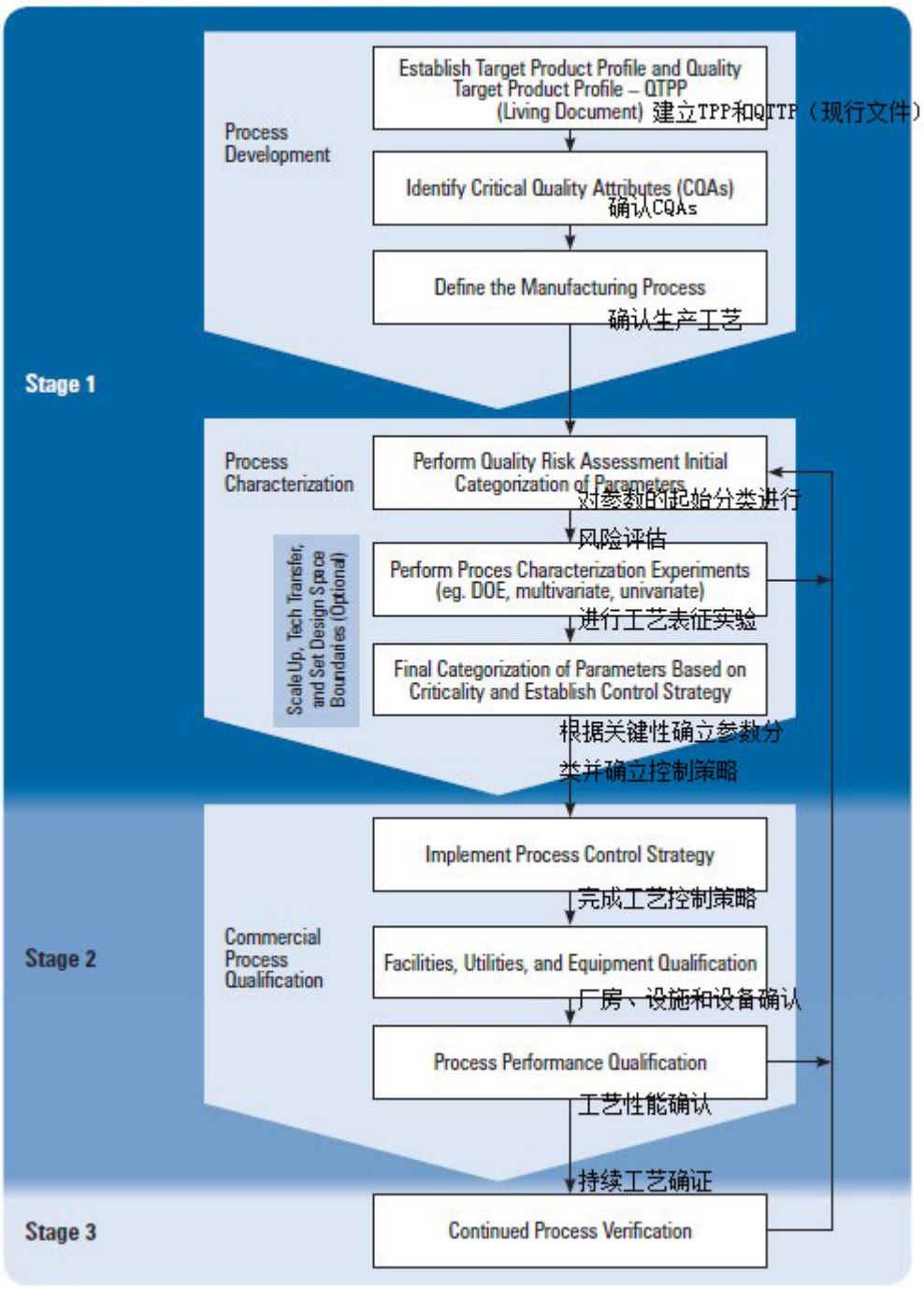
工艺验证生命周期阶段 1 之前（以及可能在过程中）可利用知识来源包括：

- Previous experience with similar processes (e.g., platform processes)
  类似工艺（例如平台工艺）的以往经验；
- Product and process understanding (from clinical and pre-clinical activities)
  产品和工艺理解（从临床和临床前活动）；
- Analytical characterization
  分析的特征描述；
- Published literature
  已发行的文献；
- Engineering studies/batches
  工程研究/批；
- Clinical manufacturing
  临床生产；
- Process development and characterization studies
  工艺研发和特征研究；

The following sections outline the Stage 1 outputs from a general lifecycle approach to Process Validation, as depicted in **Figure 3.0-1.**

下面章节概述了工艺验证一般生命周期方法中阶段 1 的输出，描述在图 3.0-1 中。

Figure 3.0-1 Overall Sequence of Process Validation Activities



3.1 Deliverables from Stage 1 Process Validation
第一阶段工艺验证应达到的目标

The list below summarizes the information needed to transition from Stage 1 (Process Design) to Stage 2 (Performance Qualification) in the Process Validation Lifecycle. The sections in this section discuss these deliverables in more detail and provide references for additional information.

下面的列表概括了在工艺验证生命周期中从第一阶段（工艺设计）到第二阶段（性能确认）转移所需的信息。本节详细讨论应转移的资料并提供额外的参考信息。

• Quality Target Product Profile (QTPP) — This is done at the initiation of Stage 1

目标产品质量概况(QTPP)-第一阶段开始就完成的。

- Critical Quality Attributes (CQAs) with corresponding Criticality Risk Assessment and desired confidence
  关键质量属性及对应的关键性风险评估和理想的置信程度

- Manufacturing Process Design
  生产工艺设计
  - Process description showing process inputs, outputs, yields, in-process tests and controls, and process parameters (set points and ranges) for each unit operation
    工艺描述：包括每个操作单元的工艺输入、输出、收率、中间检测与控制和工艺参数（设定控制点和范围）；
  - Process solution formulas, raw materials, specifications
    工艺溶液处方、原材料及规格；
  - Batch Records and production data from laboratory or pilot scale production
    批记录和来自实验室或中试生产规模的生产数据

- Analytical Methods (for product, intermediates, and raw materials)
  分析方法（包括产品、中间产品和原材料）

- Quality Risk Assessment
  质量风险评估
  - Initial risk-based categorization of parameters prior to process characterization
    工艺特性化前对参数进行基于风险的初步分类

- Criticality and Risk Assessments
  关键性和风险评估
  - Identification of Process Parameters with corresponding criticality and risk analysis
    基于关键性和风险分析识别工艺参数

- Process Characterization
  工艺特性化
  - Process Characterization Plan and Protocols
    工艺特性化计划和方案
  - Study Data Reports
    研究数据报告；

- Process Control Strategy
  工艺控制策略
  - Release Specifications
    放行标准；
  - In-Process Controls and Limits
    中间产品控制与限度；
  - Process Parameter set points and ranges

工艺参数设定点和范围；

- Routine Monitoring requirements (including in-process sampling and testing)
  日常监控要求（包括中间品取样和测试）；
- Storage and time limitations for intermediates, process solutions, and process steps
  中间产品、加工溶液的贮藏和工艺步骤的时间限度；
- Raw Material/Component Specifications
  原材料/成分规格；
- Design Space (if applicable)
  设计空间（如适用）

- Process Analytical Technology applications and algorithms (if PAT is used)
  过程分析技术应用和算法（如果使用 PAT）
- Product Characterization Testing Plan (i.e., tests not included in the product Release Test panel)
  产品特性化试验计划（即不包括产品放行检验中的试验）
- Manufacturing Technology – assessment of production equipment capability and compatibility with process requirements (may be covered in Stage 2a)
  生产技术-按工艺要求评价生产设备能力和适应性（也可以在第二阶段 2a 中进行）
  Scale-up/Scale-down Approach (Evaluation/Qualification of Laboratory Models)
  放大/缩小方法（实验室模型评价/确认）
- Development Documentation
  药品开发文件
  Process Design Report
  工艺设计报告

- Process Validation Master Plan
  工艺验证主计划

3.2 Quality Target Product Profile (QTPP)
目标产品质量概况（QTPP）

The aim of pharmaceutical development is to design a quality product with a manufacturing process that consistently delivers the intended performance of the drug product. Pharmaceutical development begins with the establishment of pre-defined objectives. These are described in the *Quality Tar-get Product Profile* (QTPP). The QTPP is defined at the initiation of Stage 1 and is referenced throughout the product lifecycle.

药物开发的目的是设计一种在制造过程中始终达到药品预期性能的高质量的产品。药物开发始于确定预先定义的目标。在目标产品质量概况(QTPP)中应有描述。QTPP 始于第一阶段开始并在整个产品生命周期中被参考引用。

The QTPP captures all relevant quality requirements for the drug product. Consequently, it is periodically updated to incorporate any new data that may be generated during pharmaceutical development. However, the QTPP should not depart from the core targets established in the drug product Target Product Profile (TPP).

QTPP 记录了全部药品相关的质量要求。而且，还要定期更新在药品开发过程中产生的新的数据。但是，QTPP 不应偏离药品目标产品概况(TPP)所建立的核心目标。

Note: TPP is used as a tool that facilitates sponsor-regulator interactions and communication. Consequently, the TPP contains such information as Drug Indications and Use; Dosage and Administration; Dosage Forms and Strengths; Contraindications; Warnings and Precautions; Adverse Reactions; Drug Interactions; Abuse and Dependence; and Overdose that are not covered under the scope of this document (25).

注：作为工具的目标产品概况(TPP)有助于申请人-监管者的相互影响与交流。因此，TPP 包括诸如药物适应症与用处、剂量与用法、剂型与规格、禁忌、警告与注意事项、不良反应、药物相互作用、滥用和依赖性、和过量等不在本文范围内的信息。

It addresses relevant characteristics that include:

目标产品概况包含的相关特性有：

- Intended use in the clinical setting (e.g., dosage form and strength, route of administration, delivery systems, container and closure system).
  临床预定用处（例如：剂型与规格、服用方法、传递系统、容器与密闭系统）。
- Drug substance quality attributes appropriate to the drug product dosage form being developed (e.g., physical, chemical, and biological properties).
  原料药质量属性：适用于开发的药品剂型（如物理的、化学的、和生物学的性质）。
- Drug product quality attributes appropriate for the intended marketed product (e.g., purity/impurities, stability, sterility, physical, and chemical properties)
  药品质量属性：适用于预期上市产品（例如：纯度/杂质、稳定性、无菌性、物理和化学性质）。
- Therapeutic moiety release or delivery, and attributes affecting pharmacokinetic characteristics (e.g., dissolution, aerodynamic performance) appropriate to the drug product.
  治疗部分的释放或传递，以及适用于药品的影响药代动力学特性的属性（例如溶解、空气动力学行为）。
- Excipient and component quality attributes, drug-excipient compatibility, and drug-container compatibility that affect the process ability, stability, or biological effect of the drug product.
  辅料和成分质量属性、药物-辅料相容性、和药物-容器相容性：影响药品的工艺能力、稳定性或生物学作用

The QTPP summarizes the quality attributes of the product that ensure safety and efficacy. It provides a starting point for assessing the criticality of product quality attributes.

QTPP 总结了药品的质量属性，保证药品的安全性和有效性。QTPP 为产品质量属性关键性评估提供了一个起始点。

3.3 Critical Quality Attributes

关键质量属性

A Critical Quality Attribute (CQA) is a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality. CQAs can be associated with drug substances, drug products, excipients, intermediates (in-process materials), and container/closure components. At an early stage of process development, the information available on product attributes may be limited. For this reason, the first set of CQAs may come from prior knowledge obtained during early development and/or from similar products rather than from extensive product characterization. The degree of criticality assigned to quality attributes is derived using risk-based

tools and the potential impact of the attributes on safety and efficacy. Following comprehensive assessments of scientific evidence and risk, quality attributes are ranked according to the degree of criticality, which may be a continuum that more accurately reflects the complexity of structure-function relationships and varying levels of uncertainty around attribute classification. Attributes not assigned as CQAs should also be considered in the development of the process.
关键质量属性（CQA）是指保证预期药品质量的物理、化学、生物学或微生物性质或特性在适宜的限度、范围或分布范围内。CQAs 可以与原料药、成品、辅料、中间产品（中间原材料）和容器/密闭系统有关。在工艺开发的早期可以限定对产品属性有效的信息。为此，起初设定的关键质量属性可能来自早期开发和/或类似产品而不是大量的产品性质。质量属性的关键程度来源于利用基于风险的工具和质量属性对安全性与有效性的潜在影响。在对科学证据和风险进行了综合评估之后，根据关键性程度对质量属性排序，这样可能更能反映结构-功能关系的复杂性和属性分类不确定性的变化程度。与 CQAs 无关的属性在工艺开发中也应加以考虑。

CQAs are not synonymous with specifications. In addition, there is not necessarily a one-to-one relationship between CQAs and specifications. Specifications are a list of tests, references to analytical procedures, and appropriate acceptance criteria that are numerical limits, ranges, or other criteria for the tests described. Several product attributes identified as CQAs may be detected by a single test method, and therefore, built into a single test specification (e.g., API solubility, hardness, porosity are CQAs evaluated using a single test: dissolution). Some CQAs may not be included in the specifications if they are very well-controlled and consistently achieved within the process (e.g., viral clearance is not tested for every batch), while some attributes not considered critical may be included in the specifications.
CQAs 与标准规格是不同义的。另外，也没有必要将 CQAs 与标准规格一一对应。标准规格是检查试验的一个列表，是分析过程的依据，是待检品可接受标准的数字限度、范围或其他标准。被确定为 CQAs 的几个产品属性可以用单一方法检查，因此，可以建立单一的测试标准（例如：API 的溶解度、硬度、孔隙度是可以用一个试验-溶出度来评价的 CQAs）。有些在工艺过程中容易控制和达到的 CQAs 可以不包含在标准规格中（如病毒清除不是每批检查），而一些不是关键性的属性也可能制定在标准规格中。

The identification of potential CQAs is an ongoing activity initiated early in product development. It makes use of general knowledge about the product and its application, as well as available clinical and non-clinical data. CQAs are subject to change in the early stages of product development, and thus require a quality risk management approach that evolves as knowledge about the product and process is generated (for discussion, see Section 6.1 “Application of Risk Management”). CQAs for commercial products should be defined prior to initiation of Stage 2 activities.
潜在 CQAs 的确定是一个始于产品开发早期的持续性活动。它需要利用产品及其应用以及临床和非临床数据等一般知识。在产品开发的初期，CQAs 是易变的，所以需要质量风险管理方法以发展产生产品和工艺的知识（有关讨论见 6.1 节“风险管理的应用”）。商业产品的关键质量属性应在第二阶段活动开始前被定义。

3.4 Define the Manufacturing Process
定义制造过程

A manufacturing process is designed to consistently provide a product that will meet its required quality attributes. As the process is being defined during development, a process description is a tool that is used to assist in execution of risk assessments and in the development of the control strategy. The

manufacturing process is described as a series of constituent unit operations in a process description, block diagram, or process flow diagram that describes each unit operation. Each unit operation in the manufacturing process should be depicted with a similar level of detail. The following information should be included in the description of each:
制造过程应设计成可以持续提供满足所需质量属性的产品。因为制造过程是在开发过程中定义的，所以，过程描述就是用于帮助风险评估的实施和控制策略开发的工具。制造过程由一系列单元操作组成，工艺描述、方块图、工艺流程图描述每个单元操作。制造过程中的每个单元操作应用相似的详细程度进行描述。每个工艺描述应包含如下信息：

- Process requirements, including raw materials, scale, and order of operations
  工艺需求，包括原材料、规模和操作指令；
- Set points and ranges for the process parameters
  工艺参数设定点和范围；
- Identification and quantity of all material flows (additions, wastes, product streams)
  鉴定和定量所有材料流（附加物、废料、产品线）；
- Testing, sampling, and in-process controls
  测试、取样和中间控制
- Hold times and hold conditions for product and additional solutions
  产品和附加溶液的保持时间和保持条件；
- Estimated step yields and durations
  估计分步产量和持续时间；
- Sizing for equipment, including such items as chromatography columns and filtration units.
  仪器选型，包括色谱柱和过滤单元；
- Specific identification (manufacturer, part number) for manufacturing (e.g., filters) and product components(e.g., vials, stoppers)
  制造商（如过滤器）和产品组分（如玻璃瓶、瓶塞）的特殊鉴定（如制造商、零件号码）；
- Other information necessary to successfully reproduce the process
- 成功再现工艺所必须的其他信息。

A process diagram for a single unit operation is presented as an example in Figure 3.3-1 and a sample description table is provided in Table 3.4-1. The evolution of process knowledge and understanding is reflected in clinical batch records; these are an important source of information for defining the manufacturing process in the process description. Data collected from clinical trial material manufacture may be useful to determine process capabilities, set specifications, design PPQ protocols and acceptance criteria, evaluate laboratory models, and transfer processes. Strategies and fundamentals of knowledge management are discussed further in Section 6.5, Knowledge Management.
图 3.3-1 描述了一个单元操作的工艺图实例，并在表 3.4-1 提供了一个工艺描述简表。工艺知识及理解的发展反映在临床批记录中。这些都是在工艺描述中定义制作过程的重要信息源。从临床试验材料制造收集的数据可能有助于确定过程能力、设定标准、设计 PPQ 方案和可接受标准、评价实验室模型和转移工艺。知识管理的策略和原则将在第 6.5 节“知识管理”中进一步讨论。

Process descriptions are documented in reports and may be incorporated into the Technology Transfer (TT) Package for the product. The process may change during Stage 1 due to increases in material demand (i.e., process and analytical development, clinical needs), improved product understanding that leads to changes

to CQAs, or improved process understanding that results in addition, elimination or adjustments of unit operations. Documentation should capture these changes and the supporting justifications. This information should be archived in the Knowledge Management System.
工艺描述是以报告的形式归档并可能编入产品技术转移（TT）文件包。由于材料要求的增加（如工艺和分析开发、临床需要），第一阶段工艺可能会改变，增进产品了解导致 CQAs 改变，工艺的进一步了解导致单元操作的增加、删除或调整。这些变化和支持性的说明应文件记录下来。。这些信息应保存在知识管理系统中。

Development and documentation of the commercial manufacturing process in Development Reports should precede formal process characterization studies. Increased knowledge gained during process characterization may require additional changes to the process description. All changes to the process should be approved through change control procedures as defined by the Quality System.
开发报告中商业制造过程的开发和归档应先于正式的工艺特性研究。在工艺特性化过程中获得的知识增加可能会要求增加工艺描述的变更。工艺的所有变更应按质量系统定义的变更控制程序获得批准。

Figure 3.4-1 Example Process Diagram for a Tangential Flow Filtration Step

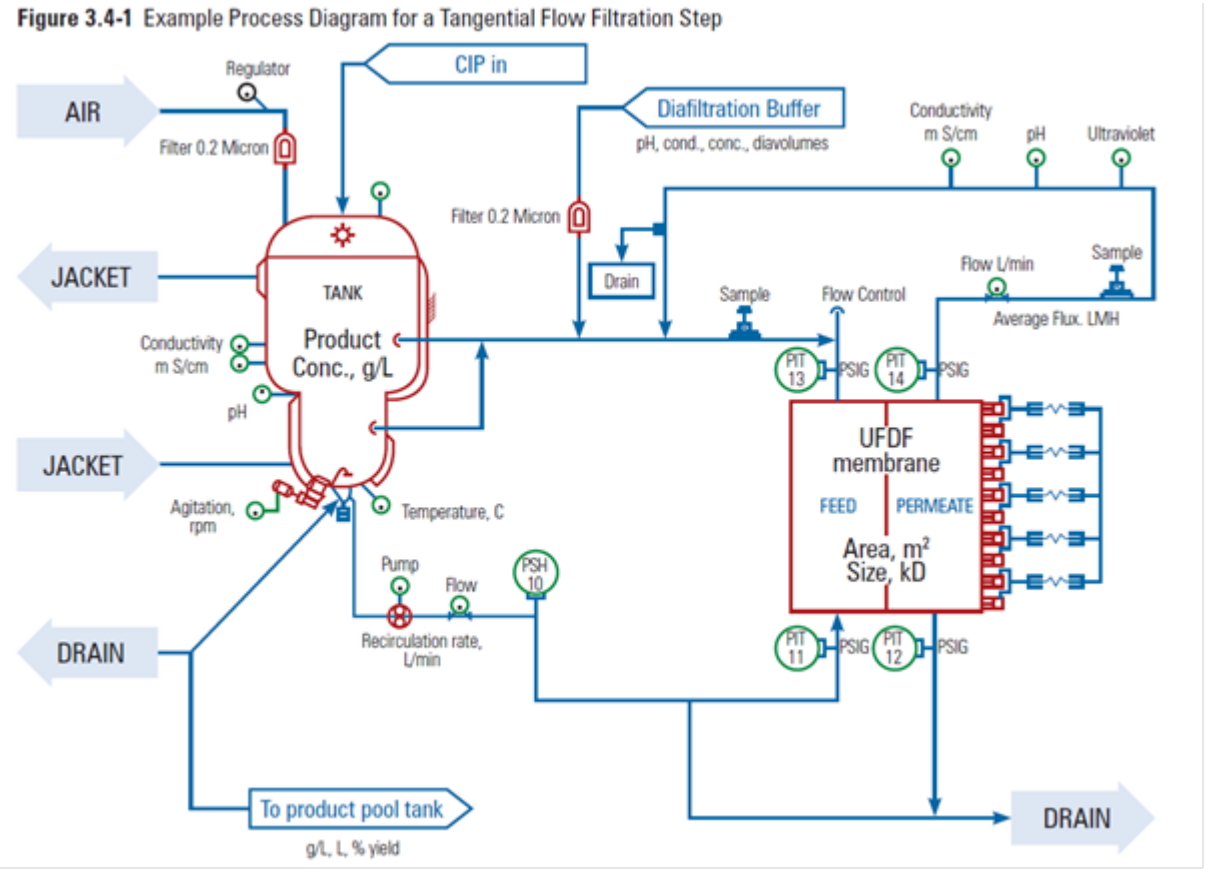
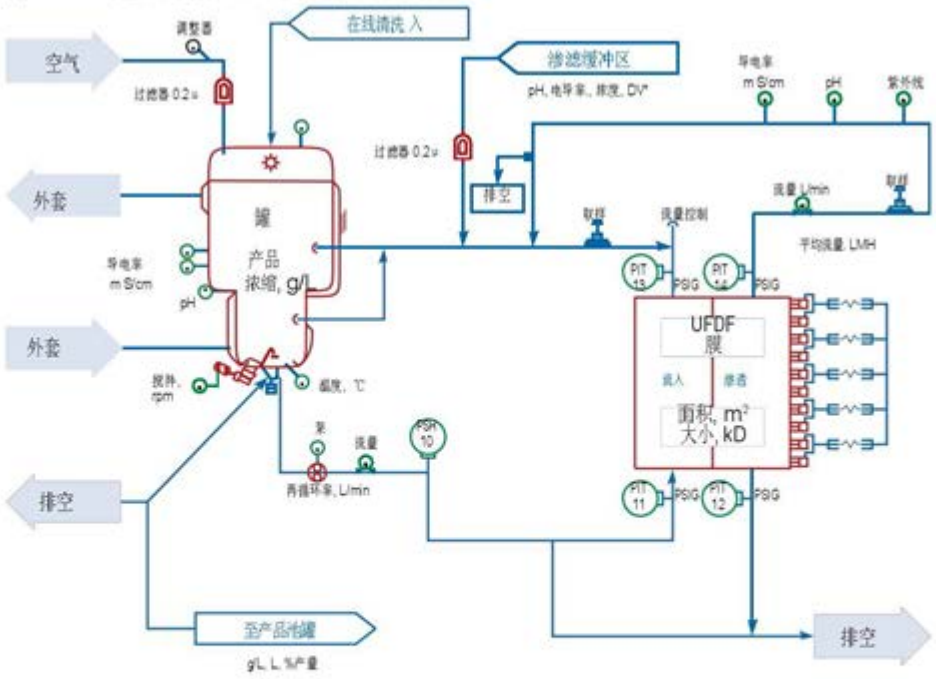


图 3.4-1 切向流过滤步骤的工艺流程示意图示例



译者注*：**Diavolume (DV 或 N)**是渗滤步骤中洗涤程度的一个度量。是指引入单元操作的渗滤缓冲液体积与保留体积的比值。在一个恒定体积的渗滤中，保留体积保持恒定，渗滤缓冲液以滤液离开的速度进入，则diavolume的计算公式为：

DV或N[-]=渗滤过程引入操作的总缓冲液体积/保留体积

Table 3.4-1 Example Process Parameter Table for a Tangential Flow Filtration Step

表 3.4-1　切向流过滤步骤工艺参数表示例

Table 3.4-1 Example Process Parameter Table for a Tangential Flow Filtration Step

Process Variable	Process Variable			Rationale	Attributes	
	Set Point	Proven Acceptable Range	Parameter Designation		Product or Process Attribute	Expected Range
General						
Membrane Area	2 m^2					
Molecular Wt Cut-Off	30 kDa					
Membrane Polymer	Polysulfone					
Pre-Use Cleaning & Flushing						
Cleaning Solution: Concentration	0.4 to 0.6 N NaOH		Non-Key	Low risk of product or process impact		
Recirculation rate	10 L/min	8 to 12 L/min	Non-Key	Adequate recirculation is needed to insure proper cleaning, but acceptable results are achieved over a wide range.		
Transmembrane Pressure (TMP)	10 PSI	5 to 15 PSI	Non-Key	Low risk of product or process impact over a wide range.		
Temperature	30 °C	25 to 35 °C	Non-Key	May impact cleaning effectiveness if far out of range. Procedural controls in place such that the risk of running outside the range is unlikely.		
Time	60 min	60 to 90 min	Non-Key	Wide range. Directly controlled to prevent running outside of the validated range.		
WFI Flush volume	20 L/m^2	≥ 20 L/m^2	Non-Key	Wide range. Directly controlled.		
Pre-Use Qualification						
Integrity Test Pressure	15 PSIG	15 – 18 PSIG	Critical	If test pressure is incorrect, the test result is invalid.		
Water Flux TMP	10 PSIG	8 – 12 PSIG	Non-Key	Water flux can be corrected for actual pressure.		
Water Flux Temperature	20 °C	18 to 22 °C	Non-Key	Water flux can be corrected for actual temperature		
Filter Integrity	Manufacturer's Specifications	Pass	Critical	Verification of filter integrity is crucial to ensure process effectiveness. Filter integrity testing is an output of the prequalification, but an input to processing the feed stream.		

工艺变量	工艺变量			基本依据	属性	
	设定点	被证实的可接受范围	参数关键性确定		产品或工艺属性	预期范围
概况						
膜面积	2 m^2					
截留分子量	30 kDa					
膜聚合物	聚砜					
使用前清洗和冲洗						
清洗溶液：浓度	0.4 至 0.6 N NaOH		非关键	对产品或工艺影响的风险低		
再循环速度	10 L/min	8 至 12 L/min	非关键	为保障正常的清洗需要充分的再循环，但达到可接受结果的范围宽广。		
跨膜压(TMP)	10 PSI	5 至 15 PSI	非关键	对产品或工艺影响的风险低，范围广。		
温度	30 °C	25 至35 °C	非关键	远离范围可以影响清洗效果。在线程序控制使得超范围运行的风险是不可能的。		
时间	60 min	60 至 90 min	非关键	范围广，直接控制以防止验证范围外运行		
WFI 冲洗体积	20 L/m^2	≥ 20 L/m^2	非关键	范围广，直接控制.		
使用前确认						
完整性测试压力	15 PSIG	15 – 18 PSIG	关键	如果测试压力不正确，测试结果无效。		
水流TMP	10 PSIG	8 – 12 PSIG	非关键	水流可以通过实际压力纠正。.		
水流温度	20 °C	18 至 22 °C	非关键	水流可以通过实际温度纠正。		
过滤器完整性	制造商标准	通过	关键	过滤器完整性确认对保证工艺有效性是关键的。过滤器的完整性测试是预确认的输出，但却是加工进料流的输入。		

Process Variable	Process Variable			Rationale	Attributes	
	Set Point	Proven Acceptable Range	Parameter Designation		Product or Process Attribute	Expected Range
System Priming						
Buffer conductivity & pH	Solution Acceptance Criteria		Critical	All process buffer specifications categorized as critical even though procedural controls are in place to prevent release of non-conforming buffers to production. Buffers outside of the established ranges may impact product quality during processing.		
Buffer volume	35 L	25 to 50 L	Non-Key	Unlikely to affect product or process. Directly controllable.		
Recirculation rate	8 L/min	4 to 12 L/min	Non-Key	Unlikely to affect product or process. Directly controllable.		
Transmembrane Pressure (TMP)	12 PSI	10 to 15 PSI	Non-Key	Unlikely to affect product or process. Directly controllable.		
Temperature	20 °C	15 to 25 °C	Non-Key	Unlikely to affect product or process. Directly controllable.		
Process – Initial Concentration Step						
Initial Product Total Mass	1225 g	900 to 1600 g	Critical	Initial product concentrations and volumes (total mass) may be critical due to relationship with system volume constraints and ability to reach DF and final concentration targets.		
Initial Product Volume	75 L	50 to 100 L	Key	In some circumstances initial product concentrations and volumes (total mass) may be critical – may be related to system volume constraints and ability to reach DF and final concentration targets. In other situations, the initial volume may be Key (affect process time and or yield).		

工艺变量	工艺变量				属性	
工艺变量	设定点	被证实的可接受范围	参数关键性确定	基本依据	产品或工艺属性	预期范围
系统启动						
缓冲液电导率和pH	溶液可接受标准		关键	全部缓冲液规格都是关键的，甚至程序控制是在线防止非符合缓冲液放行加工。加工过程中缓冲液超范围可影响产品质量。		
缓冲液体积	35 L	25 至 50 L	非关键	不可能影响产品或工艺。 直接可控。		
再循环速度	8 L/min	4至12 L/min	非关键	不可能影响产品或工艺。 直接可控。		
跨膜压 (TMP)	12 PSI	10至15 PSI	非关键	不可能影响产品或工艺。 直接可控。		
温度	20 °C	15至25 °C	非关键y	不可能影响产品或工艺。 直接可控。		
工艺-起始浓缩步骤						
初始产品总质量	1225 g	900至1600 g	关键	因为系统体积的约束和达到DF与终浓度目标的能力之间的关系，初始产品浓度和体积 (总质量) 可能是关键的。		
初始产品体积	75 L	50至100 L	重要	有些情况下初始产品浓度和体积 (总质量) 可能是关键的-也许是与系统体积的约束和达到DF与终浓度目标的能力之间的关系有关。在另外一些情况下，初始体积也许是重要的 (影响加工时间和/或产量)。		

Process Variable	Process Variable			Rationale	Attributes	
	Set Point	Proven Acceptable Range	Parameter Designation		Product or Process Attribute	Expected Range
Recirculation rate	8 L/min	6 to 10 L/min	Key	Crossflow rate can impact flux; however, only processing time is impacted unless rate is excessively low (causing significant membrane polarization of protein) Depends on impact of TMP on flux. In many cases this parameter can be categorized as "Key".		
Transmembrane Pressure (TMP)	12 PSI	10 to 15 PSI	Key	Minor impact on flux unless operated excessively high or low (outside of PAR). At low values TMP may have a significant impact on flux.		
Temperature	20 °C	15 to 25 °C	Non-Key	Minor impact on flux (approx 2% per degree)		
Process Flux (average)				Output of process conditions including TMP, recirculation rate, product concentration. May be used to track batch-to-batch consistency	Process Performance Attribute	20 to 30 LMH
Product Concentration				Output of the initial concentration stage / Input to diafiltration.	Critical Quality Attribute	30 to 40 g/L
Product (Retentate) Volume	35 L	30 to 40 L	Critical	Volume must be in range validated for proper volume control within the system during DF and within equipment/tankage constraints for total volume of DF buffer needed deliver required volumetric exchange during diafiltration.		
Process – Diafiltration Step (constant volume)						
Diafiltration Buffer pH and Conductivity	Solution Acceptance Criteria		Critical	Diafiltration buffer directly impacts the formulation of the final bulk drug substance and ultimately drug product.		
Recirculation rate	8 L/min	6 to 10 L/min	Key	Crossflow rate can impact flux; however, processing time is impacted if rate is excessively low (outside of PAR) causing significant membrane polarization of protein.		
Transmembrane Pressure (TMP)	12 PSI	10 to 15 PSI	Key	Minor impact on flux unless operated excessively high or low. Operating outside of PAR will impact process time.		

工艺变量	工艺变量			基本依据	属性	
	设定点	被证实的可接受范围	参数关键性确定		产品或工艺属性	预期范围
再循环速度	8 L/min	6至10 L/min	重要	漫流流速可以影响流量；然而如果不是流速过低（导致显着的蛋白质膜极化），则只有加工时间的影响-取决于TMP对流量的影响。在许多情况下，这个参数可以被归类为“重要的”。		
跨膜压 (TMP)	12 PSI	10至15 PSI	重要	除非过高或过低操作（超出PAR），否则对流量影响较小。在TMP值低时，对流量有显著的影响。		
温度	20 °C	15至25 °C	非关键	对流量影响较小 (每度大约2%)。		
工艺流（平均）				工艺条件的输出包括TMP、再循环速度、产品浓度。可以被用来跟踪批与批之间的一致性。	工艺性能属性	20至30 LMH
产品浓度				开始浓缩阶段输出 /渗滤输入.	关键质量属性	30至 40 g/L
产品 (滞留物) 体积	35 L	30至40 L	关键	在DF过程的系统内和在渗滤过程中设备/储罐约束的DF缓冲液体积交换传递的总体积内，体积必须在适宜体积控制的验证范围内。		
工艺-膜渗滤步骤（恒体积）						
渗滤缓冲液pH和电导率	溶液可接受标准		关键	渗滤缓冲液直接影响最终原料药和药品的配方。		
再循环速度	8 L/min	6至10 L/min	重要	漫流流速能影响流量；但是，如果速度非常低（超出PAR）引起蛋白质显著的膜极化，则工艺时间受影响。		
跨膜压 (TMP)	12 PSI	10至15 PSI	重要	除非过高或过低操作，否则对流量影响较小。超PAR操作将影响工艺时间。		

Process Variable	Process Variable			Rationale	Attributes	
	Set Point	Proven Acceptable Range	Parameter Designation		Product or Process Attribute	Expected Range
System Volume During Diafiltration	35 L	30 to 40 L	Critical	Potential to under-diafilter if variability or uncertainty in this parameter.		
Number of Diavolumes	7	7 to 10	Critical	Extent of buffer exchange is dependent on number of Diavolumes.		
Process Flux (average)				Output of process conditions including TMP, recirculation rate, product concentration. May be used to track batch-to-batch consistency	Process Performance Attribute	25 to 30 LMH
Retentate pH and Conductivity at end of step				Direct impact to product quality	Critical Quality Attribute	To Specification
Process – Final Concentration & Product Recovery						
Chase Buffer pH and Conductivity	Per solution specification		Critical	Direct impact to product quality		
Recirculation rate	8 L/min	6 to 10 L/min	Key	More likely to significantly affect flux at higher product concentrations		
Transmembrane Pressure (TMP)	10 PSI	5 to 15 PSI	Key	Impacts flux		
Temperature	20 °C	15 to 25 °C	Non-Key	Minor effect on flux. Assume no effect on product quality over fairly wide range.		
Process Flux (average)					Process Performance Attribute	15 to 20 LMH
Chase Buffer Volume	Determined by in-process measurement			Procedural controls.		
Product Concentration after Recovery & Chase				Must be in range to facilitate next process step. If final step in drug substance manufacture, must be consistent with requirements for formulating drug product.	Critical Quality Attribute	To Specification
System Cleaning & Storage						
Cleaning Solution	0.4 to 0.6 N NaOH		Non-Key	Directly controllable and unlikely to affect product or process		
Recirculation rate	10 L/min	8 to 12 L/min	Non-Key	Adequate recirculation is needed to insure proper cleaning, but range is wide.		
Transmembrane Pressure (TMP)	10 PSI	5 to 15 PSI	Non-Key	No impact to cleaning effectiveness over a wide range.		

工艺变量	工艺变量			基本依据	属性	
	设定点	被证实的可接受范围	参数关键性确定		产品或工艺属性	预期范围
渗滤过程系统体积	35 L	30至40 L	关键	该参数如果易变或不确定，对下方渗滤器（under-diafilter）有潜在风险。		
DV值	7	7至10	关键	缓冲液交换的程度取决于DV值。		
工艺流 (平均)				工艺条件的输出包括TMP、再循环速度、产品浓度。可以被用来跟踪批与批之间的一致性。	工艺性能属性	25 至 30 LMH
步骤终点滞留物pH和电导率				直接影响产品质量。	关键质量属性	至标准规格
工艺-最终浓缩与产品回收						
追踪缓冲液的pH值和电导率	每种溶液标准规格		关键	直接影响产品质量。		
再循环速度	8 L/min	6至10 L/min	重要	产品浓度越高越能显著地影响流量。		
跨膜压 (TMP)	10 PSI	5至15 PSI	重要	影响流量。		
温度	20 °C	15至25 °C	非关键	对流量影响小。在相当宽的范围内对产品质量无影响。		
工艺流 (平均)					工艺性能属性	15至 20 LMH
追踪缓冲液体积	通过在线测量确定			程序控制.		
回收和追踪后产品浓度				必须在范围内以促进下道工艺步骤。如果是原料药制造中的最后一步，必须符合药品配方的要求。	关键质量属性	至标准规格
系统清洗与存储						
清洗溶液	0.4 t至0.6 N NaOH		非关键	直接可控性，不大可能影响产品或工艺。		
循环速度	10 L/min	8至12 L/min	非关键	为保障正常的清洗需要充分的再循环，但范围很宽。		
跨膜压 (TMP)	10 PSI	5至15 PSI	非关键	在很宽的范围内不影响清洗效果。		

Process Variable	Process Variable			Rationale	Attributes	
	Set Point	Proven Acceptable Range	Parameter Designation		Product or Process Attribute	Expected Range
Temperature	30 °C	25 to 35 °C	Non-Key	May impact cleaning effectiveness if far out of range. Procedural controls in place such that the risk of running outside the range is unlikely.		
Time	60 min	60 to 90 min	Non-Key	Wide range, directly controlled to prevent running outside of the validated range.		
Storage Solution Normality	0.09 to 0.10 N NaOH		Non-Key	Directly controllable. Unlikely to affect product or process		

工艺变量	工艺变量			基本依据	属性	
	设定点	被证实的可接受范围	参数关键性确定		产品或工艺属性	预期范围
温度	30 °C	25至35 °C	非关键	远离范围可以影响清洗效果。在线程序控制使得超范围运行的风险是不可能的。		
时间	60 min	60至90 min	非关键	范围宽，直接控制防止超验证范围运行。		
存储溶液（正常状态）	0.09至 0.10 N NaOH		非关键	直接可控性，不大可能影响产品或工艺。		

3.5 Analytical Methods
分析方法
Analyses of raw materials, in-process samples, drug substance, and drug product are important aspects of the Control Strategy (Section 3.8) and process characterization studies. Analytical methods used for such studies should be appropriate for their intended use, scientifically sound, reliable, and reproducible. Strategies for qualification/ validation of the analytical methods used during development have been published, and provide approaches for evaluating tests used at this stage of the lifecycle (27). Guidance on expectations for the analytical methods is also outlined in the FDA Guidance on Process Validation (3). Information on the analytical methods used during process characterization studies should be included in the Process Characterization Plan, and documented in the study reports. Qualification of the methods should also be documented. Since process characterization studies may be performed in development laboratories, instruments must be adequately calibrated and maintained.
原材料、中间样品、原料药、药品成品的分析是控制策略（第3.8节）和工艺性质研究的主要方面。用于这类研究的分析方法应该适用于其预定的用途，科学合理，可靠性、重现性好。应颁布开发过程中使用的分析方法的确认/验证策略，并提供在生命周期该阶段测试的评价方法（27）。关于分析方法评估的指南在FDA工艺验证指南中有论述（3）。工艺性质研究中使用的分析方法信息应包含在工艺特性化计划中，并记录在研究报告中。方法确认也应该记录在案，因为工艺性质研究可能在开发实验室进行，仪器必须做适当的校准和维护。

3.6 Risk Assessment and Parameter Criticality Designation
风险评估和参数关键性设定
Risk assessment plays an important role in the development of a commercial control strategy. Risk assessments are performed by interdisciplinary teams at several points during stage 1 of the lifecycle, and serve a number of purposes. (See Section 6.1 – Application of Risk Management) Risk assessment tools provide a structured means for documenting data and rationale associated with the risk assessment outcome, and becomes part of the documented process development history.
风险评估在商业控制策略开发中具有重要作用。风险评估是在生命周期第一阶段的几个点上由跨学科团队实施的，分属于不同目标。（见第6.1节 风险管理的应用）风险评估工具提供了一个结构化的方式记录与风险评估的结果相关的数据和理由，并成为工艺开发历史记录的一部分。

As shown in Figure 3.0-1, the initial identification of critical quality attributes is followed by a quality risk assessment in stage 1. The initial quality risk assessment is a cause and effect type of analysis to identify process input parameters where variability is likely to have the greatest impact to product quality or process performance. This assessment is based primarily on prior knowledge or early development work, and the outcome of this assessment provides the foundation for process characterization studies that follow.
如图3.0-1所示，在第一阶段通过质量风险评估初步识别关键质量属性。初始质量风险评估是识别对产品质量或工艺性能影响最大的工艺输入参数变量的原因和影响分类。这个评估主要是基于已有知识或早期开发工作，评估结果为下述工艺性能研究提供基础。

Understanding the impact of process parameter variability and applying the appropriate controls is a fundamental element in development of the commercial control strategy. ICH Q8 (R2) defines a Critical Process Parameter (CPP) as, “one with variability that has an impact on a CQA, and therefore, should be monitored or controlled to ensure that the process produces the desired quality (3).
了解工艺参数变化的影响和应用适当的控制是商业控制策略开发的基本要素。ICH Q8 (R2)定义关键工艺参数（CPP）为：“对CQA有影响的可变参数，因此，应该被监测或控制以保证该工艺产生预期的质量”（3）。

Process parameters may be further categorized based on impact to the process. In certain circumstances, process performance is controlled and monitored as an additional means of ensuring a consistent state of control. Process parameters that have been shown experimentally to impact process performance may be classified as key process parameters (KPP). KPPs may impact process performance attributes (such antibody titer in cell culture processes or yield in downstream purification), but do not impact critical product quality attributes (15). In some processes, identifying and appropriately controlling KPPs is useful since process performance measures may be an important means of demonstrating intra-batch consistency.
根据对工艺的影响，工艺参数可以被进一步分类。在某些情况下，工艺性能的控制和监控是作为一

个额外的控制手段，确保控制状态的协调一致。试验显示对工艺性能有影响的工艺参数可以分类为重要工艺参数（KPP）。KPPs可以影响工艺性能属性（如在细胞培养过程中的抗体滴度或下游纯化产量），但不影响产品关键质量属性（15）。在有些工艺中，KPPs的识别和适当控制是有用的，因为工艺性能评估可能是批内一致性证明的一个重要手段。

Beyond the generally recognized definition of a critical process parameter from of ICH Q8 (R2),however, process parameter designations are not standardized and approaches may vary. For this reason, definitions for parameter designations must be clearly documented and understood within the organization. Definitions should remain consistent throughout the process validation lifecycle.
然而，除了普遍认可的定义ICH Q8（R2）的关键工艺参数，工艺参数命名会不规范、方法可能会有所不同。出于这个原因，在组织内参数命名的定义必须清楚地记录并理解。在整个工艺验证生命周期中参数命名的定义应保持一致。

Figure 3.6-1 provides an example of a decision tree developed to guide the assignment of parameter designations in conjunction with the quality risk assessments. The decision tree facilitates categorization of process parameters as critical, key, or non-key (see definitions). Decision making tools can facilitate common understanding among participants, and have the advantage increases consistency in the decision making process as well as consistent documentation of rationales as part of the risk assessment process.
图3.6-1提供了一个决策树示例，以指导结合质量风险评估进行参数命名。决策树有助于将工艺参数分类为关键、重要或非重要（见定义）。决策制定工具可以帮助参与者形成共识，并有利于提高决策过程的一致性，以及作为风险评估过程部分有理由一致的记录文档。

The decision tree can be used for risk assessments both before and after the supporting data from process characterizations studies are available.
决策树可以用于来源于工艺性能研究的支持数据前后的风险评估。

- Parameter or Attribute: Process variables can be outputs from one unit operation and inputs to another. For a given unit operation, each variable is initially established as a parameter or an attribute on the basis of direct controllability
  参数或属性：工艺变量可以是单元操作的输出和对另一单元的输入。对一个指定的单元操作，根据每个变量的直接可控性初步设定为参数或属性。

Yes — Directly controllable process input parameters can theoretically contribute to process variability.
是—直接可控的工艺输入参数理论上有助于工艺的可变性。
No — Process outputs that are not directly controllable are attributes that are monitored and may be indicative of process performance or product quality.
否—不能直接控制的工艺输出是被监测的属性，可能表示工艺性能或产品质量。

- Process Parameters: Potential impact to critical quality attributes.
  工艺参数：对关键质量属性的潜在影响。

Yes — If impact is suspected, or if data show that variability in a parameter could impact a CQA, the parameter is designated as a CPP. Although a parameter may be initially classified as a CPP, data from robustness studies conducted during process characterization may show that CQAs are not impacted despite exaggerated variations in the parameter. In these cases, the second risk assessment serves to change the assessment to non-CPP.
是—如果怀疑参数的变化对CQA有影响，或如果数据显示可能会有影响，则指定这个参数为关键工艺参数（CPP）。
No — Parameter is a non-CPP and is further evaluated
否—参数为非关键工艺参数并进一步评价。

- Non-CPP: Potential to impact process performance or consistency if run outside of defined range.
  非关键工艺参数：如果超定义范围运行，潜在影响工艺性能或稳定性。

Yes — Parameter designated a KPP
是—参数指定为重要工艺参数（KPP）。
No — Parameter has little impact to the process over a wide range. Parameter is designated a non-KPP.
否—在较宽的范围参数对工艺无影响。参数被指定为非重要工艺参数（non-KPP）。

Figure 3.6-1 Decision Tree for Designating Parameter Criticality
关键性命名决策树

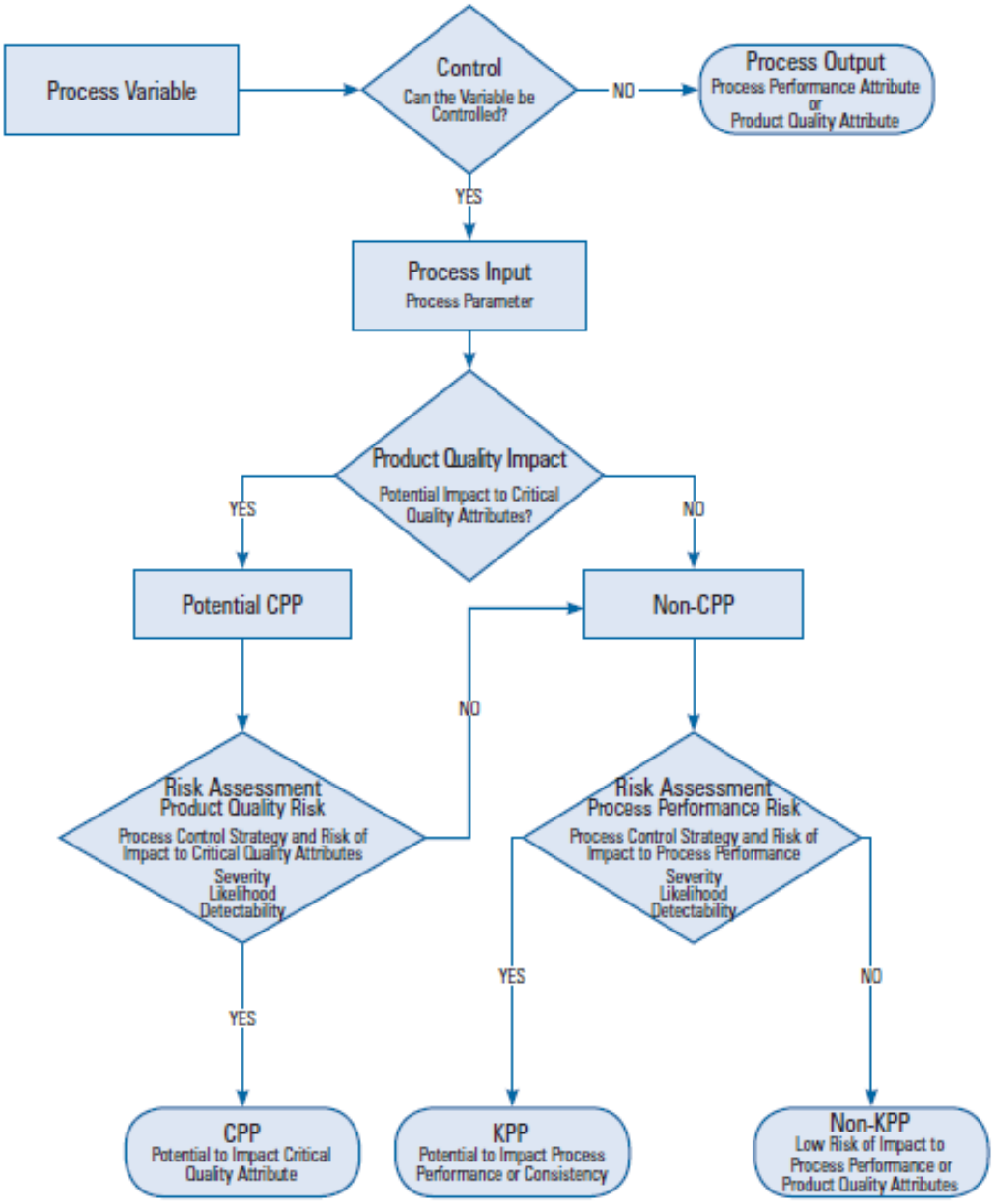
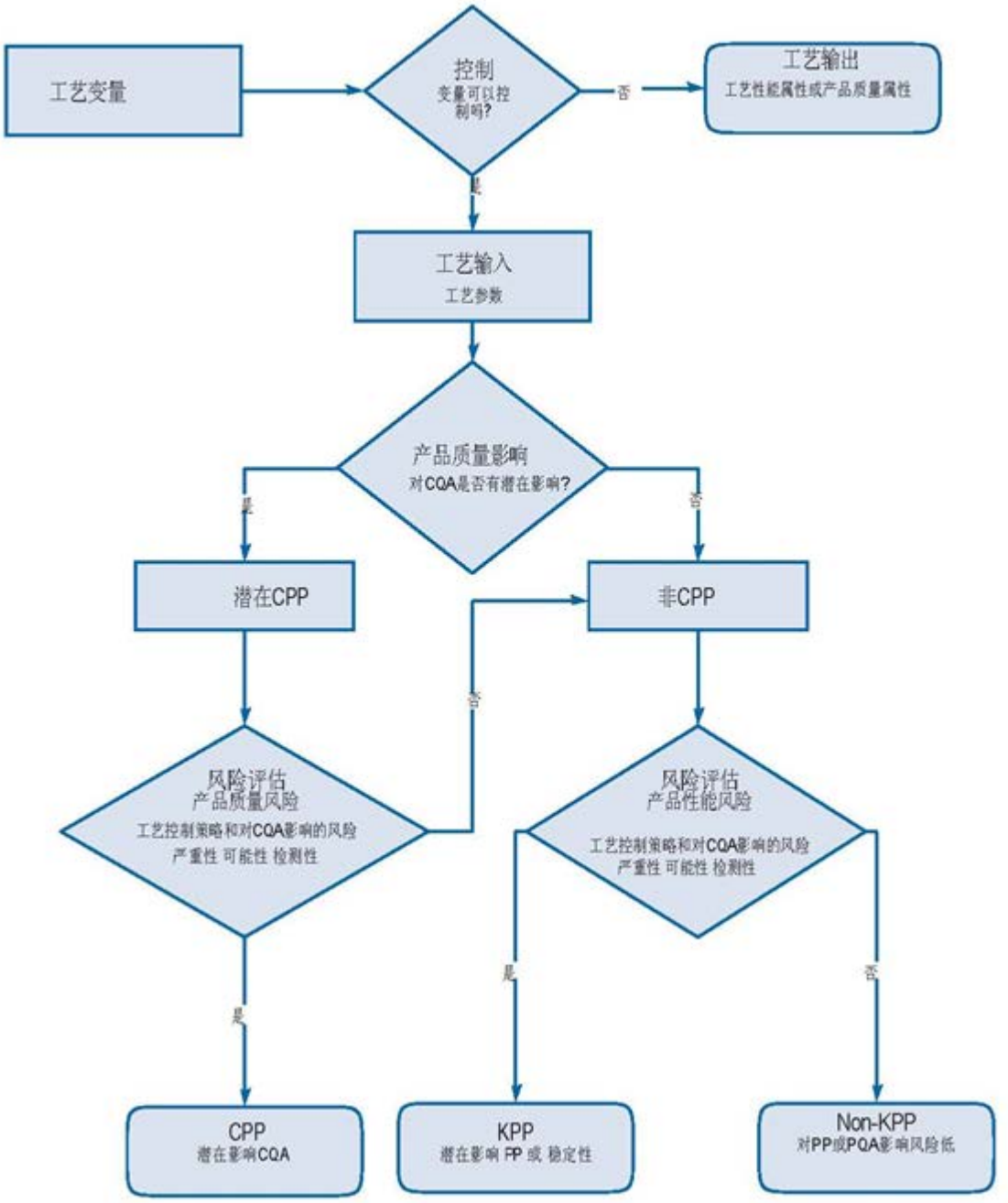


图 3.6-1 参数关键性命名决策树



3.7 Process Characterization

工艺特征描述

Process characterization is a set of documented studies in which operational parameters are purposely varied to determine their effect on product quality attributes and process performance. The approach uses the knowledge and information from the risk assessments to determine a set of process characterization studies to examine proposed ranges and interactions for process parameters. The resulting information is used to define the PPQ ranges and acceptance criteria. It can also be used to set the final parameter ranges and can be used to develop a Design Space if using an enhanced approach, i.e., incorporating advanced analytical and/or manufacturing control technologies, to process development. Experiments can be designed to examine proposed ranges and explore ones wider than those that will normally be used in operation. An element of process characterization may include multivariate designed experiments to define

process design space. While univariate approaches are appropriate for some variables to establish a proven acceptable range (PAR), multivariate studies account for interactions between process parameters/material attributes (1).
工艺特性描述是一套文档证明的研究，在该研究中操作参数被故意改变以确定它们对产品质量属性和工艺性能的影响。该方法使用来自于风险评估的知识和信息以确定一套工艺特性研究以检验提议的范围和对工艺参数的交互，结果/产生的信息被用于确定PPQ（工艺性能确认）范围和接受标准，它也能用于设置最终参数范围以及能被用于发展一个设计空间（如果用一个加强方法an enhanced approach）,例如包括先进的分析的和/或生产控制技术到工艺开发中。能设计实验以检查拟议的范围以及探索一比将用于正常运行更宽的范围。工艺特性的一个要素可能包括多变量设计实验以明确工艺设计空间，而单变量的方法对一些变化去建立一个证实的接受范围是合适的，多变量研究对工艺参数/物料属性间的交互作出了说明/解释。

Since Studies designed to characterize the process and setting acceptable ranges for process parameters are usually performed at laboratory scale. The ability of laboratory-scale studies to predict process performance is desirable. When a laboratory scale model is used in development, the adequacy of the model should be verified and justified. When there are differences between actual and expected performance, laboratory models and model predictions should be appropriately modified. In that the conclusions drawn from the studies are applied directly to the commercial-scale process, qualification of laboratory-scale models is essential. Qualification of the scaled- down models should confirm that they perform in a manner that is representative of the full-scale process. This is shown by comparing operational parameters and inputs and outputs, including product quality attributes.
由于旨在特征化工艺和为工艺参数设置可接受范围的研究通常在实验室规模执行，因而实验室规模研究预测工艺性能的能力是合适令人满意的，当一个实验室规模的模型被用在研发中时，该模型的充分性应该被证实和合理说明。当在实际和期望的性能间有差异时，实验室模型和模型预测法应该适当纠正,因为从研究中得到的结论被直接应用到商业规模工艺。实验室模型的确认是必不可少的，缩小比例的模型的确认应该证实它们的性能代表实际的生产规模工艺，这通过比较运行参数和输入输出，包括产品质量属性。

Scaled-down models for chromatography steps for protein products can be qualified by performing multiple runs with input parameters at set points and comparing the results to the full-scale unit operation. Parameters evaluated should include those that affect process consistency, such as step yields, elution profile, elution volume, and/or retention time. These should then be combined with those that represent product quality, such as pool purity and levels of process-related and host cell-related impurities.
对用于蛋白产品的色谱层析步骤的缩小比例的模型能通过在设置点输入参数执行多次运行以及比较与实际规模的单元操作间的结果来确认。评价的参数应该包括那些影响工艺一致性,诸如工序收率、洗脱图、洗脱体积和/或保留时间，然后这些应该与那些代表产品质量诸如可怜的纯度和工艺有关的水平以及与宿主细胞有关的杂质结合起来。

Pilot-scale models of small molecules that are representative of the commercial manufacturing process may be used for supportive PPQ data. In solid and liquid oral dosage forms, 10% of the commercial batch size and/or 100,000 units have been considered a representative scale (1). Scale-up effects for certain processes, such as mixing freely soluble substances, tablet compression, or liquid filling may be well-known. Batch sizes at 10% of bulk size or run times of 100,000 dosage units provide a sufficient duration to determine a degree of control and process characterization, while uncovering any preliminary major problems. Full-scale confirmation/evaluation may be carried out when small-scale studies are used to support PPQ.
代表商业生产工艺的小分子中试规模模型可能被用于支持PPQ数据，在固体和液体口服剂型，商业批量的10%和/或100000单位曾被考虑为一个代表性规模。某个工艺的放大的效果，诸如混合易溶解物质、药片压缩、或液体灌装可能众所周知。在原液10%的批量或运行100000剂量单位的倍数提供一个充分持续时间以确定控制程度和工艺特征，而未覆盖任何初步的主要问题。当小规模研究被用于支持PPQ时，实际规模确认/评估可能被执行。

For scale-down studies, the raw materials, component attributes, equipment, and process parameters should be comparable and indicative of the process intended for the commercial product.
对于缩小比例研究，其原料、组件属性、设备以及工艺参数应该是具可比性和能表明预期用于商业

产品的工艺。

3.8 Product Characterization Testing Plan
产品特征测试计划

Some product characteristics may not be tested as part of the routine release test panel. Examples of such product characteristics include residual DNA levels for biotechnology products (when DNA clearance has been established at a level that clearly exceeds safety requirements) or final product porosity for solid oral dosage products (when dissolution testing is performed). In addition to release specifications, Stage 1 deliverables should include other tests on the DS, DP, or critical intermediates that are needed in order to claim a comprehensive understanding of the product and process.
一些产品特性可能作为日常放行测试标准的一部分而不必测试，此类产品特性例子包括生物技术产品的残留DNA水平（当DNA清除率已经建立在一个能清晰超出安全要求的水平时）或固体口服制剂的最终产品的多孔性（当执行溶解度测试时），除了放行标准，阶段1可交付的成果应该包括其它对DS、DP或关键的中间体的测试为了说明对产品和工艺的全面理解。

3.9 Control Strategy
控制策略

Establishing an effective and appropriate process control strategy is one of the most important outcomes of pharmaceutical development in Stage 1. An appropriate control strategy is based on knowledge and experience gained in Stage 1 and its effectiveness will dictate the extent to which a manufacturing process remains in a state of control. As with the other aspects of stage, 1 discussed above, the development of an effective process control strategy is an iterative process. It starts, early in development and evolves as process and product knowledge increase. A robust control strategy encompasses all elements of individual unit operations in the process. All product quality attributes and process parameters, regardless of whether they are classified as critical, are included in a complete process control strategy which includes the following elements:
建立一个有效和适当的工艺控制策略是阶段1中药物研发最重要产出之一。一个恰当的控制策略是基于在阶段1中获得的知识和经验，它的效力关系到生产工艺保持受控状态的程度。正如上面讨论的阶段1的另一个方面，一个有效的工艺控制策略的开发时一个迭代过程（自我循环过程），它开始在研发早起以及成为工艺和产品知识增加。一个具耐受性的控制策略包含工艺中单个单元操作的所有元素，所有产品质量属性和工艺参数，不管它们是否被归类为关键，都将包括在一个完整的工艺控制策略中，完整的工艺控制策略包括下列元素：

Raw Material Controls
原料控制

The ability to manage the quality of the inputs (raw materials and components) to assure a consistent output is an essential aspect of a process control strategy. Inputs should be categorized based on their potential risk for introducing variability or contaminants into the product and/or process. Product variability may include changes to CQAs, whereas process variability may include inconsistencies in yield, reaction kinetics, filterability, or other non-product, quality-related effects. For many raw materials used in the manufacturing process, selection of appropriate grades (based on purity, chemical and physical characteristics, and/or microbial specifications, such as endotoxin) may be an adequate level of control. For higher risk raw materials, understanding the contribution to product and process variability may be essential to establishing specifications for those materials. Once the relationships are understood, appropriate risk reduction steps can be made part of the control strategy (see Section 6.1.4).
确保始终如一的输出的管理输入（原料和组件）质量的能力是工艺控制策略必不可少的，输入应该基于它们引入变化或污染到产品和/或工艺中的潜在风险而进行分类。产品变化性可能包括CQAs的改变，反之工艺变化性可能包括收率不一致、反应动力学、过滤性或其它非产品质量相关影响。对于生产工艺中所用的许多原料，选择适当级别（基于纯度、化学和物理特性、和/或微生物标准例如内毒素）可能是一个充足的控制水平；对于高风险原料，理解其对产品和工艺变化性的促成程度对建立那些物料的标准是必不可少的，一旦这关系被理解，适当的风险压缩步骤能采用成为控制策略的部分（见6.1.4节）。

In-Process and Release Specifications
过程和放行标准
In-process and product specifications may be related to product safety and efficacy or may assure product consistency. Confirmed failure to meet a product specification (in-process or product) disqualifies material from clinical or commercial use. Guidance on setting specifications is provided in ICH guidance documents Q6a and Q6b.
过程和产品标准可能与产品安全性和有效性相关或可能保证产品一致性，确认不符合产品标准（过程或产品）取消临床或商业使用物料资格。关于设置标准的指南在ICH指南文件Q6a和Q6b中提供。

In-Process Controls
过程控制
In-Process Controls (IPCs) are inputs to the process and are checks performed during production to monitor and, if appropriate, to adjust the process, and/or to ensure that the intermediates or product conform to specifications or other defined quality criteria. 过程控制是工艺的输入以及在在生产过程中执行检查以监控和调整工艺（如果适当），和/或确保中间体或产品符合标准或其它规定质量标准。

Performance Parameters
性能参数
Performance parameters (e.g., tablet/capsule disintegration; harvest or peak growth cell densities/ viability) are process outputs that cannot be directly controlled but are indicators that the process has performed as expected.
性能参数（例如：片剂/胶囊崩解、收获期或生长高峰期的细胞密度/活力）是工艺输出，不能直接控制单它反映工艺是否按预期。

Process Parameter Set Points and Ranges
工艺参数设置点和设置范围
Knowledge of the effects of process parameter variability on the output of each Unit Operation and on the final product evolves during Process Development and Process Characterization (Section 3.7). This information, along with process equipment capability (Section 4.1), is used to establish parameter set points and ranges (including ranges for alarms and deviations). It may also be used to assess the severity of process deviations caused by parameter excursions. Parameter ranges may be designated as normal operating ranges (NORs), or where proven by supportive data, as proven acceptable ranges (PARs).
工艺参数可变性对每个单元操作的输出和最终产品的影响的知识在工艺发展和工艺特征化过程中演变（3.7节），这信息连同工艺设备能力（4.1节）被用于建立参数设置点和范围（包括警戒限和行动限范围），也可用于评估由参数漂移所致的工艺偏差的严重性。参数范围可能被指定为正常操作范围（NORs），或当有支持数据证实时作为已证实的可接受范围（PARs）。

Process Monitoring (Data Review, Sampling, Testing)
工艺监控（数据审核、取样、测试）
Process monitoring includes measurement data (e.g., flow rates, temperatures, volumes, pH), inprocess sampling plans, and appropriate analytical assays. Data collection and analysis begins in Stage 1 and are integral parts of Stage 2, Process Performance Qualification. The data collection effort eventually evolves into the continued process monitoring program described for Stage 3, Continued Process Verification (see Section 5.0, “Continued Process Verification, Stage 3”).
工艺监控包括测量数据（例如流速、温度、体积、pH）、过程取样计划、以及适当分析检测。数据收集和分析在阶段1开始以及是阶段2不可缺少的部分。数据收集工作最终发展成为阶段3中描述的持续工艺监控程序（见5.0节）

Processing and Hold Times
加工和保留时间
Hold conditions and times are an essential part of the process control strategy for all process intermediates (or in-process materials), drug substance, bulk drug product, and prepared solutions. Studies should be performed to support these limits. Time limits for processing steps should also be part of the control strategy.
对所有工艺中间体（或过程物料）、药物成分、原液药物产品以及准备的溶液的保留条件和时间是工

艺控制策略一个不可或缺的部分，应执行研究以支持这些限度，对工艺步骤的时间限度也应该是控制策略的一部分。

Process Analytical Technology (PAT)
过程分析技术（PAT）
Process Analytical Technology (PAT) is one approach to implement the Control Strategy (28). Using PAT, CQAs are monitored in real-time (using on-line or at-line analytics), and results are used to adjust CPPs during production to decrease product variability (CQAs) or achieve consistent CQAs at desired ranges with low variability.
过程分析技术（PAT）是执行控制策略的一个方法，使用PAT，CQAs被实时监控（用在线分析），在生产过程中其结果用于调节CPPs以减少产品变化（CQAs）或得到在期望范围内的变化性小的已知的CQAs。。

PAT uses product and process knowledge as well as equipment automation and analytical instrumentation technologies. Successful application of PAT requires a thoroughly characterized process (Section 3.7) in which the relationship between CPPs and CQAs is explored using mathematical models, such as multivariate analysis. Application of this understanding to the Control Strategy (Section 3.9) also affects the design and qualification of the instrumentation and control systems in the manufacturing process.
PAT使用产品和工艺知识以及设备自动化和分析仪表技术，成功的PAT应用要求一个彻底的特征化工艺（3.7节），在该特征化工艺中，CPPs和CQAs间关系用数学模型探索，诸如多变量分析。对控制策略的理解的应用也影响生产工艺中测控系统的确认。

To support implementation of PAT, Stage 1 deliverables must describe the CQA monitoring scheme and the algorithm for adjusting CPPs based on the process response. Qualification of the equipment, measurement system, and process (Stage 2) must demonstrate the capability to adjust CPPs according to the established algorithm and confirm that these adjustments result in acceptable and predictable outputs. Therefore, PAT-based control methods need to be qualified (29).
为支持PAT的执行，阶段1交付必须描述CQA监控计划和基于工艺响应调节CPPs的算法。设备、测量系统以及工艺的确认（阶段2）必须证明安装建立的运算法则调整CPPs的能力以及确认这些调整导致的可接受的和预测的输出。因而，基于控制方法的PAT需要被确认。

3.10 Clinical Manufacturing Experience – Batch Records and Production Data
临床生产经验-批记录和生产数据
During Stage 1, clinical batches are used in clinical trials to support product approval. The data may be used along with formal process characterization data to support the establishment of manufacturing process parameters and the process control strategy. These data also comprise the beginning of the process monitoring that will continue after PPQ. Early-batch data may not include all controls implemented in the final commercial process, but the information is still valuable for evaluating the process performance. If used to support ranges and limits, clinical batch data should be included in the final process design report that will justify the process and the control strategy. The final batch records should be generated at the end of Stage 1. They will support the finalized commercial process and serve as a prelude to Stage 2.
在阶段1过程中，临床批被用于临床试验中以支持产品批准，这数据可能连同正式的工艺特征数据一起被用于支持生产工艺参数和工艺控制策略的建立，这些数据也包含PPQ之后将继续的工艺监控的起始数据。早期的批数据可能不包括所有在最终商业工艺中执行的控制，但这信息对评估工艺性能仍然有价值。如果用于支持范围和限度，临床批数据应该包括在最终工艺设计报告中用于证明工艺和控制策略。最终批记录应该在阶段1结束时产生，它们将支持最终的商业工艺和充当阶段2的前奏。

In some cases, it may be appropriate to use data from clinical batches to support the PPQ Stage 2. The rationale for this approach should be documented and included in the Process Validation Master Plan.
在一些情况下，用来自于临床批的数据支持PPQ阶段2可能是适当的，这个方法的原理应该被记录且包括在工艺验证主计划中。

3.11 Process Design Report
工艺设计报告
The process design report is also a Stage 1 output. As a living document that describes in detail the

intended commercial process, it may have various titles in internal procedures. Stage 1 study data are used to support this document and to justify the ranges, and process control strategy. Additional data and process knowledge are gained gathered as the manufacturing process changes, and are incorporated during Stages 2 and 3. The process design report, this document should be updated to include this new information. This comprehensive document includes:
工艺设计报告也是阶段1的输出，作为一份详细描述预期的商业工艺的动态文件，它可能在内部程序里有各种各样的主题名称。阶段1研究数据被用于支持这个文件以及证明范围和工艺控制策略。生产工艺变更时收集到的额外的数据和工艺知识收集起来病囊括在阶段2和3中工艺设计报告应该被更新以包括这信息的更新，这全面的文件包括：

- Reference to CQAs and supporting risk assessments
  参考CQAs和支持风险评估
- Process flow diagrams
  工艺流程图
- Process description tables
  工艺描述表
- Inputs (in-process controls)
  输入（过程控制）
- Outputs (in-process tests and limits, in-process specifications)
  输出（过程测试和限度，过程标准）
- Process parameters and ranges
  工艺参数和范围；
- Classification of parameters for risk of impact to CQAs and process performance
  对CQAs和工艺性能有影响风险的参数分类
- Design space, as appropriate
  设计空间，视情况而定；
- Justification and data supporting all parameter ranges (e.g., characterization data, development studies, clinical manufacturing history)
  支持所有参数范围的合理说明和数据（例如，特征数据、开发研究、临床生产历史）；

3.12 Process Validation Master Plan
工艺验证主计划
A process validation master plan may be initiated during Stage 1 to prepare for Stage 2 activities. It should outline the validation strategy and supporting rationale, and typically includes:
一个工艺验证主计划可能在阶段1到准备阶段2活动期间被发起，它应该描绘概述验证策略和支持原理，通常包括：

- Process characterization plan
  工艺特征计划；
- Description of the manufacturing process and control strategy
  生产工艺和控制策略的描述；
- Functions and responsibilities
  部门与责任；
- PQ or PPQ plan:
  PQ和PPQ计划；

PPQ strategy (e.g., single unit operations or a combination of unit operations, bracketing, family, or matrix approaches) and a list of individual protocols; applicable ancillary studies, (e.g., mixing, media preparation, inprocess pool hold time, resin lifetime)
PPQ策略（例如单个单元操作或单元操作的合并、bracketing、家族法或矩阵法）和单个草案、可适用的辅助研究清单（例如混合培养基准备、过程持续时间、树脂生命周期）；

- List of equipment and facilities to be used

所用的设备和设施清单；

- List of analytical methods and their status
  分析方法和它们状态清单；
- Sampling plan
  取样方法；
- List of protocols to be executed under the plan
  在计划下将被执行的草案列表；
- Proposed timeline and schedule of deliverables
  建议的时间表和交付计划；
- Procedures for handling deviations and revisions
  处理偏差和再版的程序；
- Continued Process Verification plan
  持续工艺确证计划；

3.13 Stage 1 Manufacturing and Technology Considerations
阶段 1 生产和技术考虑

The capability of the production equipment and procedures has a significant influence on the ability to maintain process parameters within pre-set limits. The measurement and control capability of the process equipment is one of the subjects of Stage 2, Process Qualification, and can be found in Section 4.1 Equipment qualification exercises should confirm the suitability of equipment for its intended use.
生产设备的能力和程序对维护工艺参数在预设定限度里的能力有关键影响，工艺设备的测量和控制是阶段2科目之一，工艺确认，4.1部分有介绍。。设备确认活动应该确认设备对预期用途的适宜性。

Compatibility of the process streams with the equipment and materials that they contact (e.g., polymeric membranes, elastomers, disposable bags, and other plastic parts) is necessary to ensures product safety and efficacy. Product contact materials as well as extractables and leachables need to be evaluated for compatibility. This work should begin in Stage 1, may include studies that require long lead times, and should be completed in conjunction with Stage 2.

工艺物料流与设备和他们接触的材料（例如聚合膜、橡胶、免洗袋和其它塑料部分）的相容性要能保证产品的安全和有效。产品接触材料和溶出物、萃取物需要评价他们的相容性。这个工作在第一阶段开始，可能包括一些需要长的前置时间的研究，并且应该结合阶段二来完成。

Compatibility of the process streams with equipment surfaces is a measure of their reactivity, absorption, and stability when in contact during manufacturing. Compatibility tests should demonstrate that the material properties of the equipment surfaces are not altered by contact with the solutions or other product-related materials. In addition, the contact materials should not alter the process solutions or materials (either by adsorption of product components or excessive leaching that could adulterate the product).

工艺物料流与设备表面的相容性是对在生产接触时他们的反应、吸收和稳定性的衡量。相容性测试是为了证明设备表面的材料性质不会因接触溶液或其它产品相关物料而改变。另外，接触材料也不应该改变工艺溶液或物料（通过吸附产品组分或者过量吸出而掺混产品）
Extractables are components of a material (e.g., a product contact surface that is used in drug manufacture or storage) that are recovered by use of an exaggerated force (solvent, time, temperature). Leachables are contact material components from process equipment or storage containers that migrate into the product under normal conditions of use.
萃取物是一种材料的成分(例如用于药品生产或储存的产品接触表面),通过使用一种夸大的外力(溶剂、时间、温度）而得到。浸出物是来自工艺设备或存储容器的接触材料的成分，它们在正常使用状态下转移到产品中。

The identity and quantity of leachables from polymeric wetted components (plastic storage containers, filters, primary packaging materials, gaskets and O-rings) used in drug manufacture, storage, and

packaging must be documented to assure that the product is not adulterated. A combination of literature reviews, risk assessments, and laboratory studies can be used to address leachables. Various approaches to determine the extent of testing and identification of leachable species, and the setting of acceptable levels, have been published.
来自于用于药品生产、储存、包装得聚合膜盒的组件（塑料存储器、滤器、内包装材料、垫片、O形圈）的浸出物的种类和数量必须通过文件列明以此保证产品不会被掺入杂质。要结合文献查阅、风险评估和实验室研究来说明浸出物。各种确定测试的程度和浸出物种类的鉴别。还有可接受水平的设定的方法都已经出版。

• *"Safety Thresholds and Best Practices for Extractables and Leachables in Orally Inhaled and Nasal Drug Products"* ***(30)***
• *"Evaluation of Extractables from Product-Contact Surfaces"* ***(31)***
• *"Application of Quality by Design (QbD) Principles to Extractables/Leachables Assessment: Establishing a Design Space for Terminally Sterilized Aqueous Drug Products Stored in a Plastic Packaging System"* ***(32)***
• *"Leachables Evaluation for Bulk Drug Substances"* ***(33)***

"口服吸入和鼻喷药物的萃取物和浸出物的安全阈值和良好实践"（30）
"产品接触表面的萃取物的评价"（31）
"使用QbD对萃取物/浸出物评估的原则：为储存在塑料包装系统的最终灭菌的液体药物确立设计空间"（32）
"原料药的浸出物的评价"（33）

4.0 Process Qualification (Stage 2)
工艺确认（第二阶段）

Process Qualification (PQ) during Stage 2 demonstrates that the process works as intended and yields reproducible commercial product. It should be completed before release of commercial product lots, and covers the following elements:
第二阶段的工艺确认为了证明工艺能按照设计的进行，商业生产能重现，保证产量。工艺确认应该在商业生产批次放行之前执行，包括以下的要点:

1. Design and qualification of the facility, equipment, and utilities (this should be completed prior to qualification of the process)
   设施、设备、公用工程系统的设计和确认（需在工艺确认之前）
2. Process Performance Qualification (PPQ), which demonstrates control of variability and the ability to produce product that meets predetermined quality attributes.
   工艺性能确认 工艺性能确认为了证明工艺变量的可控以及生产出符合预定质量属性的产品的能力。

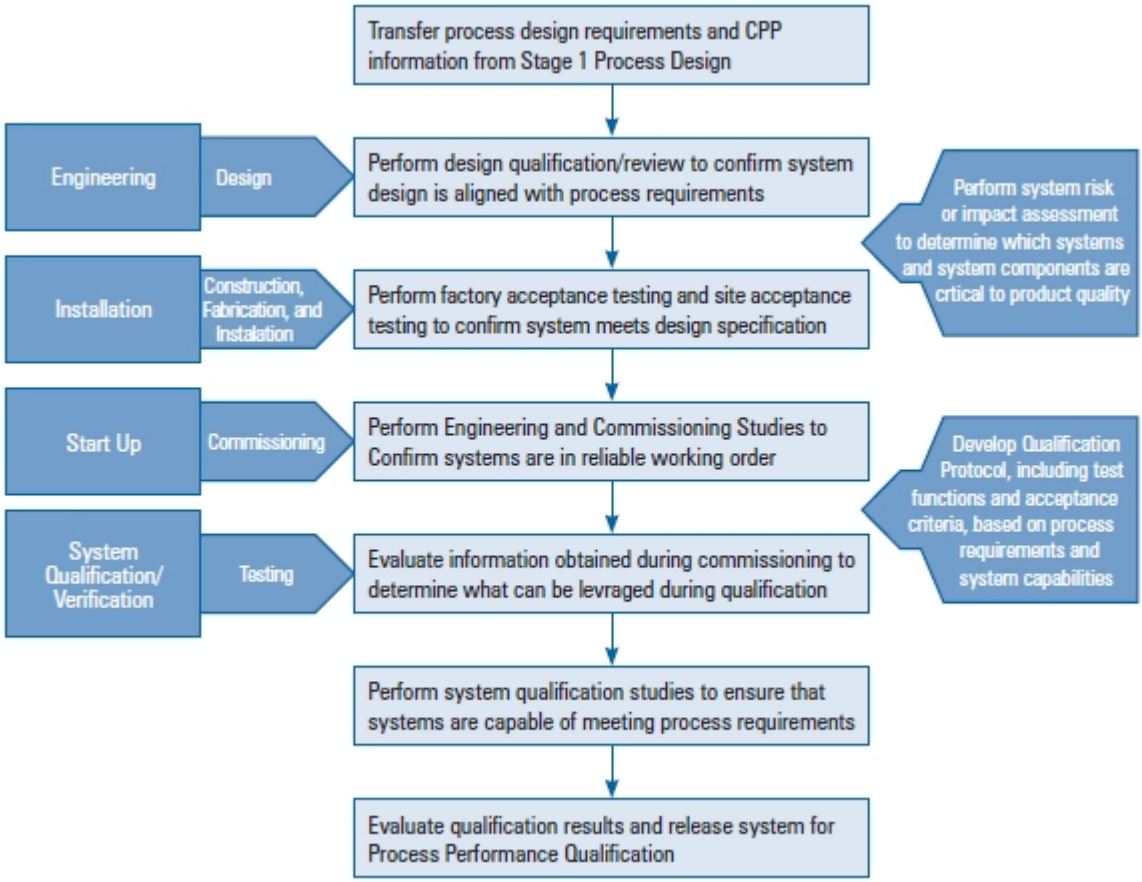
4.1 Strategies for System Design and Qualification
系统设计和确认的策略

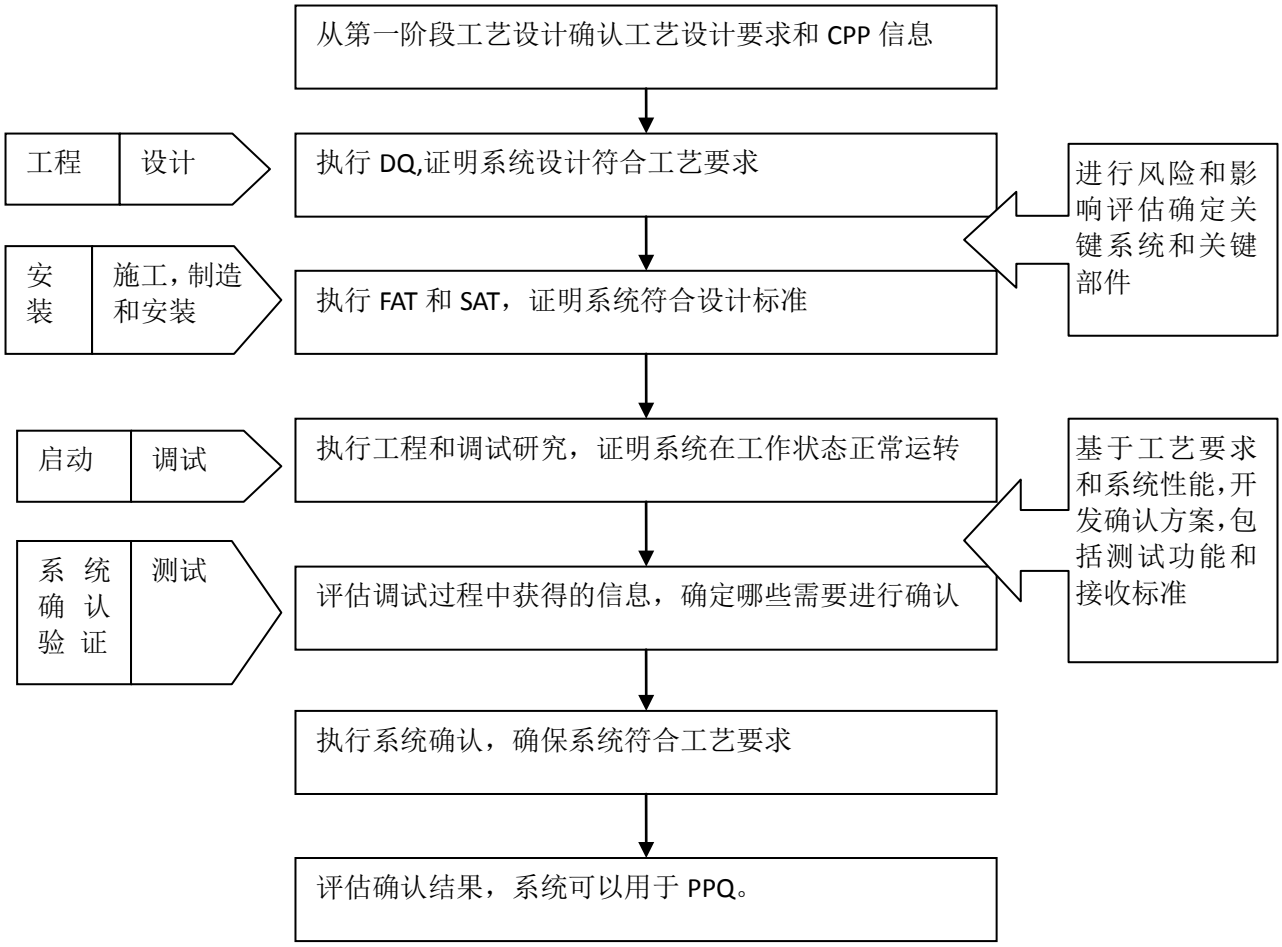
Facilities, equipment, utilities, and instruments (collectively referred to as systems) used in the manufacturing process should be suitable and capable for their intended process use, and their performance during the operation should be reliable. Systems that affect product quality should be qualified to re-duce the equipment performance as a process variable. The review and qualification of these systems should be performed according to a pre-defined project plan. System qualification should precede Stage 2 PPQ activities. Qualification studies should be completed, reviewed, and approved, with all deviations addressed, prior to the start of PPQ studies.
生产工艺中使用的设施、设备、公用工程和仪器（统称为系统）应该是合适的，并符合预定的工艺能力要求，生产操作中系统的性能需可靠。对于影响产品质量的系统应进行确认，以此减少设备的性能方面的工艺变量。系统的确认和回顾应依据工程计划执行。在第二阶段PPQ执行之前进行系统确认，在PPQ开始之前确认需完成，回顾并经批准，偏差需有记录。

The following section provides considerations for preparation and performance of system qualification. More information on approaches to planning and performing system qualification may be found in several sources (26,34,35). Figure 4.1-1 presents a typical sequence of activities that support the system qualification effort.

下面章节描述了系统确认准备和执行过程中的注意事项。关于计划及执行系统的确认，更多的信息见三个资料（26,34,35）。图4.1-1为一个典型的系统确认的活动程序。

Figure 4.1-1 Typical System Qualification Sequence
图4.1-1 典型的系统确认程序





4.1.1 Engineering and Design
工程和设计

Facility, equipment, and utilities should be designed to meet process requirements. The design of the facility and commissioning of the equipment and utilities should assure the capability of operating as required for routine manufacturing. These activities and all commissioning-related tasks should be conducted according to Good Engineering Practices (GEP), and recorded according to Good Documentation Practices (GDP), with oversight by the Quality Unit. Risk-based approaches may be used to assure adequate controls and verification.

设施、设备、公用工程需经设计符合工艺要求，设施的设计，设备和公用工程的调试应确保符合日常生产的运行能力。调试相关的活动遵循GEP执行，根据GDP记录数据，并由质量部门监管。可以采用风险控制方法来保证足够的控制和确证。

System design should be based on process parameters, control strategies, and performance requirements developed or identified during Stage 1 Process Design. This information is transferred to those designing engineering requirements for facility and manufacturing systems. Design qualification involves a review of the system design to assure that it is aligned with process control strategy and performance requirements.

系统设计应基于工艺参数，控制策略和性能要求，这些由第一阶段工艺设计开发和确认。这些信息可以转到符合工程设计中设施和生产系统的要求即可。DQ需对系统设计进行审核，确保其符合工艺控制策略和工艺性能要求。

In situations where the process is being transferred to an established facility with qualified equipment, a risk assessment should be performed to identify any equipment control gaps. These can be addressed through equipment modifications (which may require requalification) or through operational controls.

在工艺被转移到经过确认的已建好设备的情况下，应执行风险评估，确认是否有设备没有被控制。这些可以通过设备改造来解决（有可能会涉及到再确认）或者通过操作进行控制。

4.1.1.1 Risk Assessment
风险评估

Risk assessments determine which systems and system components have an impact on the establishment and maintenance of process parameters and conditions that affect product quality. This information helps develop system qualification plans, protocols, test functions, and acceptance criteria. The process steps and systems that affect product quality, the mode of effects, and the correlation between system performance and control of process variables should be understood. For more information on risk assessments, see **Section 6.1.**

通过风险评估确定哪些系统及哪些系统部件对工艺参数的建立、维护及对产品质量有影响。通过评估得到的信息，可以帮助开发系统确认计划，方案，测试功能和接收标准。我们应该去充分理解工艺步骤，影响产品质量及失效模式的系统，系统性能和工艺变量控制之间的关联。更多关于风险评估的信息见章节6.1。

4.1.2 Installation
安装

Upon completion, system testing and inspection should be used to verify that the systems have been fabricated, constructed, and installed to engineering, and process specifications. The information from this verification should be accurate, reliable, and useful. If so, then information from these activities may be leveraged or used to support qualification testing.

风险评估完成后，通过系统测试和验收确认系统已经按照工程和工艺的标准进行了施工，制造和安装。系统测试和验收中得到的信息是准确的，可靠的和有用的，如果是这样，这些信息可利用或用来支持确认中的测试。

The start-up and commissioning of these systems should confirm that they are in good working order and operate as designed. Engineering studies can provide confidence that the systems will perform under process conditions. Adjustments to the systems to achieve the specified level of performance and operation may be needed. Information on modifications or adjustments should be documented and transferred to the team preparing the qualification plans and protocols.

系统的　启动和调试应确保其能很好的工作和按照设计运行。工程方面的研究，为系统在工艺条件下执行提供更大的帮助。为了达到规定的性能要求，系统的调整和运行还是需要的。准备确认计划和方案的团队需知道系统的变更和调整，这些变更和调整也应有记录。

4.1.3 Qualification Plan
确认计划

The qualification plan may be developed at any time once the process requirements and correlation to process systems are understood. Early development of the qualification plans may provide valuable guidance to the design, installation, and commissioning efforts. However, to capture any changes that result from start-up and commissioning, it may be prudent to complete the qualification plans and protocols after all information from the commissioning has been transferred. This approach also enables a better understanding of the type and amount of information that can be leveraged from pre-qualification activities. This approach means that Stage 2 activities may be underway during and prior to completion of all Stage 1 activities.

只要充分理解了工艺要求和工艺系统的关联性，系统确认计划开发报告随时可以起草。确认计划早期的开发方案应包括有价值的指南，这些指南可以指导系统的设计，安装和调试。为了了解到从启动到调试过程中的任何变更，在收集到调试中的所有信息后，再去完成确认计划和方案还是很明智的。同时，这样也能更好的了解信息的类型和数量，这些信息需要用在确认前的活动中。这也意味着，在第一阶段期间或者之前，第二阶段已经正在开展了。

Table 4.1.3-1 presents examples of some of the information that can be used to help develop test functions and acceptance criteria.
表格4.1.3-1一些可以帮助开发测试功能和接收标准的信息举例

Information信息	**Purpose目的**
Control Capability 控制能力	Assessment for each controlled parameter indicating control bandwidths under test conditions that are relevant to the process that is being qualified. Analysis conducted in conjunction with process control requirements and may impact process parameter designations. 评估每一个控制参数，这些参数已经标明了与被确认的工艺相关的测试条件下的控制范围。之前的分析和工艺控制要求可能会影响工艺参数类型。
Capacity 能力	Range of operating capacities for each unit operation or step, demonstrating consistency with proposed process. 对于每一个单元操作或步骤，操作能力的范围证明了过程的一致性。
Detection Capability 检测能力	Assessment of monitoring instruments and sampling points showing accuracy of instrument outputs and sampling limitations. (To be used in performing Risk Assessment and establishing the monitoring strategy for the process.) 监测设备和取样点的评估说明了设备输出的准确性和抽样限制。（用来执行工艺风险评估和建立监测策略）
Alarms and Interlocks 警报和联动装置	Check for consistency with process requirements and safety concerns. 用来检查工艺要求和相关安全方面的一致性
Process Stream/Product Contact Material 产品线/产品接触的物料	Listing of all contact materials for all equipment used to process products or materials added to the product stream. Used for compatibility assessment and leachables / extractables analyses. 对所有的设备，列出所有用于处理产品和添加到产品线中的物料的设备中直接接触的物料的材料。这些物料需进行相容性研究和析出物分析
Maintenance and Calibration Programs 维护和校验项目	Documentation of required equipment service and calibration of all instrumentation. 需要设备服务的文件和所有仪表的校验

4.1.3.1 Test Functions and Acceptance Criteria
测试功能和接收标准

System qualification tests or studies should be based on knowledge gained from previous activities, including Stage 1 Process Design, and engineering studies. Test functions should be based on good scientific and engineering principles designed to demonstrate and assure that anticipated operating parameters will be met throughout the manufacturing process in a consistent and predictable manner. Acceptance criteria should be based on sound scientific rationale; the criteria should be useful, attainable, and where appropriate, quantifiable.
系统确认测试和研究应基于先前活动中的经验，包括第一阶段的工艺设计以及工程方面的研究。测试功能应基于良好的，科学的工程原理，测试功能的设计应能证明和确保预期的操作参数在整个生产过程中一致和可预测性。接收标准应基于科学原理，标准是有用的，可实现的，如果适用的话，也要求是可量化的。

If sufficient process understanding is not available, or the scale-up effect is unknown, existing knowledge may be used during design and commissioning to define user requirements.
如果工艺理解不够，或者批量放大效果也未知，那么，在设计和调试期间现有的知识可以用来定义URS.

Formal system operating and maintenance procedures or instructions should be in place prior to the execution of test functions. Operators and those conducting studies should be trained in the operation of the systems and conduct of the tests. These should be conducted under GMP conditions and documented according to GDPs. All measuring and test instruments should be calibrated and traceable to appropriate standards.
在执行测试功能之前，应有正式的系统操作和维护保养规程或者说明书。关于系统的操作和检测的

执行，操作者和相关指导性研究都应该被培训。所有这些都应遵循GMP并通过GDP记录。所有测量和测试仪器应校准并能追溯到合适的标准。

Deviations in the execution of qualification testing should be documented, investigated, and addressed. Conclusions should be based on the suitability and capability of the system to meet the processrequirements. When necessary, systems may be modified and studies repeated.
执行确认测试过程中的偏差应记录，并调查和处理。结论应包括系统的适用性和能力是否符合工艺要求。如有必要，系统需变更和重新研究。

4.1.4 Maintaining Systems in a State of Control
处于控制状态的维护保养系统

Qualification studies ensure that the manufacturing systems, as designed and operated, are in a state of control. For the process to remain valid and controlled, the systems must be maintained in a state similar to that demonstrated during qualification.
确认方案确保生产系统处于控制状态。为了工艺的有效和受控，系统需保持与确认所证明的状态一致。

Periodic assessment and evaluation of the system to determine its control status is important. The assessment should include a review of information that indicates or supports assurance of control. This information may include, but is not limited to, such items as:
定期对系统的评估及评价来决定系统是否处于控制状态是非常重要的。评估应包括对信息的回顾，这些信息如下：

- Calibration records
  校验记录
- Preventative and corrective maintenance records
  预防和纠正性维护保养记录
- Equipment logs
  设备运行记录
- Training records
  培训记录
- Standard Operating Procedures
  标准操作规程
- Change requests
  变更要求
- Work orders
  工作指令
- Monitoring results and trends
  监测结果和趋势
- Non-conformance reports and deviations
  不合格品报告和偏差
- Failure investigations
  失败调查
- Re-qualification studies
  再确认研究

Periodic assessment of systems may lead to additional qualification-related activities or testing. In addition to periodic assessment, event-driven assessments and re-qualifications may arise from process-related changes, out-of-specification results and trends, and investigations. The System assessments and the events that trigger event-driven assessments should be recorded in a formal procedure that also addresses the mechanism for deciding when re-qualification is warranted, the criteria for doing so, and those responsible. It is recommended that Subject matter experts and the quality unit should also be involved in these decisions.

对系统的定期评估可能会导致额外的确认相关活动或测试。除了定期评估之外，工艺相关的变更、OOS、趋势和调查都会引起事件驱动的评估和再确认。系统的评估和引起评估的事件均需按照正式的规程进行记录。在规程中，需说明什么情况下，再确认需批准，这样做的质量标准是什么，以及相关的责任人。建议项目专家和质量部门均应参与这些决定。

4.2 Process Performance Qualification
工艺性能确认

Process performance qualification marks the transition from development and clinical manufacturing to routine commercial production. Process Performance Qualification (PPQ) demonstrates the validity of the process design and the suitability of the process control strategy at the commercial manufacturing scale. PPQ provides confidence that the systems of monitoring, control, and procedures in routine manufacturing are capable of detecting and compensating for potential sources of process variability over the product lifecycle.
工艺性能确认标志着从产品开发和临床生产转移到日常商业生产。工艺性能确认（PPQ）证明了在商业生产规模下工艺设计的有效性和工艺控制策略的适用性。在日常生产中，系统的监测、控制和操作规程应能及时发现和修正产品周期中潜在的工艺变化。这些，PPQ提供了一定的保障。

The number of “successful” batches executed during the PPQ study should not be viewed as the primary objective of a PPQ campaign. While successful runs of commercial-scale batches can indicate overall operational proficiency and sound process design, these batches should also be viewed as a means to obtain information and data needed to demonstrate that the process control strategy is effective. The type and amount of information should be based on understanding of the process, the impact of process variables on product quality, and the process control strategy developed during Stage 1 Process Design. As appropriate, other prior knowledge should be used as well. The number of batches needed to acquire this information and data, may be based in part on a statistically sound sampling plan that supports the desired confidence level. It may also be influenced by the approach selected to demonstrate that the batch-to-batch variability of CQAs is acceptable.
在PPQ研究中，已执行的成功批次数不应该作为PPQ的主要目的。虽然商业放大批成功运行批次数量可以说明操作的熟练以及充分的系统设计。通过这些批次，可以收集信息和数据，用来证明工艺控制策略是有效的。信息的类型和数量应建立在对工艺的理解上，建立在工艺变量对产品质量的影响上，建立在第一阶段工艺设计中开发的工艺控制策略上。如果适用的话，已有的知识也应该被利用。批次的数量被用来获取信息和数据，通过一定的方法证明批与批之间变化，CQA依然是可以接受的，这个方法的选择也会影响批次的数量。

This section will discuss design strategy for the PPQ, recommended content for the protocol and report, and the transition to Stage 3 of the process validation lifecycle.
本章节将讨论PPQ的控制策略，建议方案和报告的内容，以及如何过度到验证生命周期中的第三阶段。

4.2.1 PPQ Readiness
PPQ准备

The transition from Stage 1 to Stage 2 of the process validation lifecycle is not strictly sequential. Completion of some Stage 1 activities may overlap with those from Stage 2. Likewise, some preparative Stage 2 activities will be initiated in parallel with those from later Stage 1 activities. Components of Stage 1 PPQ activities (as discussed in **Section 3.1)** include, among others: drafting of the Process Validation Master Plan; initiation of the qualification of facilities, utilities, and equipment; drafting of protocols for the PPQ studies; training of personnel; or drafting an initial CPV plan. Although initiation of PPQ activities does not is not depend on completion of all Stage 1 activities, a readiness assessment should be conducted to determine the timing of sufficient information and completion of activities to support moving forward with PPQ batch manufacture. The readiness assessment should include deliverables from Stage 1 (as outlined previously in **Section 3.1)** and other elements:
验证生命周期中，第一阶段过渡到第二阶段，不是严格按照顺序的。部分第一阶段工作可能与第二阶段工作同步完成。同样，部分第二阶段工作也会与第一阶段的后期工作同时启动。PPQ的第一阶段的内容（见章节3.1）包括：起草工艺验证主计划，设施；公用工程，设备的启动，起草PPQ方案，人员培训以及起草最初的CPV计划等。尽管PPQ不需要第一阶段全部完成后才可以启动，但是应该

有充分的风险评估为了决定PPQ活动完成和获取充分信息的时间，这些可以保证PPQ批量生产的推进。充分的风险评估应包括第一阶段的结论（见3.1中的概述）和以下要素：

Quality Target Product Profile —Initiated in at the start of Stage 1, but updated to reflect knowledge obtained from Stage 1 prior to initiating PPQ.
目标产品质量概况-第一阶段的开始已经启动，但是在启动PPQ之前需根据第一阶段获得的知识进行更新。
Critical Quality Attributes with Criticality Assessment —CQAs are identified early in Stage 1. They are confirmed to account for additional analytical characterization, clinical and/or non-clinical data and information gathered during Stage 1. CPPs that impact CQAs are reviewed and updated based on detectability and occurrence ***(11,36).***
关键质量属性与关键评估-在第一阶段的早期阶段，CQA已经被明确定义。被证实的CQA来解释额外的分析特性，临床或者非临床的数据和第一阶段收集的信息。基于可检测率和发生的概率，影响CQA的CPPs应定期被审核和更新。

Commercial Manufacturing Process Description —This is started in Stage 1 and updated to reflect the finalized commercial process supported by Stage 1 studies/data. These include elements outlined in **Section 3.4,** and any changes resulting from the qualification of the facilities, utilities, and equipment as outlined in **Section 4.1.**
商业生产工艺描述-商业生产工艺描述第一阶段已经开始并更新，来表现由第一阶段研究/数据支持的最终商业工艺。这些也包括3.4章节所概述的内容和4.1章节设施，设备和公用工程确认导致的变更。

Analytical Methods —Appropriately validated or suitably qualified methods should be identified and their status documented. Methods for product release and stability should be fully validated according to ICH requirements prior to initiating PPQ batch testing. Additional tests beyond normal release testing used to support PPQ should be identified and suitably qualified/validated prior to being used to test PPQ batches. The justification of the status for use in the PPQ studies (qualified and/or validated) should be fully documented for each analytical method.
分析方法-应确认分析方法已经验证或确认，他们验证状态应该被记录。根据ICH的要求，在PPQ批测试开始之前，产品放行和稳定性试验的方法应充分被验证。除了正常的批放行测试，新增的测试方法用于支持PPQ的，新的测试方法啊也需在PPQ批测试之前被验证。在PPQ的研究中，每一种分析方法验证状态评估（已确认或已验证）均需被记录。

Approved commercial batch records —Changes may be made to batch records during Stage 1 should enhance, clarify, or optimize manufacturing instructions and/or to reflect knowledge gained during process characterization. Batch records reflecting the final commercial process to be studied in PPQ should be approved prior to PPQ batch execution.
批准的商业批批记录-第一阶段，批记录有变更，在工艺特性确定期间，这些变更应该提高，清晰或者优化生产指令，并反映出该期间获得的知识。 批记录反映了最终的商业批工艺，应在PPQ执行之前批准批记录。

Process Design Report —This report (as described in **Section 3.11)** is the repository for the process design justification, and includes parameter risk ranking, and ranges for the process that will undergo PPQ study. The data summarized in this report will support the selection of the elements of the PPQ studies and proposed PPQ acceptance criteria. The process development summary should provide the link between the detailed process description, risk assessments, control strategy description, characterization reports, rationale for parameter designations, and clinical manufacturing history. It is a best practice for this information to be finalized prior to PPQ study design since it provides the scientific support to justify the PPQ acceptance criteria.
工艺设计报告-工艺设计报告（3.11章节由描述）是工艺设计理由的依据，包括工艺参数风险排序，工艺范围，这些PPQ研究中都需描述。工艺设计报告中总结的数据用来支持PPQ中要素的选择和支持提出的PPQ接收标准。具体的工艺描述，风险评估，控制策略描述，工艺特性确认报告，参数类型的基本原理很临床生产历史这几者的关系在工艺开发报告中有概述。在PPQ研究之前，这些信息的完成是一个很好的实践，因为这些信息给PPQ的接收标准提供了可以的依据。
Process Validation Master Plan (PVMP) —Drafting of the process validation master should begin in

Stage 1 and be finalized prior to PPQ study initiation. Elements of the Process Validation Master Plan are outlined in **Section 3.12.**
工艺验证主计划(PVMP)-工艺验证主计划应在第一阶段进行草早，在PPQ启动之前完成。工艺验证主计划要素的概述见章节3.12.

Quality System and Training —Qualified and trained personnel will be integral to the PPQ studies. Detailed, documented training specific to the PPQ is recommended for functional groups directly involved in the execution of the study. To minimize the risk of human error, personnel should understand their role in protocol execution to minimize the risk of human error. Quality Unit approval of PPQ activities should be completed prior to PPQ study initiation, and all PPQ studies should be conducted within the quality system.
质量系统和培训-有资质的和经过培训的人员是PPQ研究中必须要求的。相关的职能人员需进行关于PPQ的详细的，有记录的培训。同时，这些职能人员应直接参与到PPQ研究的执行中。为了尽量减少人员操作失误的风险，人员应理解他们在方案执行中的角色。在PPQ执行之前，质量部门应批准PPQ活动，同时，所以的PPQ研究应在质量系统的指导下进行。

Approved protocols for PPQ Studies —Protocols for each study should be approved and qualification protocols is discussed in **Section 4.4.**
PPQ研究方案的批准-每一个研究的方案均需被批准，确认方案在章节4.4中进行讨论。

4.3 Design Strategy for Process Performance Qualification (PPQ)
工艺性能确认（PPQ）的设计策略

4.3.1 Use of Prior Knowledge and Stage 1 Data to Support PPQ
使用已有的知识和阶段1的数据来支持PPQ

In a lifecycle approach to process validation, sources of data and information outside of the PPQ batches may be used to support a high degree of confidence in an ongoing state of process control. Prior knowledge is that which has been gained from similar products and processes. It may come from experience with a portfolio of similar molecules, where platform manufacturing strategies have been developed using existing facilities and equipment (e.g., platform manufacturing processes for monoclonal antibodies), or from similar process and unit operations. Leveraging the body of data from similar products and processes may provide an additional level of confidence in the process control of a product and process that uses a similar control strategy and unit operations.
工艺验证采用生命周期方法时，在持续的工艺控制状态下，PPQ批外的数据和信息用来进一步支持验证。已有的知识是指从类似产品或工艺中获得的知识。它可能来自于一组类似分子的生产经历，利用了已有的厂房和设备采用平台生产策略（例如单克隆抗体的平台生产工艺），或者来自于相似的工艺和单元操作。借助从类似产品和工艺中获得的数据可以为那些使用类似控制策略和单元操作的产品和工艺提供额外的支持。

By contrast, first-in-class molecules and/or products manufactured in new facilities/equipment will not have a similar depth of prior knowledge and data prior to development. In these instances, increased emphasis on data gathering in Stage 1 may be applied to support PPQ readiness. To gather sufficient data to demonstrate an acceptable level of confidence in the commercial manufacturing process when little prior knowledge or Stage 1 data are available, the scope and extent of PPQ may be greater. The rationale and scientific justification for the use of existing data (prior knowledge) to support the PPQ Stage should be documented in the process validation master plan. All prior knowledge and Stage 1 data used in to support PPQ must be retrievable, traceable, verified, and generated using good scientific practices.
与之相对，首类分子和/或在新的厂房/设备中生产的产品在开发前不会有已有的知识和数据。这时，尤其要注意收集第一阶段的数据来支持PPQ的准备。当只有少量的以前知识或第一阶段数据可以利用时，要收集到足够的数据来证明商业生产工艺可以信赖，那PPQ的范围和程度都要更大。使用已有数据（以前知识）支持PPQ的理由和科学说明要记录在工艺验证主计划中。所有用于支持PPQ的以前知识和阶段一的数据都必须可检索、可追踪、确认过、使用科学的实践产生的。

Figure 4.3.1-1 illustrates the relationship of the amount of knowledge to Stage 1 and 2 activities. Where there is greater prior knowledge or process design for a new product or process, PPQ studies may be decreased. Less prior knowledge will require more Stage 1 and/or PPQ data.
图4.3.1-1显示了阶段1和2的行动与知识量的关系。对于一个新的产品或工艺，以前的知识或工艺设计越多，PPQ研究可以降低。已有的知识越少，就需要更多的阶段1和/或PPQ数据。

Figure 4.3.1-1 Relationship of Prior Knowledge to the Amount of PPQ Data Required
图4.3.1-1 已有知识与要求的PPQ数据量的关系

Some examples of cases where prior knowledge may be useful to for PPQ include:
先验知识对PPQ有用的一些例子包括：

- Setting of acceptance criteria in PPQ studies: For example, bioburden and endotoxin in-process acceptance criteria in cases where facility history and limits for other processes can be applied to similar processes that employ the same facility and equipment. (Assumes the limits for the previous product are appropriate for the quality of the new product.)
  PPQ研究中可接受标准的设定：例如，生物负荷和内毒素中控可接受标准的设定，若其他工艺的限度和设施历史可被应用于使用相同设施和设备的相似产品。（假设前一产品的限度对新产品的质量是适当的。）

- Use of data from other product PPQ supportive studies: For example, in platform purification operations where same or similar buffer formulations will be used in the same vessels, buffer hold studies already performed for a different product can be used to support the PPQ for buffers used for the new product.
  使用其他产品的PPQ支持性研究数据：例如，在平台纯化操作中，相同或相似的缓冲液配方将用于相同缓冲容器中，对另一个不同的产品已进行的缓冲液贮存研究可以用于支持将用于新产品的缓冲液的PPQ研究。

- Using prior experience on similar processes: In non-sterile solid and liquid dosage manufacturing, such as granulating and film coating solution preparations, or bulk solution mixing and filling, prior experience with similar solutions or filling equipment may be applied to justify the number of PPQ batches for those unit operations.Past knowledge of common excipients, such as fillers, binders, disintegrants, lubricants, and preservatives in the formulation and process is also an important factor.
  使用相似工艺的先前的经验：在非无菌的固体或液体制剂生产中，例如制粒和薄膜包衣溶液的制备，药液混合或灌装，可以应用相似溶液或灌装设备的先前的经验来合理说明验证这些单元操作

的 PPQ 的批次数目。。通用辅料的过去的知识也是一个重要的因素，例如处方和工艺中的填料、粘合剂、崩解剂、润滑油和防腐剂。

Use of Stage 1 Data for PPQ
第 1 阶段的数据用于 PPQ

Processes and products for which there is little or no prior knowledge may require a greater emphasis on Stage 1 and PPQ activities to demonstrate an acceptable level of confidence in the process control strategy. Data from Stage 1 process characterization studies and clinical manufacturing are generally used to support the establishment of the control strategy for new products, as discussed in **Section 3.0.** Stage 1 data may be used to support PPQ if sufficient scientific evidence for its use is available. At a minimum, the studies claimed to support PPQ should represent the commercial manufacturing scale (e.g., be scale independent) or derived from qualified small-scale model(s) proven to represent the full-scale process. In some cases, data from clinical manufacturing batches may be used in conjunction with that gathered during PPQ to increase the amount of data that can be used to achieve an acceptable level of confidence in the process. Some examples of the use of Stage 1 data to support the PPQ include (see **Section 7.1** for details):
对于仅有极少或没有已有知识的工艺和产品，可能要求更强调第 1 阶段和 PPQ 活动来证明工艺控制策略的可接受的置信水平。如第 3.0 节所讨论，通常可以用第 1 阶段工艺特性研究和临床用样品生产的数据来支持新产品控制策略的确定。第一阶段的数据可被用来支持 PPQ，如果其使用有充分的科学证据。声明支持 PPQ 的研究至少应代表商业生产规模（例如，应是规模独立的）或是来自已证明代表全规模工艺的经过确认的小规模模型。在某些情况下，可以联合使用临床用样品生产批次的数据与 PPQ 期间收集的数据，以增加用于实现工艺的可接受的置信水平的数据的数量。使用第一阶段数据来支持 PPQ 的一些例子包括（有关详细信息，请参见第 7.1）：

- Large molecule example
  大分子的例子

- Past experiences in clinical, and stability, and pilot batch manufacturing. Process evaluation batches help determine the amount of PPQ data. For example, in an oral solid dosage form of multiple strengths, at least 8 Stage 1 batches with the same commercial formulation were from clinical supply manufacturing, stability, pilot, process evaluation/design, and plant demonstration batches. The firm had extensive experience with the components, equipment, and unit operations for the dosage form: wet granulation, fluid-bed drying, milling, blending, compression, and film coating. These 8-plus batches played instrumental roles in the justification of the number of PPQ batches.
  临床、稳定性和中试批生产的过去的经验。工艺评估批次有助于确定PPQ数据的数量。例如，多规格的口服固体制剂，至少8批具有相同处方的第1阶段的批次是来自于临床试验样品生产、稳定性、中试、工艺评估/设计和工厂实证批次。公司有关于组份、设备和该剂型单元操作（湿法制粒、流化床干燥、粉碎、混合、压片和包衣）的丰富经验。这8+批次对证明PPQ批数合理性有至关重要的作用。

In some cases, Stage 1 data that supports PPQ may be supported in some cases by adding stricter testing for a defined number of batches to confirm the results obtained in the Stage 1 studies and the PPQ batches. For example, small-scale column lifetime studies may be used to support column reuse limits. These are then confirmed with a heightened level of impurity monitoring until the reuse period has been reached at full scale.
在某些情况下，可通过对规定的批数增加更为严格的检验来支持用于支持 PPQ 的第 1 阶段的数据来证实第 1 阶段研究和 PPQ 批次中获得的结果。例如，可用小规模的柱寿命研究来支持柱重复使用的限度。可在之后通过加强杂质监测来证实，直到重复使用时间 达到全量。。

4.3.2 PPQ Study Design
PPQ研究设计

Process Performance Qualification is a means to demonstrate that all important elements of a process unit operation are under the appropriate degree of control, and that all important variables and elements of the unit operation have been considered (facility, utilities, equipment, personnel, process, control procedures,

and components). During PPQ, critical process parameters and critical quality attributes are monitored along with process performance parameters. Their evaluation is useful in demonstrating consistency and can enhance confidence in the overall process control strategy when included in the PPQ. All parameters and attributes intended for ongoing Continued Process Verification in Stage 3 should be included in the PPQ.
工艺性能确认是证明一个工艺单元操作的所有重要要素都处于适当程度的受控状态以及证明已考虑了单元操作的所有重要的变量和要素（设施，公用设施，设备，人员，流程，控制程序，组件）的一种方法。在 PPQ 期间，关键工艺参数和关键质量属性随同工艺性能参数一道被监测。它们的评价对证明一致性是非常有用的，并且当包括在 PPQ 中时，可以提高对总体的工艺控制策略的信心。所有打算用于第 3 阶段持续的工艺核实中的参数和属性都应被纳入到 PPQ 中。

4.3.2.1 Number of Batches
批数

The PPQ should be viewed as a means to evaluate and confirm a sound process design, an effective control strategy, and operational proficiency at commercial scale. The number of batches in the PPQ study(ies) will be influenced by many factors such as
PPQ 应被视为在商业规模水平上评估和证实一个良好工艺设计、一个有效的控制策略和操作熟练程度的一种方法。PPQ 研究的批数受到多种因素的影响，例如：

- the performance and acceptance criteria,
  性能和验收标准
- the analyses to be performed and the type and amount of data necessary to perform those analyses.
  所要开展的分析以及开展这些分析所必要的数据的类型和数量。
- the level of process knowledge and understanding gained from Stage 1,
  从第1阶段获得的工艺知识和工艺理解的水平
- the type and complexity of manufacturing technology employed in the various unit operations,
  在不同单元操作中所应用的生产技术的类型和复杂性
- knowledge from previous experience with similar well controlled processes
  从先前的相似充分受控的工艺经验中获得的知识
- the inherent/known variability of the process resulting from raw materials, age of the equipment, operator experience,
  由原材料、设备年龄和操作人员经验导致的内在的/已知的工艺变化性

Using risk-based approaches allows a balance between the number of batches studied and the risk of the process. They can also be used in conjunction with objective approaches to determine the number of batches to include.
基于风险的方法的使用允许在所研究的批数和工艺的风险之间进行平衡。这些方法也可以联合使用客观方法以确定所需包括的批数。

Where practical, statistical methods are recommended to guide the determination of the number of PPQ batches needed to achieve a desired level of statistical confidence (see Sections 6 and 8 on statistical approaches to determining the number of batches and sampling plans). However, this approach alone may not always be feasible or meaningful. One such example where is PPQ studies of a protein drug substance process with a limited number of clinical batches. This dearth of output could be due to such factors as manufacturing scale or product indications (e.g., orphan drug) where infrequent future manufacturing campaigns are to be performed. In addition to limitations on manufacturing batch production, the nature of protein drug substance manufacturing makes increased sample sizes of the process streams of limited usefulness to achieve a statistically-based sample size. When it is not feasible or meaningful to use conventional statistical approaches, a practical, scientifically-based, holistic approach may be more appropriate. In this case, the following factors may be used to support the rationale for the number of PPQ batches selected:
若现实可行，推荐统计学方法指导实现满意的统计置信水平（参见第 6 节和 8 节确定批数和取样计划的统计方法）所需的 PPQ 批数。然而，这一方法单独可能并不总是可行或有意义。这样的一个例

子是有限临床批数的蛋白质原料药工艺。这一输出缺乏可能是因为生产规模或产品适应症（并不经常生产，例如孤儿药）这些因素。除了批生产的限制外，蛋白质原料药生产的性质使得增加工艺流的样品量对实现基于统计学的样品量的作用有限。当使用传统的统计学不可行或没有意义时，一个实用的、基于科学的整体的方法可能更合适。在这种情况下，以下因素可被用来支持所选择的 PPQ 批数的基本原理。

- Prior knowledge and platform manufacturing information/data
  已有知识和平台生产信息/数据
- Risk analysis of the process to factor the level of risk into the batch number selection
  工艺风险分析以将风险水平分解到批数选择
- Increased reliance on Stage 1 data to support that the process is under control and to add to the data set
  增加对第1阶段数据的依耐性以证明工艺处于受控状态，并加入到数据组中。
- Continuation of heightened sampling/testing plans during continued process verification until a sufficient dataset to achieve statistical confidence has been accumulated.
  在持续的工艺确证期间，增强的取样/检验计划持续直到已积累为实现统计置信的充分的数据组。

When a combination of approaches and data are used, the rationale and justification should be clearly documented in the process validation master plan. Also, references to all supporting source data should be included.
当使用方法和数据的组合时，其基本原理和合理性证明应清楚地记录在工艺验证主计划中。此外，应包含所有引用的支持性的数据。

4.3.2.2 PPQ at Normal Operating Conditions
正常操作条件下的 PPQ

PPQ studies are typically conducted in a manner that demonstrates a state of control under normal operating conditions to assess process variability expected during routine production. Process characterization (robustness) studies conducted during Stage 1 serve as the foundation for establishing normal operating ranges, proven acceptable ranges, and design space, if appropriate. Effects of scale should also be considered if scaled-down models are suitably qualified, well-planned, and executed. Study data on robustness should support conducting commercial-scale PPQ under routine manufacturing conditions. Supplemental engineering studies at scale may be appropriate to evaluate extremes of the normal operating range (e.g., line speed or compression speed). In most cases, available Stage 1 data make it unnecessary to execute PPQ over the entire operating range during the commercial manufacturing process. The process validation master plan should provide the justification for the approach used and reference all source data.
通常，PPQ 研究应证明在正常操作条件下的受控状态以评估日常生产期间可能的工艺变化性。第 1 阶段期间所开展的工艺特性（耐用性）研究可以作为建立正常操作范围、已证明的可接受的范围和设计空间的基础，如果适当。也应考虑规模效应，如果规模成比例缩小的模型经过适当地确认，良好计划并执行。耐用性研究数据应支持在日常生产条件下商业规模 PPQ 的开展。适当规模的增补的工程研究对评估正常操作范围（例如线速度或压片速度）的极限可能是适当的。在绝大多数情况下，已有的第 1 阶段数据使得在商业生产过程中没有必要在整个操作范围内执行 PPQ。工艺验证主计划应提供所用方法的合理性证明并应用所有原始数据。

4.3.2.3 PPQ Using Individual Unit Operation Studies
使用单个单元操作研究的 PPQ

PPQ of a manufacturing process can be achieved by performing PPQ studies on each individual unit operation (or related groups of operations). This approach calls for the writing of individual protocols that outline the studies to be conducted on each unit operation. The overall objective is achieving PPQ for the entire process. By emphasizing unit operations that have more variability, higher risk of impact on CQAs, or more limited Stage 1 data available to support assurance of process, this strategy may facilitate more flexibility in PPQ design. Protocols should define the testing performed and acceptance criteria for the output of the unit operation (intermediate). They and may also require that the final drug substance or drug product meets all specifications and predefined acceptance criteria.

可以通过对每一个单个的单元操作（或相关的操作分组）进行 PPQ 研究来实现生产工艺的 PPQ。这个方法要求对每个单元操作要进行的研究编写单个方案。。总体目标是整个工艺的 PPQ。通过强调有更多变化性、对关键质量属性的影响有更高风险、或更少第 1 阶段数据保证工艺的单元操作，这一策略可能为 PPQ 的设计提供更多的灵活性。方案应规定单元操作的输出（中间体）所要做的检测以及可接受标准。他们也可能要去最终原料药或成品药应符合所有的标准和预定的可接受标准。

4.3.2.4 PPQ Using Bracketing, Matrix, and Family Approaches
PPQ 使用括号法、矩阵法和分组法

Many operations involve similar or identical process operations or equipment. In these cases, designs where grouping is used may be considered. Some process variables that might be amenable to approaches using bracketing, matrix, or family grouping PPQ include:
许多操作包含相似或同样的工艺操作和设备。在这些情况下，可以考虑在设计时使用分组法。一些易变的工艺可使用括号法、矩阵法，或分组法进行 PPQ，包括：

- Batch sizes
  批量
- Drug product dosage strength
  药品剂量规格
- Identical equipment
  同样的设备
- Different size vessels, tanks, or similar configurations of the same design and operating principle or in-kind equipment
  不同尺寸的容器，罐子，或具有相同设计和操作原则的结构相似的或同类的设备
- Various vial sizes and/or fill volumes of the same drug product (e.g., smallest and largest vial size)
  相同药品的不同小瓶尺寸和/或灌装体积（如最小和最大小瓶尺寸)
- Filling line speeds (e.g., fastest and slowest line speed)
  灌装线速度（如最快和最慢线速度）
- Product packaging (e.g., bottle heights or dosage counts)
  产品包装（如瓶子高度或剂量计数）
- Transport validation for biological products
  生物制品运输验证

4.3.2.5 Bracketing Approach
括号法

Bracketing qualifies processes that represent the extremes of process variables under the premise that the extremes are fully representative of intermediate groups. The bracketing strategy is used when a single process element can be varied while all other variables remain fixed.
括号法确认了代表工艺变量极端情况的工艺，前提是极端情况可以充分代表中间情况。括号法策略用于单个工艺元素可变但同时其它全部可变条件保持固定。

Examples of cases where the use of bracketing approaches may be considered:
可考虑使用括号法的情况示例：

- Use of a common blend or solution, i.e., identical-strength tablets or those very closely related in composition(e.g., for a tablet range made with different compression weights of a similar basic [common] granulation, or a capsule range made by using different fill weights of the same basic composition into different size capsule shells).
  使用相同的混合物或溶液，如，相同规格的药片或组分非常相似（如，一种药片具有不同的压缩重量，由相似基本（相同）颗粒制得，或一种胶囊具有不同的灌装重量，由相同的基本组分分装到不同大小的胶囊壳中制得）。
- A blend concentration of 50 mg active ingredient /100 mg powder, could be compressed into a 100 mg active (per 200 mg tablet weight), 200 mg active (400 mg tablet weight), and 300 mg active (600 mg tablet weight). The same powder blend is common to the three tablet strengths.
  混合浓度为100mg含50mg活性物质的粉末，可以被压成200mg片重含100mg活性物质，400mg片

重含200mg活性物质，600mg片重含300mg活性物质。同种粉末混合成三种片剂规格很常见。

- Capsules or liquid fills where common blends or solutions are used for filling into the final dosage form.
  使用相同的混合物或溶液灌装到最终的剂型中。
- Different container sizes or different fill volumes in the same container closure system.
  不同的容器大小或相同容器密闭系统中不同的灌装体积。

The rationale for selection of representative groups and numbers of batches should be scientifically justified, risk assessed, and outlined in the process validation master plan and PPQ protocols.
选择代表性组和批数的理由应经过科学论证，风险评估，并在工艺验证总计划和 PPQ 方案中概述。

4.3.2.6 Matrix Approach
矩阵法

A matrix approach is appropriate for commercial manufacturing PPQ when configurations of the same process and product have more than one variable. The approach is based on the assumption that the batch configurations selected for inclusion in the PPQ fully represent processes for all combinations. The rationale for the selection of combinations, and the number of batches representing each combination, should be scientifically justified, risk assessed, and documented in the process validation master plan and PPQ protocols. Some processes require a comprehensive PPQ. In those cases, it is advisable select batches or lots from all combinations.
矩阵法适用于相同的工艺和产品结构有不止一种变化时的商业化生产的 PPQ。该方法基于的假设是选定的包括在 PPQ 中的批次的结构可代表所有组合情况下的工艺。选择组合和每种组合的代表性批数的理由，应经过科学判断，风险评估，并在工艺验证总计划和 PPQ 方案中文件化。在那些情况下，从所有组合中选择批数是合理的。

An example of a matrix design is shown for a PPQ of a filling process where manipulation of three variables results in multiple drug product strengths. Variables in this example include:
示例中，矩阵设计用于一种具有多个药品规格 3 种变量的灌装工艺。该示例中的变量包括：

- Fill Volume
  灌装体积
- Bulk Drug Product Solution Concentration
  药品原液浓度
- Final Drug Product Strength
  成品规格

Table 4.3.2.6-1 Illustration of a Matrix Approach for Filling Process PPQ
表 4.3.2.6-1 灌装工艺 PPQ 矩阵法示例

Fill Volume (mL) 灌装体积	Bulk Drug Solution Concentration (mg/mL) 原液浓度	Final Drug Product Strength (mg) 成品规格	Batch included in PPQ? 批次是否包括在 PPQ 中?	Rationale 理由
0.10	2.00	0.2	是*	Lowest drug product strength; 最小成品规格; Lowest Bulk Drug Product concentration; 最小浓度; Lowest fill volume 最小灌装体积
	4.00	0.4	否	Covered by matrix 被矩阵覆盖
0.15	4.00	0.6	否	Covered by matrix 被矩阵覆盖
	8.00	1.2	是*	Highest drug conc. in fill solution 最大浓度
0.30	4.67	1.4	否	Covered by matrix 被矩阵覆盖
	6.00	1.8	否	Covered by matrix 被矩阵覆盖
	6.67	2.0	是*	Highest drug conc. in final Drug Product 最大成品规格; Highest fill volume 最大灌装体积

*Based on the assumption that process variability is highest at these conditions
*基于工艺最大变化包括在这些情况中的假设。

Rationale for selection of representative groups and number of batches should be scientifically justified and outlined in the process validation master plan and PPQ protocols.
选择代表性组合和批数的理由应经过科学判断并概述在工艺验证总计划和 PPQ 方案中。

4.3.2.7 Family (Grouping) Approach
分组法

A family approach is appropriate when multiple related but different entities can be grouped so that a single one represents the common characteristics or worst case of each group. The rationale for family groups and justification for the representative selection should be included in the validation master plan and PPQ protocol. All variations in the formulation or method of manufacture should be described and evaluated in detail. Two examples of the use of the family approach for PPQ are provided.
分组法适用于有多个相关但不同的实体能被分组以便单个的实体能代表共同的性质或每个组的最差情况。分组和选择代表性情况的判定理由应包括在验证总计划和 PPQ 方案中。所有制造配方或方法应详细描述和评估。提供了 2 个使用分组法进行 PPQ 的示例。

Equipment Family
设备分组
Cell culture for biological product manufacturing can be performed in multiple trains using the same equipment and process in each one. Use of a family or grouping approach may be valid for the PPQ for the fermentation unit operations. This example shows how such an approach, which limits the number of

batches for the PPQ versus repeated multiple runs from each fermenter, could be used. In this case, each equipment train was evaluated for similarity of the equipment (identical equipment trains with duplicated equipment of the same model and manufacturer). Identical equipment trains reduce the number of batches needed to show that the process is reliable in each one. In this case, there is ample prior knowledge on the performance of the process. Use of a reduced number of batches in a family approach should take into consideration the amount of prior knowledge of the process, the number and impact of the critical process parameters, and the ability to control the parameters within the ranges. For a unit operation with no critical parameters, use of fewer batches may be appropriate. In these cases, the approach should be clearly justified with reference to supporting data in the validation protocol.
生物制品制造时的细胞培养能够使用同样的设备和工艺在多个行列中进行。使用分组法进行发酵单元操作的 PPQ 是有效的。这个示例中展示了如何使用这种方法，限定 PPQ 的批数 Vs.每个发酵罐的多次重复运行，能够被使用。在这种情况下，每个设备行列经评估是类似的（由同样型号和生产商的重复设备组成的同样的设备行列）。相同设备行列减少批数需要显示每个的工艺是可靠的。在这种情况下，在工艺性能方面有充足的先前知识。分组法中减少批数应考虑工艺已有知识的量，关键工艺参数的数量和影响，以及控制参数在范围内的能力。对于一个没有关键工艺参数的操作单元，使用较少的批数是适合的。在这些情况下，分组法应在验证方案中经过清晰的论证，论证要有支持数据参考。

Example 1
示例 1

Equipment Family–Production Bioreactor **设备分组——生物反应器**	**Assessment** **评估**	**PPQ Runs (Unit Operation)** **PPQ 运行次数（单元操作）**	**Supporting Data** **支持数据**
#1 #2 #3	Compare: 对比： • Physical design 结构设计 • Design specs 设计规格 • Materials of construction 材质 • IQ IQ • Acceptance criteria 验收标准 • Operating principles 操作原理 • Process control instruments and software 工艺控制仪器和软件	Bioreactor #1-3 batches Bioreactor #2-1 batch Bioreactor #3 -1 batch 生物反应器#1—3 批 生物反应器#2—1 批 生物反应器#3—1 批	Multiple small-scale process characterization runs available to support ranges 多个小规格 过程特性描述 运行能够支持参数范围

Buffer Family Grouping Example
如何对缓冲液分组举例
In assessing the stability of solutions and buffers to support commercial-scale bulk protein drug substance manufacturing, buffers and solutions of similar formulations and storage vessel types may be assigned to family groupings.
进行溶液和缓冲液的稳定性分析以支持商业化大规模的蛋白药品生产时，配方和储存容器类型相似的溶液和缓冲液可以分为一组。之后通过进行浓缩、与容器的潜在相互作用、是否容易污染以及其他适当因素的分析，从每一组中找出“最差条件”的代表性缓冲液。这一代表性缓冲液应符合验证方案中的所有实验。代表性的缓冲液可以证明这一组所有的缓冲液和溶液符合验证条件。这些应在基本原理和工艺验证主计划和方案中概述。

4.3.2.8 Process Analytical Technology

过程分析技术

After developing a control strategy that incorporates PAT (Section 3.9, Section 6.3), process qualification is performed to confirm that the monitoring, measurement, and process control or adjustment systems are suitable, capable, accurate, and reliable. The key to effective PAT process control is the reliable operation of instruments and equipment.

在结合 PAT(Section 3.9, Section 6.3)的控制策略发展后,通过执行工艺确认来证明监控、测量、过程控制或调节系统的适宜性、适用性、准确性和可靠性。有效的 PAT 过程控制的关键是仪器和设备的可靠操作。

The use of PAT controls can provide an alternate approach to PPQ. If a PAT system is used to control every commercial batch, then the PPQ stage will have a different focus. For example, if a powder blending or solution mixing operation is controlled by a PAT system, such as NIR (near infrared) assays, the PPQ will involve demonstrating the control model and system and the process model works as predicted in commercial manufacturing.

PAT 控制的应用为 PPQ（工艺性能确认）提供了很多变化。如果使用 PAT 系统控制每一个商业批次，之后的 PPQ 阶段就有了不同的关注点。例如：一个粉末混合或溶液混合的操作采用了 PAT 的系统，如 NIR（近红外光谱）检测，那么 PPQ 就要包括证明控制模式、系统和过程模式能够在生产中像预期的一样工作。

Qualification of the equipment, measurement system, and process must demonstrate the capability to adjust CPPs according to the established algorithm and confirm that the adjustments result in acceptable and predictable outputs. In other words, a PAT-based control method needs to be qualified（20）.

设备、测量系统和工艺的确认必须证明有能力调节 CPP（关键工艺参数）使之符合确立的法则，并且证明这个调整的结果是可接受的而且输出是可预期的。换句话说，基于 PAT 控制的模式需要验证（20）。

4.3.2.9 Sampling Strategy
取样策略

During the PPQ, increased sampling and analytical testing is expected to verify that the process is under control, and to demonstrate consistency at intermediate steps, as well as in the final product. Sampling plans for discrete units should include the statistical rationales that underlie the plans. (See Section 6 and Appendix 8 for further information on statistically-based sampling plans.)

在 PPQ（工艺性能确认）过程中，应适当增加取样和分析实验来证明工艺受控和中间步骤、成品的一致性。各独立单元的取样计划应包括基于计划的统计学依据。（基于统计学的取样计划详见 Section 6 和 Appendix 8。）

For processes or individual unit operations that yield a single homogenous pool of material, statistically based sampling plans may not be useful in ascertaining the level of intra-batch process variability. For example, analysis of multiple samples from a homogeneous bulk solution or API provides information on the variability of the analytical method only, not intra-batch variability of the process. In these cases, extended characterization of intermediate pools and non-routine sampling performed at certain points in the process and comparison of the data between batches can demonstrate process control and reproducibility.

在物料单一、均匀的工艺过程或个别操作单元中，基于统计学的取样计划不适用于确定批内的工艺差异水平。例如：从均匀的溶液或原料中取多个样品进行分析只能提供分析方法差异方面的信息而非工艺中的批内差异的信息。在这些情况下，增加中间体的特性描述、在工艺中的某些点进行非常规取样以及对批间数据进行对比可以证明工艺的受控和重现性。

4.3.2.10 Setting PPQ Acceptance Criteria
建立 PPQ（工艺性能确认)的接受标准

The acceptance criteria for PPQ should be based on the body of data available from Stage 1, prior knowledge, and equipment capabilities. The approach used to determine the acceptance criteria should be outlined in the process validation master plan, and the justification of the individual acceptance criteria for each unit operation should be documented in the PPQ protocols. Statistical approaches should be used where appropriate, and each product and process variable should be evaluated individually. Process justification documented in the Process Design Report (see **Section 3.11**) provides the scientific basis and

reference to the data supporting the acceptance criteria for process parameter ranges, and product attributes. The rationale for PPQ acceptance criteria should be clearly described. When sufficient data are available and statistical methods are used, the method(s) used and the rationale for selection of that method should be described.
PPQ 的接受标准应建立在从第一阶段获得的有效数据、已有知识和设备能力的基础之上，用于接受标准的判定的方法应在工艺验证主计划中概述，各单元操作个别接受标准的调整应在 PPQ 方案中记录。应在适当的部分使用统计学方法，每个品种和批量应单独评估。工艺设计报告（见 **Section 3.11**）中的工艺调整部分提供了科学依据和参考数据支持工艺参数范围和产品属性的接受标准。PPQ 的接受标准依据应明确描述。当数据充分，并使用了统计方法时，所使用的方法和选择该方法的依据应该描述清楚。

When establishing acceptance criteria for PPQ, the following considerations should be taken into account:
当建立 PPQ 的接受标准时，应将下列项列入

- Historical data / prior knowledge
  历史数据/已有知识
- Preclinical, development, clinical, and pre-commercial batches
  临床前、开发、临床和试生产批次
- Early analytical method suitability (if data is used from clinical lots)
  早期的分析方法适用性（如果数据是从临床批次获得）
- Amount of data available (level of process understanding)
  有效数据量（对工艺的理解水平）
- Sampling point in the process
  工艺取样点
- Compendial requirements can be met with high confidence
  高可信度符合药典要求

An overview of the factors considered for determining PPQ acceptance criteria should either be described (or referenced, if included in a different document). Criteria for determining inter-and intra- batch consistency should be defined. All parameters and attributes designated for tracking and trending in Stage 3 Continued Process Verification should be included in PPQ acceptance criteria.
Acceptance criteria may include:
决定 PPQ 接受标准需要考虑的因素也应该描述（如果在其他文件中包含，则应该引用）。批内和批间的一致性判定标准应当明确。PPQ 的接受标准中应包括第三阶段持续的工艺验证中所有用于追溯和趋势分析的参数和属性。接受标准应包括：

Incoming material — Meets designated criteria (may be raw material or the output of a preceding step).
来料 **—** 符合特定标准（可能是原料，也可能是上一生产步骤的中间产品）

Process Parameters — All process parameters are expected to remain within Normal Operating Ranges; particular attention is focused on parameters with Critical or Key designations.
工艺参数 **—** 所有的工艺参数保持在正常的操作范围；特别要注意关键或重要参数。

- Critical Process Parameters (CPP) with the potential to impact critical quality attributes
  关键工艺参数（CPP）有可能影响关键质量属性。
- Key Process Parameters (KPP) with the potential to impact process performance.
  重要工艺参数（KPP）有可能影响工艺性能

Attributes — All product quality and process performance attributes should meet pre-defined acceptance criteria and include statistical criteria where appropriate.
属性 **—** 所有的产品质量和工艺性能属性应符合预期的接受标准，适当的时候还要包括统计标准。

- Process performance attributes: may be impacted by KPPs (e.g., step yield or bioreactor titer) and demonstrate process consistency between batches.

工艺性能属性：可以受KPP影响（例如：一步生产的收率或生物反应器的效价）并证明工艺各批次间的一致性。

- Critical Quality Attributes: have the potential to impact safety or efficacy (e.g., impurities).
  关键质量属性：有可能影响安全性或有效性（例如：杂质）。
- Quality attributes: do not necessarily impact safety or efficacy, but can be used as a surrogate at certain process steps to demonstrate process consistency (e.g., deamidation or oxidation that does not impact potency or safety/immunogenicity)
  质量属性：并不是必然影响安全性和有效性，但是可以在某些工艺步骤用来表示工艺的一致性（例如去酰胺或氧化不影响效价或安全/免疫原性）。

4.4 PPQ Protocol
工艺性能确认方案

PPQ protocols are a documented plan for executing the PPQ studies. Protocols are reviewed and approved by cross-functional groups that include the quality unit. Protocols must be approved prior to commencement of PPQ activities. PPQ protocols typically contain the following sections.
PPQ 方案是执行 PPQ 研究的计划文件。方案由包括质量部门在内的跨职能团队进行审核和批准。方案必须在 PPQ 开始前批准。典型的 PPQ 方案包括以下部分.

Introduction
介绍
The introduction should include a description of the process and/or specific unit operations under qualification, including the intended purpose of the operations in the context of the overall manufacturing process. The introduction should provide an overview of the study(ies), and important background information.
介绍应包括要确认的工艺和/或特殊的单元操作的描述。包括这些操作在整个生产工艺环境下的预期目的。在介绍部分应提供整个工艺性能确认研究的概述和重要的背景信息。

Purpose and Scope
目的和适用范围
Describes the objective of the study and provides an overview of the study strategy, i.e., how it will be performed, how data will be analyzed, and the expected outcome. Justifications or cross-referencing to documents that contain justifications, such as the process validation master plan, should be included.
描述工艺性能确认研究的目标并提供研究策略的概述。即：如何执行，数据如何分析，以及预期的结果。方案的解释或含有解释内容的文件（例如工艺验证主计划）的交叉引用应包含在内。

References
参考文献
References to relevant documents related to the study should be included in the protocol:
相关研究引用的有关文件应在方案中包括。

- Development and/or Process Characterization Reports that provide supporting data for Operational Parameter and Attribute ranges
  为运行参数和属性范围提供支持数据的开发和/或工艺特性鉴定报告
- Process Design Report
  工艺设计报告
- Process Validation Master Plan
  工艺验证主计划
- Commercial manufacturing batch records
  商业生产的批记录
- Related qualification documents (facilities, utilities, equipment, other PPQ studies)
  相关确认文件（设施、公用工程、设备、其他PPQ研究）
- Analytical methods
  分析方法
- Specification documents

标准

- Approved batch records
  批准的批记录

Equipment and Materials
设备和物料
A list of equipment, instrumentation, and materials necessary to perform the study should be included. References to qualification of utilities and equipment should be provided as appropriate.
应包括设备、仪器以及执行确认所必须的物料的清单。视情况应适当的提供设备和公用工程的验证资料。

Responsibilities
职责
A designation of various functional groups and their responsibilities as they relate to execution of the study, and verification that appropriate training has been conducted for all contributors.
确定涉及确认实施的跨职能的团队以及他们的职责。并确认所有的参与者均进行了适当的培训。

Description of Unit Operation/Process
单元操作/工艺的描述
The objective of PPQ is to provide confidence that all elements of unit operation/process are under the appropriate degree of control. A comprehensive discussion of the control strategy similar to the level of detail provided in the commercial manufacturing control strategy is appropriate to demonstrate that all process elements have been considered. Although all elements are described, only a subset of the process variables will comprise PPQ acceptance criteria. (See Acceptance Criteria.)
PPQ 的目标是为所有的操作单元/工艺的元素均在适当的控制之下提供信心。从商业化生产控制策略的详细的水平进行一个全面的控制策略的讨论适用于证明所有的工艺元素都是经过深思熟虑的。虽然所有的工艺元素都被描述，但是只有一部分的工艺变量含有 PPQ 接受标准。（见接受标准）

Methodology
方法学
The step-by-step procedure needed to perform the study. This section clearly identifies the critical and key process parameters under qualification and the methods by which the operation will be monitored and recorded. A brief explanation of the relevance of these parameters and their potential relationship to process performance and quality attributes is useful to further describe the PPQ strategy. Documents containing the detailed rationale for critical and key parameter designations should be referenced.
每一步的流程都需要执行确认研究。这一节要明确确认中的关键工艺参数和重要工艺参数、还有操作的监控和记录所采用的方法。将这些参数之间的相关性和它们与工艺性能和质量属性之间的潜在联系做一个简要的解释对进一步描述 PPQ 的策略是非常有用的。包含确定关键和重要参数指标的详细原理的文件应在这里引用。

A discussion of the number of batches planned should be included, and the rationale should be stated. The level of confidence expected at the conclusion of the PPQ study should be included as applicable.
应包括对计划批数的讨论并阐明理论依据。如适用，应包含 PPQ 结果的预期置信水平。

Data Collection
数据收集
Roles and responsibilities for various functional groups as they relate to collection and analysis of PPQ data and documentation should be included. The list of process data to be collected and how it will be analyzed should be stated.
应包括与 PPQ 数据的收集、分析和文件编制相关的跨职能团队的人员和职责。应阐明要收集的工艺数据的列表以及数据要如何分析。

Sampling Plan

取样计划

A description of a defined prospective sampling plan and its Operating Characteristic Curve with details on the number of samples, frequency of sampling, and sampling points supported by statistical justification, as applicable:

描述明确的预计取样计划以及它的基于取样数量、取样频率和取样点的细节的抽样特性曲线，要有统计解释支持，如适用。

- Sampling points
  取样点
- Number of samples and statistical basis for sampling, as appropriate
  样品数量和取样的统计基础，如适用。
- Sample volume
  取样体积
- Non-routine sampling for extended characterization
  扩展特性的非常规取样
- Sample storage requirements
  样品的储存要求
- Analytical testing for each sample
  每个样品的分析实验

See **Section 6** and **Appendix 8** for further information on statistically-based sampling plans.

基于统计学的取样计划详见**Section 6** 和**Appendix 8**

Analytical Testing

分析实验

The overall validation package includes the methods used for all analytical testing performed, from assessment of raw materials to extended characterization of the drug product. A listing of all analytical methods used in each protocol and the validation or qualification status of each (and references to source documents) should be included. Analytical method validation should also be included as part of the process validation master plan.

包括从原料的评价到产品的扩展特性所有执行分析实验所使用的方法。在每个方案中的所有分析方法以及每个的验证或确认状态（还有源文件的引用）都应包括在内。分析方法验证作为工艺验证主计划的一部分应包括在内。

Deviations

偏差

All potential deviations cannot be anticipated regardless of the level of characterization and knowledge. A general framework for defining the boundaries of qualification is appropriate, for example:

无论特征和知识处于什么水平，所有潜在的偏差都是不可预期的。适用于制定一个总体框架来定义确认的界限。如：

- Out-of-specification or out-of-limits test results.
  超标或超限度检验结果
- Failure of a CPP to remain within normal operating range; a CPP is designated as such due to the potential impact on a corresponding CQA. Failure to control may indicate overconfidence in an immature control strategy. This would be grounds for protocol failure.
  在正常运行参数范围内的CPP（关键工艺参数）失败；认为对相应的CQA（关键质量属性）有潜在影响的CPP失败。控制失败则可能预示目前的控制策略是不成熟的。这都可能导致方案的失败。
- Missed samples or samples held under incorrect storage conditions
  未取样或样品未在规定的条件下储存。
- How individual batches or lots failing to meet validation acceptance criteria will impact the study.
  什么程度的不符合验证接受标准会对确认研究有影响。

Acceptance Criteria for PPQ

PPQ（工艺性能确认）的接受标准

The objective of PPQ is to demonstrate that the commercial manufacturing process is in a state of control, and the elements of the process control strategy provide confidence that a state of control will be maintained. The expectation for PPQ is that all process variables will remain within their designated ranges or meet acceptance criteria; subsets of these are used to define the PPQ acceptance
criteria. The protocol should clearly document the acceptance criteria to be met in order for the PPQ to be considered successful. Acceptance criteria may be shown in tabular format in the protocol (see the following example).

Table 4.4-1 Example of PPQ Acceptance Criteria Table

PPQ 的目的是证明商业化生产工艺处于受控状态，工艺控制策略的各元素则为这个受控状态可以被持续维持增加信心。PPQ 的预期是所有的工艺变量维持在设计的参数范围内或符合接受标准；他们被用来定义 PPQ 的接受标准。方案应以文件形式明确规定符合什么样的接受标准可以认为 PPQ 是成功的。接受标准可以通过列表的方式在方案中体现（见下例）。

Table 4.4-1 Example of PPQ Acceptance Criteria Table

表 **4.4-1 PPQ 接受标准列表举例**

Process Parameter **工艺参数**	**Designation** **指标**	**Normal Operating Range** **正常运行范围**
Parameter 1 参数 1	CPP	(x.xx - x.xx)
Parameter 2 参数 2	CPP	(x.xx - x.xx)
Parameter 3 参数 3	KPP	(x.xx - x.xx)
Parameter 4 参数 4	KPP	(x.xx - x.xx)
…	…	…
Attributes **属性**		**Acceptance Criteria** **接受标准**
Recovery 回收率	Process Performance 工艺性能	(x.xx - x.xx)
Quality Attribute 1 质量属性 1	Quality Attribute 质量属性	(x.xx - x.xx)
Quality Attribute 2 质量属性 2	Quality Attribute 质量属性	(x.xx - x.xx)
Critical Quality Attribute 1 关键质量属性 1	Critical Quality Attribute 关键质量属性	(x.xx - x.xx)
Critical Quality Attribute 2 关键质量属性 2	Critical Quality Attribute 关键质量属性	(x.xx - x.xx)
Critical Quality Attribute 3 关键质量属性 3	Critical Quality Attribute 关键质量属性	(x.xx - x.xx)
Critical Quality Attribute 4 关键质量属性 4	Critical Quality Attribute 关键质量属性	(x.xx - x.xx)
…	…	…

4.5 PPQ Report
PPQ 报告

A report should be prepared for each study and will typically include the following sections:

每个确认研究都应准备报告，通常报告包括以下部分：

Introduction

介绍

The introduction should include a concise description and outline of the unit operations or group of unit operations that have been qualified. It should summarize the overall results of the study, providing

background information and explanations as necessary.
介绍应包括简要描述，以及已经进行确认的单元操作（或采取分组方式验证的单元操作）的概述。应总结所有的验证结果、背景信息以及必要的解释说明。

Methods and Materials
方法和材料
A clear and concise summary of how the study was performed. It should identify how the objectives of the study were accomplished using both methodology and references to appropriate procedures and protocol requirements.
说明验证研究如何执行的一个简洁清晰的简要报告。它要通过同时使用方法学和引用合适的规程和方案要求来明确的描述研究的目标是如何达到的。

Deviations
偏差
A summary of the deviations and corresponding root causes, as well as a discussion of the potential impact to the PPQ, should be included. Corrective actions resulting from deviations should be discussed. Their impact on the process, the PPQ, and on the affected batches should be provided.
偏差及偏差的根本原因的简要报告，对 PPQ 的潜在影响的讨论也应包括在内。偏差的纠正措施应讨论。他们对工艺、PPQ 以及受影响的批次的影响应包括。

Protocol Excursions
方案偏离
Protocol excursions and unexpected results should be included and fully described in the report. A reference to the root cause analysis should be provided if documented separately from the PPQ report. Any corrective actions and their impact on PPQ should be outlined in the report.
报告应包括方案偏离和意外结果并充分描述。如果根本原因分析的文件不在 PPQ 报告中，则应进行引用。所有的纠正措施以及他们对 PPQ 的影响应在报告中概述。

Discussion: PPQ Results
讨论：PPQ 结果
This section should restate the key and critical process parameters and give the actual range of values occurring during the PPQ. It should include how the data were collected as well as references for analytical methods used.
这一部分应再次说明关键和重要工艺参数并给出在 PPQ 实施过程中的实际范围值。应包括数据是如何收集的以及使用的分析方法的引用。

Data summarized and compared with pre-defined acceptance criteria should be presented in tabular or graphical format whenever possible, and data used from Stage 1 studies should be clearly identified. A reference to the original study should be provided when data is used from outside the of PPQ is used to augment the PPQ data set for statistical manipulation or other support.（注 1）The level of statistical confidence achieved should be stated. If the desired level of statistical confidence was not achieved, the reasons for this and follow up actions should be discussed.
应尽可能的使用列表或图像的形式来将数据与预期的接受标准进行总结和比较，从第一阶段研究取得的数据应明确标注。当使用 PPQ 范围之外的数据来增加数据进行统计处理的建立或其他支持时，应提供最初研究的引用。应阐明达到的统计置信水平。如果没能达到预期的统计置信水平，应讨论原因和随后的行动。（注 1：原文此处没有句号，应该是错误，否则翻译不通。）

The discussion should provide support for any study conclusions. The impact of ranges and deviations should be discussed if they affect the study results. Risk assessment and any follow-up conclusions, including corrective actions, should be stated.
讨论应为所有的验证结论提供支持。如果参数范围和偏差影响验证的结果，那么应对影响进行讨论。应阐明风险评估和所有结论包括改正措施。。

Findings associated with batches or lots that fail to meet the acceptance criteria in the protocol should be referenced in the final PPQ package; likewise, with any corrective measures taken in response to the cause

of failure
不符合方案中的接受标准的所有批次及相关的调查结果；以及对失败结果采取的所有相应的纠正措施应在最终的 PPQ 文件中引用。

Conclusions
总结
Conclusions as to whether data demonstrate that the process is in a state of control should be provided. Pass or fail results should be stated for each acceptance criteria and corresponding results.
总结应提供数据是否显示了工艺处于受控状态。应阐明每个接受标准的通过或失败的结果以及相应的结论。

When a unit operation approach is used, PPQ reports prepared for each unit operation study. A summary executive report that unifies all the study results to support the overall process PPQ should be written.
只要单元操作的方法确定了，就要为每个单元操作的确认研究准备 PPQ 报告。应写一个结合所有确认研究结果的简要执行报告以支持全过程的 PPQ。

4.6 Transition to Continued Process Verification
过渡到持续工艺验证
Following a successful PPQ, the CPV plan can be finalized and implemented. Any adjustments to be made on the basis of the PPQ should be in place prior to manufacture of post-PPQ batches and should be handled through the change control procedures. When appropriate, enhanced PPQ-level sampling is recommended for a period of time following PPQ. However, this may not be necessary in all cases. Further information is presented in **Section 5.**
PPQ 成功后，就可以进行 CPV（持续工艺验证）计划的敲定和实施。所有在 PPQ 基础上的要做的调整应在 PPQ 之后的批次开始生产前，并应通过变更控制程序进行处理。如适用，推荐在 PPQ 之后的一段时间仍然按照 PPQ 的水平进行取样，当然，不是所有的情况都必须这样要求。进一步信息详见 **Section 5.**

5.0 Continued Process Verification (Stage 3)
持续工艺确证（第三阶段）

5.1 Establishing a Monitoring Program
建立监控程序

5.1.1 Purpose and Strategy
目的和策略

A program of Continued Process Verification (CPV) provides a means to ensure that processes remain in a state of control following the successful Process Qualification stage. The information and data collected during Stages 1 and 2 set the stage for an effective control strategy in routine manufacturing and a meaningful CPV program. The understanding of functional relationships between process inputs and corresponding outputs established in earlier stages is fundamental to the success of the CPV program.
持续工艺确证（CPV）程序提供了确保工艺成功确认后保持受控状态的一种方法。阶段 1 和阶段 2 收集的信息和数据为建立后续日常生产有效控制策略和有价值的 CPV 程序做好了准备。对前阶段建立的工艺输入和相应输出关系的理解，是 CPV 程序的成功基础。

Continued monitoring of process variables enables adjustments to inputs covered in the scope of a CPV plan. It compensates for process variability, to ensuring that outputs remain consistent. Since all sources of potential variability may not be anticipated and defined in Stages 1 and 2, unanticipated events or trends identified from continued process monitoring may indicate process control issues and/or highlight opportunities for process improvement. Science and risk-based tools help achieve high levels of process understanding during the development phase, and subsequent knowledge management across the product life stages, facilitates implementing continuous monitoring (see Sections 3.0 and 4.0).
对工艺变量的持续控制使对 CPV 计划中的输入进行调整成为可能。这可以补偿工艺变化，保证输出稳定。因为不是所有的变化来源都能在阶段 1 和阶段 2 预计和确定，持续工艺监控发现的不可预期事件或趋势可能提示工艺控制问题和/或工艺改进机会。在工艺开发阶段，以及产品生命周期的后续知识管理阶段，采用科学和基于风险的工具有助于加强对工艺的理解，促进持续控制的实施（见 3.0 和 4.0 节）。

5.1.2 Documenting the CPV Program
持续工艺确证计划制订

Planning for CPV begins during the establishment of the commercial-scale control strategy (Stage 1).
设计持续工艺确证开始于建立商业规模的控制策略（阶段 1）。

High-level quality system policies/documents outline how various departments interact and how information is compiled and reviewed to ensure maintenance of the validated state. Under that policy document as well as a process validation master plan, a product-specific CPV plan should include the following elements:
高级别的质量方针/文件概述了不同部门如何协作，如何起草、审核文件，保证处于已验证状态。在质量方针以及工艺验证主计划之下，特定产品的持续确证计划应包括以下要素：

- Roles and responsibilities of various functional groups
  不同职能部门的作用和职责
- Sampling and testing strategy
  取样和测试策略
- Data analysis methods (e.g., Statistical Process Control methods)
  数据分析方法（例如过程控制统计方法）
- Acceptance criteria (where appropriate)
  可接受标准（适当时）
- Strategy for handling Out of Trend (OOT) and Out of Specification (OOS) results
  OOT 和 OOS 结果处理策略
- Mechanism for determining what process changes/trends require going back to Stage 1 and/or Stage 2
  决定何种工艺变更/趋势需返回阶段 1 和/或阶段 2 的机制
- Timing for reevaluation of the CPV testing plan
  持续工艺确证测试计划再评价时限

Figure 5.1.2-1 illustrates an example of the development of a CPV monitoring strategy throughout the lifecycle stages. Ideally, the majority of the control strategy is established prior to Stage 2, when PPQ is conducted. When adopting the concept of Continued Process Verification for legacy products, the same general approach should be taken to document and execute the CPV program (see Section 5.1.3, Legacy Products and Continued Process Verification).
图 5.1.2-1 举例说明了产品生命周期中持续工艺确证控制策略形成。理想情况下，控制策略的大部分在阶段 2（工艺性能确认）前建立，当持续工艺确证概念应用于老产品时，应采用同样的方法形成、执行持续确证计划（见 5.1.3，老产品的持续工艺确证）

Because Stage 3 is part of the lifecycle validation approach (5.1.2-2), Continued Process Verification should be governed by both an overarching quality system for validation practices and a process validation master plan. At a minimum, the process validation master plan should make high-level commitments for both Process Design (Stage 1) and Continued Process Verification (Stage 3) in addition to Process Qualification (Stage 2). The specifics of the CPV sampling/testing strategy may not be finalized until completion of PPQ. Therefore, the process validation master plan may include general commitments to the planned CPV strategy. These are then further clarified in a separate CPV Plan referenced in the process validation master plan. It is still possible that a process validation master plan can be considered complete at the end of Stage 2 (i.e., not left open-ended for the entire commercial lifecycle) if the requirement that CPV activities, as required, are be initiated per the defined CPV Plan.
因为阶段 3 是生命周期验证方法（5.1.2-2）的一部分，持续工艺确证应符合验证质量体系和工艺验证主计划的要求。除了工艺确认（阶段 2），工艺验证主计划至少应涵盖工艺设计（阶段 1）和持续工艺确证（阶段 3）。持续工艺确证取样/测试策略的具体内容直到完成工艺性能确认才最终确定。因此，工艺验证主计划可包括持续工艺确证策略的一般要求，并进一步在工艺验证主计划中提及的单个持续工艺确证计划中明确。如果 CPV 活动按照确定的 CPV 计划启动，也可认为工艺验证主计划在阶段 2 后期结束（就是说不得在整个产品生命周期中始终处于开放状态）

Figure 5.1.2-1 Development of a Continued Process Verification Plan
CPV（持续确证）计划的制订

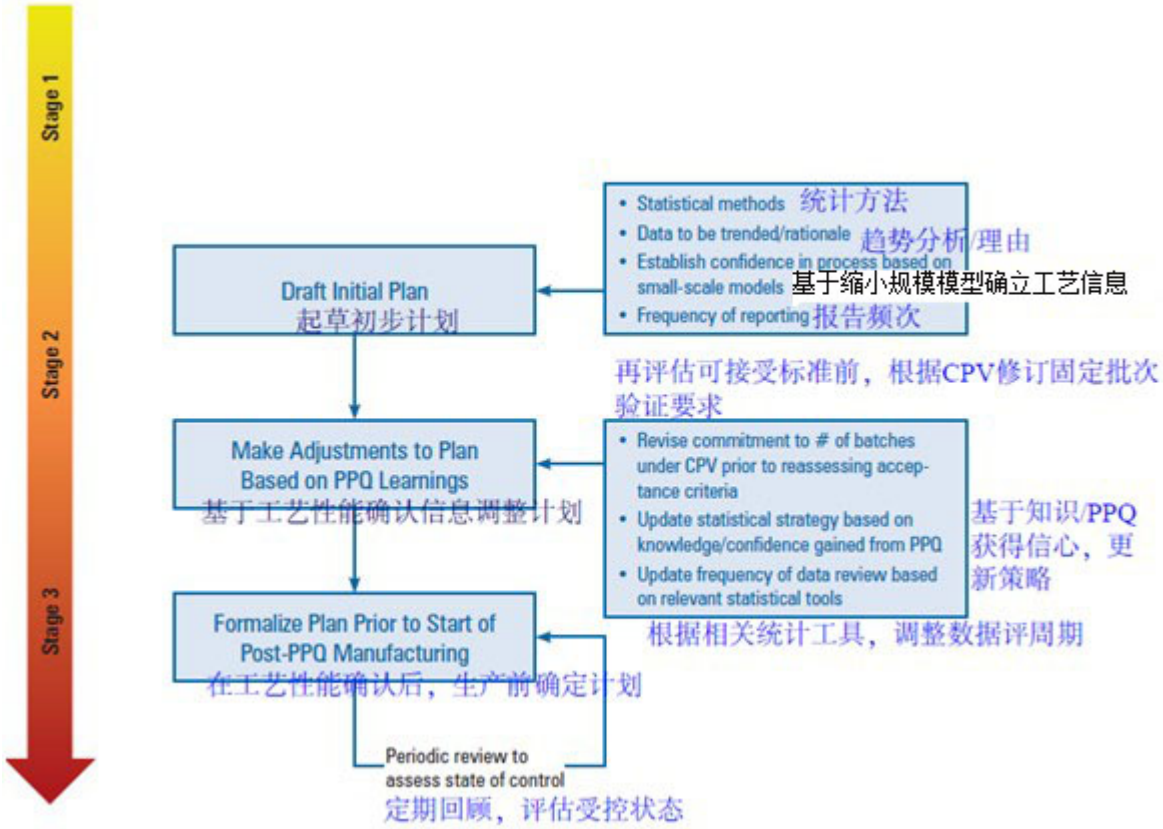


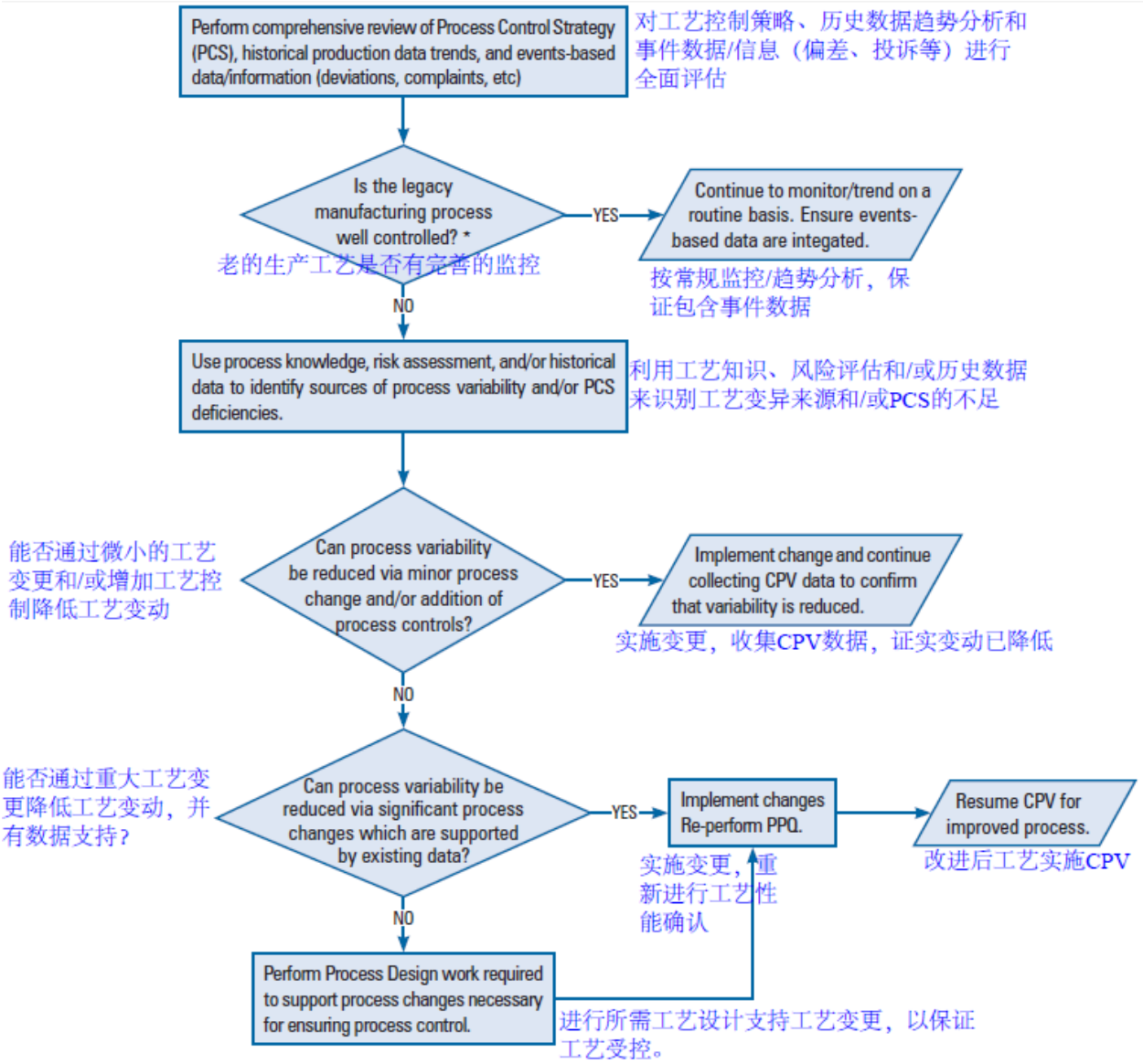
Figure 5.1.2-2 CPV Plan within Validation Documentation System
验证文件体系下的 CPV（持续工艺确证）计划

5.1.3 Legacy Products and Continued Process Verification
老产品的持续工艺确证

Figure 5.1.3-1 outlines one possible approach to assessing what is necessary to apply the lifecycle approach to a legacy product. It may be the case that a legacy process is well-controlled and monitored, and not much action is required. However, this decision should be based on an evaluation of the large body of historical process and monitoring data and an assessment of process variability. In this approach, the historical data is used to determine the current state of control of the process. Measures such as performance capability (Ppk) and other statistical approaches should be considered (see **Section 6.0**) for assessment of the process. In addition to assessing process performance, the adequacy of the set of parameters being used to monitor the performance of the process should also be evaluated. Part of assessing the appropriateness of the current process control strategy is to provide a foundation for determining what, if any, additional sampling/monitoring should be included during Continued Process Verification for the legacy product. A period of enhanced sampling will help generate significant variability estimates that can provide the basis for establishing levels and frequency of routine sampling and monitoring and should be considered. It is recommended that this ongoing monitoring also be captured under a formal plan as outlined in **Section 5.1.2,** Documenting the CPV Program.
图 5.1.3-1 概述了老产品应用生命周期概念时，评估所需完成活动的一种方法。老产品通常有完善的监控，不需要采取太多行动。然而，应基于对历史工艺和监控大量数据以及工艺变化的评估做出决定。采用该方法时，应该用历史数据评价工艺控制的现状。评价工艺时，应考虑采用过程能力和其他统计学方法。除了评价过程能力外，也应评估用于工艺监控的参数充分性。对现有工艺控制策略适宜性评估，可以作为决定老产品持续工艺确证中是否需要其他额外取样/监控的基础。应考虑进行一段时间的加强取样，以获得大量变量评估数据，作为设定日常取样和监控水平和频次的基础。建议将持续监控写入 5.1.2 节“持续工艺确证计划制订”中正式计划中。

In considering whether the sampling plans for legacy products are adequate, it may be determined that a statistically-driven approach should be applied. However, the amount and type of data may also lead to a decision that statistical justification of the sampling plan is unnecessary. This determination should be part of the initial assessment of the historical data and monitoring approach. Although statistically-derived models may not be required, the sampling plan should be scientifically sound and representative of the process and each batch sampled.
判断老产品的取样计划是否充分时，可采用统计学的方法。然而，根据数据的数量和类别不同，也许没有必要对取样计划进行统计评价。该决定应作为对历史数据和监控方法进行初步评估的一部分。尽管也许不需要统计模型，取样计划应科学合理，并能代表所取的工艺和每批产品。

Figure 5.1.3-1 CPV Plan Determination for Legacy Products
老产品 CPV 计划的制订



* Is an appropriate Process Control Strategy (demonstrating understanding of the impact of process parameters on CQAs) defined and does statistical of data show that variability is controlled?
是否确定了适当的工艺控制策略（能够证明理解了工艺参数对于关键质量特性的影响），统计数据是否显示变化处于受控之中。

5.1.4 Demonstrating Continued Process Verification
持续工艺确证的证实

Two primary sources of data that need to be included in a Continued Process Verification (CPV) plan are:
CPV 计划中数据的两个基本来源为：

1. Process parameters (i.e., process performance and product quality indicators)
   工艺参数（即工艺性能和产品质量指标）

2. Potential sources of variability that are not defined process parameters. Examples of such sources of data/ information may include:
   可变性潜在来源为没有确定的工艺参数。例如：

a. Raw material quality 原辅料质量

b. Redundant equipment and instrumentation comparability 冗余的设备仪表可比性

c. Personnel impact on process (i.e., shift-to-shift consistency) 人员对工艺的影响（如班次之间一致性）

Critical and key input parameters and the corresponding outputs related to process performance and product quality attributes are established during Process Design (Stage 1) (see **Figure 1.1-2).** At the commercial scale, Process Qualification (Stage 2) batches are produced to confirm that the process operates as intended and to verify that the Process Control Strategy results in the consistent manufacture of product that meets its predefined quality characteristics. The Process Control Strategy should then also be used as the starting point for identifying the process data/information to be included in a CPV plan.
与工艺性能和产品质量特性相关的关键输入参数和相应输出在工艺设计中(阶段 1)确定(见图 1.1-2)。商业生产时，生产工艺确认（阶段 2）批，以证实工艺运行符合预期要求，并证实工艺控制策略可稳定地生产符合预定质量特性的产品。工艺控制策略也应作为出发点，识别 CPV 计划中应包含的工艺数据/信息。

5.1.5 CPV Monitoring Plan
CPV监控计划

Routine sampling will generate some data for the CPV Program, but non-routine sampling should also be considered. The sampling/testing plan moving forward from Stage 2 into Stage 3 should be a dynamic; it needs to be updated and reviewed periodically. An enhanced sampling plan (that may include both off-line and on-line analyses) may be required to ensure that the appropriate data set is collected. Since the PPQ Protocols already specify those process parameters and attributes (inputs and outputs) that must be maintained within the specified ranges in order to make a product that meets predefined quality attributes, the PPQ sampling plan is a logical foundation for the CPV sampling plan. PPQ may provide sufficient assurance that certain parameters are well-controlled at the commercial scale and do not need to be carried forward into a CPV plan. A biological process, for example, requires sufficient clearance of a process residual (e.g., antifoam) or a process-related impurity (e.g., DNA). These may be successfully demonstrated during PPQ batches, eliminating the need for ongoing sampling and testing during CPV. In cases, where either historical data are limited or where the data show a high degree of variability, testing and trending may be required post-Stage 2 to ensure a high level of assurance that a particular impurity is well-controlled. This should be determined on a case-by-case basis via risk assessment and/or statistical assessment of historical data.
常规取样将获得部分数据并用于 CPV 计划，但也应考虑非常规取样。取样/测试计划应动态地由阶段 2 前进到阶段 3；并应定期更新和审核。一个增强的取样计划（可同时包括在线和离线分析）可保证收集到适当的数据。因为工艺性能确认方案已指明那些必须保持在一定范围的工艺参数和质量特性（输入和输出），以使产品符合预定质量特性，工艺性能确认取样计划是 CPV 取样计划的逻辑基础。工艺性能确认可提供充分保证，大生产时部分参数良好受控，不需要纳入 CPV 计划中。例如，生物工艺要求充分清除工艺残留（例如消泡剂）或工艺相关杂质（例如 DNA）。这可在工艺性能确认批中得到证实，不需要在 CPV 时继续取样和测试。当历史数据有限或数据显示较大变动时，阶段 2 后应继续进行取样和趋势分析，以充分保证某一特定杂质受到控制。这应根据具体情况通过对历史数据的风险评估和/或统计分析做出决定。

The prospective CPV plan should provide specific instructions for analysis conducted to a limited degree, and subsequently discontinued once a sufficient number of data points are accumulated to determine process control. The number of batches sampled and the frequency of sampling within a batch should be stated in a Stage 3 enhanced sampling plan. Depending on the data generated, samples collected and analyzed for information only (FIO) should have a designated end-point. A more open-ended approach, where no specific number of batches is identified, could be used to address data trends and results. A plan that describes an approach to reduce (step-down) or increase (step-up) sampling and testing as a result of trending and results is also an option.
预期的 CPV 计划应提供具体说明，部分分析只进行到一定程度，一旦收集到足够数据确定工艺受控，便可终止。取样批次和一批内取样频次应在阶段 3 的增强取样计划中说明。根据产生的数据，用于参考目的的取样和分析应有指定的终点。一个更开放的方法，不指明具体批次，可用于数据趋势分

析和结果讨论。另一种选择是根据趋势分析和结果降低或增加取样以及测试。

5.1.6 Data Analysis and Trending
数据分析和趋势分析

The CPV plan should clearly state how the data collected will be analyzed. In some cases, it will be compared to pre-defined acceptance criteria, especially for those data that are tightly controlled (e.g., a gradient elution slope for a critical column chromatography step). In other cases (e.g., unit operation yields), data may be statistically assessed to evaluate process trends. In such cases, the statistical methods and rules used for continued process monitoring should be specified in the CPV plan. Control charts are commonly used to evaluate process control over time. They are appropriate for both evaluating statistical process control and for detecting process trends. Under CPV, control charts are generated and evaluated on a per batch basis (see **Section 6.2,** Statistical Analysis Tools and **Appendix 8.1,** Statistical Methods for Determining the Number of Lots for discussion of statistical data analysis).
CPV 计划应清楚说明收集的数据如何进行分析。在部分情况下，可与预定的可接受标准比较，特别对于严格受控的数据（例如柱色谱的一个梯度洗脱曲线斜率）。另一种情况（如工序收率）是，可进行数据的统计分析，评估工艺趋势，此时应在 CPV 计划中指定持续工艺控制的统计方法和规则。通常用控制图评估一段时间后工艺控制情况，其适用于评价统计过程控制，以及发现工艺趋势。根据 CPV 要求，控制图以批为基础建立和评估（见 6.2 节统计分析工具和附录 8.1 确定统计数据分析所需批次的统计方法）。

Establish prospective criteria to ensure that the process is in a state of control. However companies define it, an “out of control” result (e.g., Out-of-Trend, Out-of-Control, Out-of-Specification, outside Action Limit) should trigger actions per the Quality System (e.g., investigation, impact assessment to validated state). Specific actions will vary on a case-by-case basis, but the CPV plan should specify what types of action. **Section 6.0,** Tools for the Process Validation Lifecycle, describes the tools available to address trending statistical trending and SPC, along with risk-based evaluations.
应建立前瞻性标准保证工艺处于受控状态。不管公司如何定义它，一个超出控制范围的结果（如趋势超标、超出控制限、检验结果超标、超出行动限）将触发根据质量体系采取行动（如调查、对验证状态的影响分析）。采取的行动随具体情况不同而不同，但应在 CPV 计划中说明何种行动。6.0 节“用于工艺验证生命周期的工具“，描述了用于趋势统计分析和统计过程控制的工具，应结合风险评估使用这些工具。

Section 5.1.4 covers, sources of process variability that may not be parameter-related (e.g., raw materials, personnel, and environment). As part of the overall CPV assessment, high-risk potential sources of variability should be risk-mitigated, and also assessed and demonstrated to be under control. Trends in purity for a critical raw material, for example, may indicate subtle differences between suppliers. Even seemingly innocuous changes by a supplier may lead to out-of-trend or out-of-specification events. These should be evaluated in light of overall process consistency and product quality.
5.1.4 节涵盖了非参数相关（原料、人员和环境）的工艺变化来源。作为整个 CPV 评估的一部分，应降低高风险变化来源的风险，并评估是否已处于可控范围。例如对关键原料的纯度进行趋势分析，可能看出不同供应商的微小差别。即使表面看是个供应商的微小的变更，可能导致趋势超标或检验结果超标。应从整个工艺一致性和产品质量角度对此进行评价。

5.2 Incorporation of Feedback from CPV Monitoring
CPV 监控结果的整合

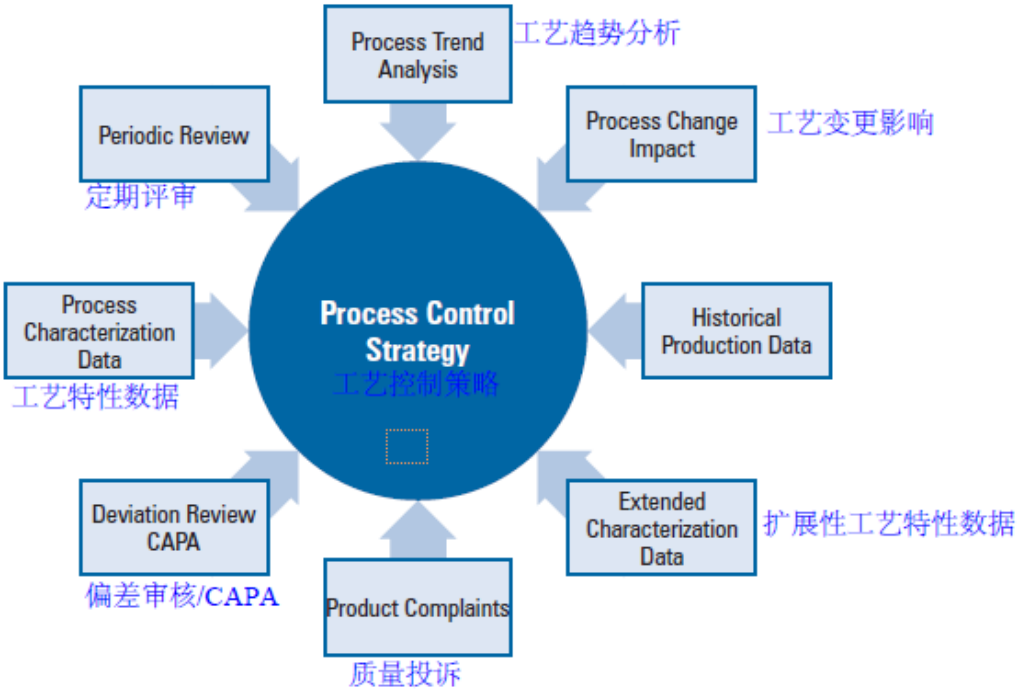
5.2.1 Quality Systems and CPV
质量体系和持续工艺确证

The best tools for continued confirmation and refinement of process control are the quality system elements that provide feedback and objective measures of process control. The tools are based on product and process understanding, and are enabled by procedures that monitor, measure, analyze, and control the process performance ***(37).*** Once in commercial production, maintenance of the validated state requires an events-based system of review, in addition to process trending described in **Section 5.1,** Establishing a Monitoring Program. Communication of review outcomes to the manufacturing, quality, and regulatory

stakeholders to modify the control strategy (for improvement and/ or compliance reasons) is an iterative and essential part of the CPV. Feedback mechanisms can vary between immediate (intra-batch or real-time), after each batch, or after a series of batches or a defined time period. The CPV Plan should address when each of these mechanisms should be used.
对工艺控制进行持续确认和细化的最好工具是能够提供反馈并客观评价工艺控制的质量体系元素。这些工具是基于对产品和工艺的理解，并通过监视、测量、分析和控制工艺性能的程序实现（37）。一旦处于商业生产中，除了 5.1 节所述的工艺趋势分析外，对已验证状态的维护还需要一个基于事件的审核系统，并建立一个控制计划。生产、质量以及监管部门就审核结果进行沟通，修订控制策略（为了提高和/或法规符合），是 CPV 的一个重复和基本部分。反馈机制可以是立即的（批内或及时）、每批后或一系列批次后或一段时间后。CPV 计划应说明各种反馈机制应在何时采取。

Figure 5.2.1-1 depicts sources of data that contribute to continuous improvement of a manufacturing process. While not intended to be an all-inclusive list, the figure shows typical categories of data associated with product production and performance.
图 5.2.1-1 描述了用于持续改进生产工艺的数据来源。尽管不是详尽的清单，该图展示了与生产和工艺性能相关的数据的典型分类。

Figure 5.2.1-1 Body of Knowledge and Maintenance of Process Control
知识构成和工艺控制的维护



5.3 CPV Data Review and Reporting
持续工艺确证数据审核、报告

The CPV plan needs to include a frequency of review of the information from data collection mechanisms as well as Quality Systems. It should also identify circumstances for, and a process to allow for, an immediate review based on significant issues identified with a process or product, and identify the participants in the review. Per ICH Q10, this review must include senior management. They are key stakeholders in the maintenance of an effective pharmaceutical quality system and advocates for continual improvement.
CPV 计划需要包括数据收集机制和质量体系所获得信息进行审核的频次，也应指明哪些情况下需立即对工艺或产品的一些重大问题进行评审，以及评审程序、参与评审的人员。按照 ICH Q10，该评审必须包括高层管理人员。他们是维护一个有效药品质量体系，并持续改进的关键人员。

The frequency of data review will depend heavily on risk. The period of review for various processes and sub-processes is likely to vary greatly depending upon the levels of associated risk and the complexity of control. The starting point for defining the review period will be the most recent process risk communication document. As more production data is generated, deeper process understanding is gained and control is likely to be more easily demonstrated. Thus, the period or intensity of review may be reduced.
数据审核频次主要取决于风险大小。不同工艺和工序的评审周期因风险的水平和控制的复杂程度而不同。应采用最新的工艺风险沟通文件，确定评审周期。随着生产数据的产生，对于工艺的进一步理解，对工艺有更好的控制，可降低评审的周期或强度。

An annual commercial data compilation effort in preparation for Annual Product Review (APR) may be sufficient. However, more frequent data reviews and comparisons to defined acceptance criteria may help manufacturers be more proactive and less reactive. APR packages are necessary, as per regulatory guidelines. However, APR exercises are likely to become high-level reviews and summaries of multiple, more frequent CPV data reviews. The APR will identify any gaps in the CPV data reviews and will summarize long-term trends, but more frequent CPV data reviews should be performed by the manufacturer at defined intervals.
将年度商业生产数据汇总起草年度产品质量回顾也许是足够的。但更频繁的数据审核，并与确定的可接受标准比较可帮助生产商更具有前瞻性和减少波动。根据法规要求，年度产品质量回顾是必须的，但年度回顾可能变成对多重、更频繁的 CPV 数据评审进行的更高一级别的评审和汇总。年度产品质量回顾可识别 CPV 数据评审中发现的问题，汇总长期趋势，但生产商应在规定时间间隔内进行更频繁的 CPV 数据评审。

Note: FDA 21 CFR 211.180(e) requires an evaluation at least annually. The periodicity of the review is to be established by the manufacturer, but should be at least annually.
注：FDA 21 CFR 211.180（e）要求至少每年进行一个评估。审核频次由生产商确定，但应至少每年进行一次。

6.0 Process Validation Enabling Systems and Technology
基于生产系统及技术的工艺验证

This section presents tools and methods to assist in the planning and performance of the process validationprogram. It includes sections on risk and knowledge management, statistical methodology, process analytical technology, and technology transfer. These tools can be used to identify, capture, and communicate information needed for the design and assurance of process control.They facilitate informed decision making,prioritization of activities, and interpretation of results related to the process validation effort.
本章节讲述计划和实施工艺验证时使用的工具和方法。包括风险和知识管理、统计方法学、过程分析技术和技术转移等章节。这些工具可用于鉴别、获得和交流用于设计和保证工艺控制的信息。其有助于形成合理的工艺验证结论、确定工艺的优先顺序，并对工艺验证效果提供合理的解释。

6.1 Application of Risk Management
风险管理的应用

This section addresses aspects of risk management specific to the process validation lifecycle approach.A detailed explanation of a Quality Risk Management program used to support the process validation effort can be found in **Section 5** of *PDA Technical Report No. 54: How to Use Quality Risk Managementas an Enabler **(13).*** In addition, comprehensive lists of risk management tools can be found in PDA Technical Report No. 54 and ICH Q9. For a comparison of risk management tools, see Technical Report No. 54, **Table 4.2-1: Comparison of Common Risk Management Tools.**
这个章节对工艺验证生产周期法的风险管理进行各个方面的论述。用于支持工艺验证效果的质量风险管理的详细解释详见PDA NO.54 技术报告的第五章：如何有效地应用质量风险管理。另外，全面的风险管理工具列表详见PDA NO.54 技术报告和ICH Q9。风险管理工具的对比详见NO.54 技术报告，表4.2-1：常用风险管理工具的对比。

The Quality Risk Management system is an “enabler” or “enabling system.” When correctly applied,it adds supportive elements to the product lifecycle and other systems (e.g., the Pharmaceutical QualitySystem). The application of risk management principles and approaches is instrumental to effective decision-making in the Process Validation Lifecycle.
质量风险管理系统是一个“使能器”或“使能系统”。一旦正确应用，能给产品生产周期和其他系统（例如：药品质量系统）增加有利的支撑元素。风险管理原理和方法的应用有助于工艺验证生命周期中有效结论的形成。

Management of variability is one example of applying risk management in the validation lifecycle.The level of control required to manage variability is directly related to the level of risk that variability imparts to the process and the product. The use of risk management to address variability requires understanding of:
对变量的管理是在验证生命周期中应用风险管理的一个例子。对变量管理的控制水平直接与变量对工艺和产品的风险水平相关。应用风险管理对变量进行控制必须对以下方面进行了解：

- The origin of the variability
  变量的来源
- The potential range of the variability
  变量可能的范围
- The impact of the variability on the process, product, and ultimately, the patient
  变量对工艺、产品和最终用户病人的影响

Risk assessment should occur early in the lifecycle, be controlled appropriately, and effectively communicated.Risk Management increases product and process knowledge, which translates into greater control of product and process variability, and a lower residual risk to patients.
风险评估应该在生命周期前期执行，应正确控制和有效的沟通。风险管理可促进对产品和工艺的理解，这种理解可以促进对产品和工艺变量的更好控制，可尽可能降低产品对病人的风险。

The process validation lifecycle provides continued assurance that processes will manufacture product in a predictable and consistent manner. Where decisions related to product quality or process performanceare made, risk can be assessed at several points throughout the process validation lifecycle.
工艺验证生命周期法能给工艺提供持续的保证，保证工艺按照预定和可持续的方式生产产品。当做与产品质量相关的决策或工艺性能发生改变时，风险应该通过工艺验证生命周期法进行几个方面的评估。

Quality Risk Management applications throughout the process validation lifecycle include the following(see **Figure 6.1.1):**
质量风险管理应用贯穿整个工艺验证生命周期，包括以下方面（**详见图表6.1.1**）

Stage 1 — Process Design
第1阶段-工艺设计

- Identification of product attributes that may affect quality and patient safety
  影响质量和病人安全的产品属性的鉴别

- Criticality analysis of product quality attributes (CQA identification)
  产品质量属性的关键性分析CQA鉴别）

- Cause and Effect Analysis or Risk Ranking and Filtering, which link the process steps and parameters to process performance or product quality attributes. These can be used to screen potential variables for future process characterization (e.g., DoE) and testing.
  关乎工艺性能或产品质量属性的工艺步骤和工艺参数需要采用因果分析或风险排序和筛选。这样可以筛选未来工艺特性（例如：DoE）和检测存在的可能变量。

- Preliminary Hazards Analysis (PHA) or early FMEA
  初步危害分析（PHA）或早期的FMEA

Stage 1-2 — Transition from Process Design to Process Qualification
阶段1-2—工艺设计到工艺确认的转移

- Determining process control strategies that address the risk of failure for each process step
  论述每个工艺步骤失败的风险，以确定过程控制策略

- Evaluation of residual risk remaining or created as a result of risk mitigation, process improvement, and processknowledge
  评估通过风险降低、工艺改进、工艺知识后残留的风险或者新产生的风险

Stage 2 — Process Qualification
第二阶段—工艺确认

- Determination of process steps and parameters to test in PPQ, including sampling plans and the confidence and coverage they provide.
  确定PPQ中哪些工艺步骤和工艺参数需要检测，包括取样计划和取样的代表性及覆盖率

- Facility and equipment impact assessments to prioritize qualification efforts [may want to reference ISPE Baseline Guide ***(34)***]
  设备和设施的影响性评估优先于性能验证（可以参考ISPE的基本指南（34））

- Determination of effective acceptance criteria for each test function
  制定各个功能测试有效且可接受的标准

- Analytical test results and deviations

分析测试结果和偏差

Stage 3 — Continued Process Verification
第三阶段—持续工艺验证

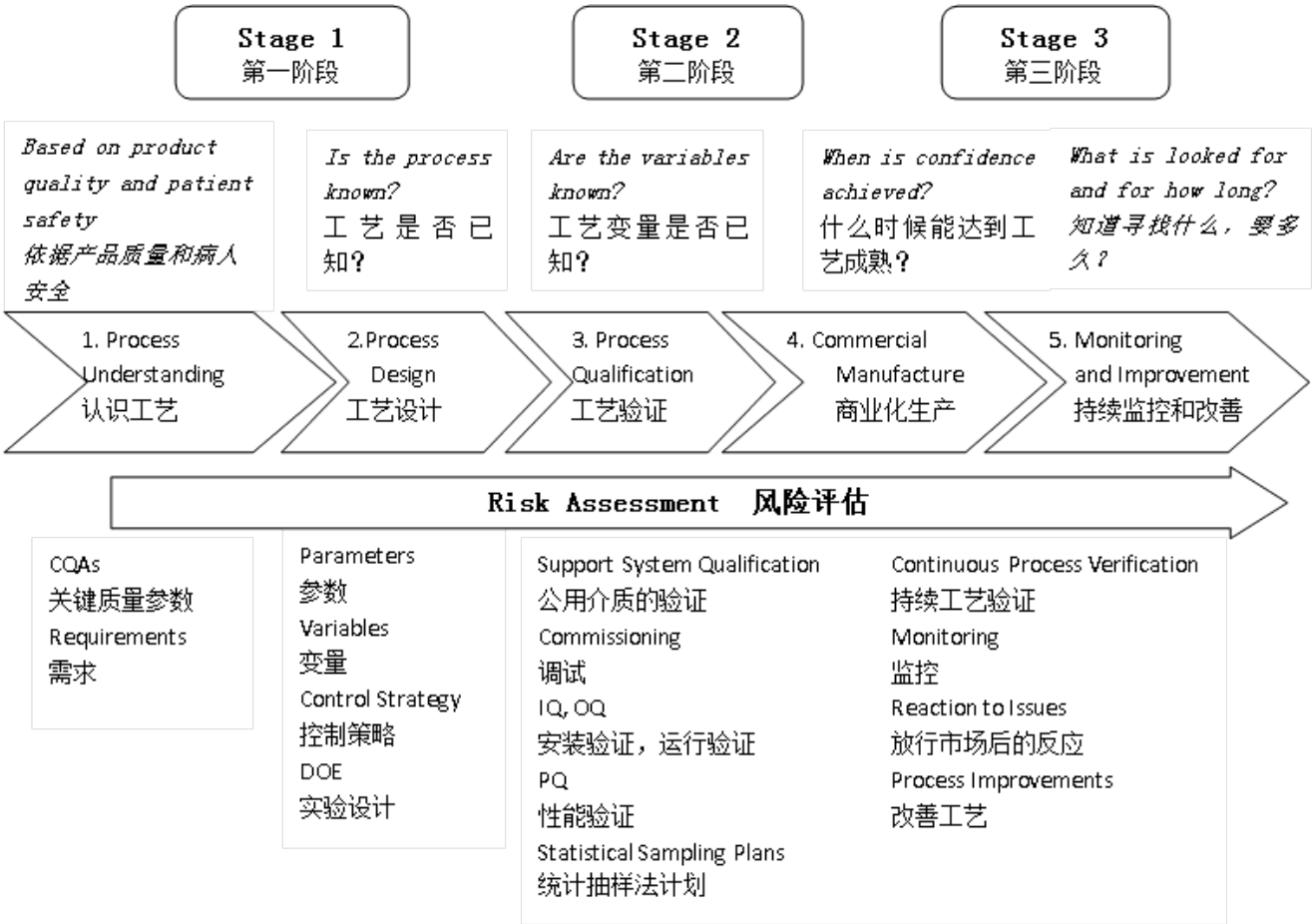
- Determination of parameters that should be monitored as well as how they should be sampled and analyzed(e.g., sampling plans, confidence required and length of enhanced sampling).
  制定需要监控的参数，并制定其取样及分析的方法（例如，取样计划，取样代表性和加强取样的程度）

- Evaluation of commercial manufacturing data to determine the best course for process improvement
  评估商业生产数据以便确定最好的工艺改进过程。

Figure 6.1-1 depicts a quality risk management lifecycle tool for process development and validation ***(21).***
图表6.1-1 利用质量风险管理生命周期法工具以进行工艺开发和验证的描述

Figure 6.1-1 Quality Risk Management: A Lifecycle Tool for Process Development and Validation
图表 6.1-1 质量风险管理：用于工艺开发和验证的生命周期工具

Process Validation Sequence
工艺验证顺序



6.1.1 Risk Management in Stage 1 -Process Design
风险管理第一阶段—工艺设计

Conducting risk assessments during Stage 1 Process Design lays the groundwork for variables to be controlled and monitored. It also determines the extent to which continued monitoring will ensure a state of control during routine manufacturing. This begins with a criticality analysis: an initial definition of Product Quality Attributes and an assessment of their relative importance. Inputs for the criticality analysis are:
在第一阶段工艺设计期间执行风险评估为制定控制和监控变量做准备。也能决定持续监控应该进行到什么程度才可以保证常规的商业生产处于控制状态。这一切从关键性程度分析开始：产品质量属性的最初定义及其相关重要性的评估。重要性程度分析输入包括：

- QTPP (quality target product profile)
  QTPP（目标产品质量概况）

- All relevant prior knowledge for the product being evaluated
  评估产品时需要的所有以前的知识

- Outputs from the criticality analysis are:
  关键性程度分析的输出为：

- Initial CQA list
  最初的关键质量属性的列表

- Initial relative severity listing of the CQAs
  关键质量属性最初的相关严重性列表

Criticality of product attributes is assessed along a continuum; i.e., it not a yes or no question. This is accomplished by performing a risk assessment analysis that uses Severity and Uncertainty, rather than the usual Severity and Occurrence. The process, which is iterative, is based on building product and process knowledge. The level of severity assigned is based on the potential patient impact, while uncertaintyis based on how much information (product knowledge and clinical experience) is availableto determine the potential severity level for the specific attribute. Part of the output of this assessment will be further scientific studies to reduce the amount of uncertainty for higher risk attributes ***(21).***(See **Figure 6.1-2,** Product Attribute Criticality Risk Assessment Example.)
产品属性的关键性程度是一个持续评估的过程；也就是说其不是“是”或“不是”的问题。而是伴随风险评估分析存在的，应使用严重性和不确定性，而不是通常的严重性和发生率来执行风险评估分析。最初的工艺是根据产品的生产和工艺知识来构建的。严重程度根据对病人的潜在影响来确定，同时不确定性是根据可获得的产品知识和临床经验的多少来决定药品特殊属性的潜在的严重程度。该部分评估的部分输出结果是需要经过进一步的科学研究来减少高风险属性的不确定性的数量（21）。（详见图表6.1-2，产品关键性属性的风险评估例子）

Assessm

Figure 6.1-2 Product Attribute Criticality Risk Assessment Example
图表 6.1-2 产品属性关键性的风险评估例子

		Uncertainty 不确定性		
		Low 低 (Large amount of inhouse knowledge, largebody of knowledge in literature) （具有大量的自身知识，大量的文献知识）	*Medium 中 (Some in-house knowledge and scientific literature) （具有一些自身知识和一些科学文献）*	*High 高 (No/little in-house knowledge, very limited information in scientific literature) （没有/仅有一些自身知识，有限的科学文献）*
Severity 严重性	*High (catastrophic patient impact) 高（对病人有灾难性的影响）*	Critical 关键	Critical 关键	Critical 关键
	Medium (moderate patient impact) 中（对病人有中等的影响）	Potential 中度	Potential 中度	Potential 中度
	Low (marginal patient impact) 低（对病人有极少的影响）	Non-Critical 非关键	Non-Critical 非关键	Potential 中度

6.1.2 Risk Management in Stage 2 -Process Qualification 风险管理第二阶段—工艺确认

Risk Management in Stage 2, the process qualification stage of the process validation lifecycle, is much more tactical. Assessments assist in deciding where tests will be performed and at what level.They are also used to fine-tune the control strategies drafted in the Process Design stage.
风险管理第二阶段，工艺验证生命周期中的工艺确认阶段具有更多的策略性。评估可以帮助确认在工艺的什么阶段需要进行什么级别的检测。可以用于对设计阶段的工艺控制策略进行微调。

Risk management is commonly applied during the Facilities, Utilities, and Equipment Qualification phaseof Stage 2. Functional specifications are reviewed to help plan qualification activities. Higher-risk itemsrequire a higher level of performance output, while lower-risk items can be satisfied by use of commissioning activities with appropriate risk reviews and control. Risk assessment output ratings can be applied against standard criteria to create the plan (see **Table 6.1.1).**
在第二阶段的仪器、公用设施和设备确认通常会进行风险管理。利用对功能说明的审核来帮助计划确认活动。高风险的项目需要更高级别的性能输出，同时低风险的项目仅需要适当的风险审核和控制的调试活动就可以满足。风险评估的输出评级可以用来根据质量标准制定相关的计划。

Table 6.1-1 Risk-Based Qualification Planning
表 6.1-1 基于风险的确认计划

Risk Assessment Output Ratings *风险评估的输出评级*	*Qualification Planning* *确认的计划*
High *高*	*Testing to satisfy validation requirements will occur during qualification. Documentationand sampling requirements are high.* *在确认过程中会发生需要检测来满足验证的需求，文件化和取样的要求为高。*
Medium *中*	*A blend of Qualification and Commissioning activities can be used to satisfy validation requirements. Sampling requirements are moderate given appropriate controls and riskreviews.* *需要确认和调试一起来满足验证的需求。如果对取样适当的控制和风险审核的话，取样的需求为适度。*
Low *低*	*Testing to satisfy validation requirements can occur during commissioning phases.Appropriate controls and risk reviews should be in place.* *调试阶段需要检测以满足验证要求。适度的控制和风险审核应该提前定义。*

Risk assessments performed during Stage 2 not only help prioritize qualification activities, but also aid in the ongoing collection of knowledge and the planning of statistical sampling. Generally, threefactors - Severity, Occurrence, and Detection (also known as controls) - are evaluated to determine the relative risk of specific failure modes. Each factor contributes to the validation plan in a different way.
在第二阶段执行风险评估不但可以对确认活动排出优先顺序，还可以持续收集知识并制定统计抽样计划。一般而言，有三个因素----严重性，发生率和可检测性（也可称为控制方法）用于评估和制定特定失败模式的相关风险。每种因素对验证计划有不同的益处。

Severity —Determines the level of testing required during Stage 2. The higher the severity rating for a particular attribute, the higher the statistical confidence required (see **Table 6.1-2).**
严重性—确定第二阶段的检测级别。对于特定的属性，严重级别越高，越需要更高的统计置信限。

Occurrence —The occurrence rating is tied directly to variation. High Occurrence rates may require further testing or development to reduce variation and increase process knowledge. Testing at this stage reduces additional and more costly testing during Stage 3. When the true occurrence rate is unknown, additional development or engineering studies may be required. When testing is complete,the occurrence ranking and overall risk rating for the failure mode can be updated with the new process knowledge.
发生率—发生率跟变量直接相关。高发生率需要进一步的检测或研究以缩小变量的范围并提高工艺知识。该阶段的检测可以减少第三阶段的额外和高成本的检测。当真实的发生率不可知时，需要额外的开发和工程研究。当检测完成时，失败模式的发生可能性的级别和全面风险评分需要根据新的工艺知识而变更。

Detection (controls) —If the level of assessed controls is zero, the control strategy may need to be updated or new controls created. Controls do not have to be technology-based. The HACCP system is an example of a control, as are procedures and training.
可检测性（控制方法）--如果控制评估的级别为零，控制策略需要升级或建立新的控制方法。控制方法并不一定要以科技为本。HACCP（危害分析和关键环节控制点）系统就是作为控制的一个例子，是程序和培训。

Table 6.1.2 Severity Rating and Sampling Requirements
表 6.1.2 严重性和取样要求

Risk Severity Rating 风险严重性	Statistical and Sampling Requirements 统计抽样的要求	Example Confidence Level Required 抽样置信限级别的要求
High 高	+++	99%
Med 中	++	95%
Low 低	+	90%

6.1.3 Risk Management in Stage 3 -Continued Process Verification
第三阶段的风险管理—持续的工艺确证

The Continued Process Verification stage is the longest segment of the process validation lifecycle. It starts with an assessment of process capabilities and continues through a review of the output from process characterization, PPQ, and historical data. The level of enhanced sampling that may be inplace when commercial manufacturing commences can be determined by a statistical review of the PPQ data. The capabilities of the processes help determine the level of enhanced sampling for an attribute and the length of time that sampling should continue at that level (see **Section 6.2).** The statistical capability of the process is directly tied to the occurrence rating in the risk assessments. The more robust a process, the lower the occurrence rate for a potential failure and the lower the overall risk to the process. The level of risk can also determine the review period for certain product and process attributes ***(14),***
持续工艺确证是整个工艺验证生命周期中最长的一个部分。其开始于工艺能力的评估，通过对工艺表征、PPQ和历史数据的输出的审核来保持持续。。当商业化生产开始是由对PPQ数据的审核确定的时候，需要采用加强的取样方式。工艺能力可以帮助确定某一属性的加强取样的级别，并确定应该保持该级别取样的持续时间（详见6.2部分）。在风险评估当中，工艺的统计学意义与发生率直接相关。工艺越稳定，潜在失效模式发生率会更低，工艺整体的风险越低。风险的等级也可以确定一定产品和工艺属性的审核周期。

6.1.4 Raw Material Risk Management Considerations
原料药风险管理注意事项

Sources of variation should be understood, and where possible, mitigated for process validation to succeed. In this context, using quality risk management to assess raw material quality and the potential impact on the process is important **(38)**. Risk identification through focused risk assessments is the first step toward attaining the desired level of process control from both a risk-to-patient and risk-to-business perspective. The assessment identifies risk in relation to the raw material, and how it could impact the process and quality of product. The number and complexity of raw materials used in pharmaceutical manufacturing is quite large, and all potential issues (e.g., fraud/counterfeiting) should be addressed in the management of raw materials and components.
变化的源头应该了解，因为其有可能会减少工艺验证成功的机会。在这章节中会说到，利用质量风险管理去评估原料质量和工艺潜在的影响是很重要的（38）。通过关键风险评估得到的风险鉴别是获得对病人的风险和对商业的风险这两种风险的最理想的工艺控制级别的第一步。风险评估识别与原料药相关的风险，以及它将如何影响工艺和产品质量。用于制剂生产的原料药的数量和复杂程度是很大的，而且所有的潜在问题（如，欺骗或假冒）应该在原料和成分的管理中被讨论。

Risks-to-patient should also be addressed during commercial production. This can be done, through a risk assessment process that builds on current understanding of risk and process knowledge, combined with the Continuous Process Verification Program. QRM is a lifecycle process, with ssessments that occur throughout the lifecycle of the product.
在商业生产中，对病人的风险也应该被讨论。通过建立在当前风险和工艺知识上的风险评估过程，

结合持续的工艺验证项目，这可以做到。质量风险管理是具有生命周期的过程，其跟评估贯穿产品的整个生命周期。

Often subtle changes in raw materials can lead to significant and unforeseen variations in production.The cause of a change in elution profile was lot-to-lot variation in particle size distribution in a chromatographic resin***(39).*** Applications like Near Infrared (NIR) or even Nuclear Magnetic Resonance (NMR) can be used to ensure that raw materials meet their specifications and CQAs. An important risk mitigation strategy is for drug manufacturers to work with their suppliers so that each can understand the other's quality systems and demands.
通常原料的细微变更会引起产品的关键的和非预见性的改变。洗脱曲线的变化的原因是层析用树脂中粒径分布的批间变化。应用近红外光谱（NIR）或进一步用核磁共振（NMR）可以确保原料符合其特定的标准和关键质量属性。一个重要的减轻风险的策略是药品生产商与他们的供应商合作，这样大家都能够理解彼此的质量系统和要求。

6.2 Statistical Analysis Tools
统计分析工具

Successful process validation depends on sound, scientific data and information. **Table 6.2-1** illustrates where various statistical methods are most commonly used in the validation lifecycle process. Three of the methods - Design of Experiments, Statistical Process Control, and Process Capability - are described in more detail in the sections that follow. Additional information on statistical methods can be found in PDA *Technical Report 59: Utilization of Statistical Methods for Production and Business Processes* as well as **Appendix 8.1** of this technical report ***(14).***
成功的工艺验证依据合理的、科学的数据和信息。图表 6.2-1 阐明了在验证生命周期过程中普遍使用的各种各样的统计方法。其中三种方法—实验设计，工艺控制的统计分析和工艺能力—在接下来的章节中会讲述更多的细节。统计方法的 其他信息详见 PDA 技术报告 59：产品和商业化生产中使用到的统计分析方法，及本技术报告附录 8.1（14）。

Table 6.2-1 Statistical Methods and the Typical Stages at Which They Are Used
图表 6.2-1 统计分析方法和其使用的特定阶段

Statistical Tool 统计分析工具	Stage 1 第一阶段 Process Design 工艺设计	Stage 2 第二阶段 PQ 性能确认	Stage 3 第三阶段 CPV 持续工艺验证
Descriptive tatistics – Mean, standard deviation, etc. 描述性统计—平均值，标准偏差等	X	X	X
Statistical Process Control Charts 工艺控制统计图表	X	X	X
Statistical Power and Sample Size Determination 统计能力和样品量大小	X	X	X
Process Capability Study and CapabilityIndices 工艺能力研究和能力指数	X	X	X
Design of Experiments 实验设计	X		
Measurement Systems Analysis (Gauge R&R) 检测系统分析（量具重现性与再现性）	X		

Statistical Tool 统计分析工具	Stage 1 第一阶段 Process Design 工艺设计	Stage 2 第二阶段 PQ 性能确认	Stage 3 第三阶段 CPV 持续工艺验证
Robust Process Design / Tolerance Analysis / Taguchi Methods 工艺设计的稳定性/耐用性分析/田口方法	X		
Multi-Vari Chart 多变量图	X		
Regression and Correlation Analysis 回归与相关分析	X		
Analysis of Variance (ANOVA) 方差分析（ANOVA）	X	X	X
Levene/Brown-Forsyth, Bartlett, Fmax Tests for Variation 列文/布朗-福赛斯,巴特莱特，Fmax测试变化	X	X	X
Hypothesis Tests / Confidence Intervals 假设检验/置信区间	X	X	X
Pareto Analysis 柏拉图分析	X		X
Acceptance Sampling Plans 验收抽样计划		X	X
Normal and Nonparametric Tolerance Intervals 正常的和非参数允许区间		X	X

6.2.1 实验设计

The statistical design of experiments (DoE) is a powerful tool often used during Stage 1 Process Design. Goals of DoE are to:
实验设计是一种非常有效的工具，经常在工艺验证的第 1 阶段（工艺设计）使用。实验设计的目标是：

- Determine which process input parameters have a significant effect on the output quality attributes
  确定那些工艺参数(输入)对质量属性（输出）有显著影响。
- Help determine the “design space” levels of the input parameters that will produce acceptable output quality attribute results
  帮助确定能产生可接受质量属性输出结果“设计空间”水平的输入参数。
- Optimize the output of quality attributes, such as yield and acceptable levels of impurities
  优化众多质量属性的输出(如：产量和可接受的杂质水平)。
- Determine the levels of input parameters that will result in a robust process that reduces its sensitivity to parameter variability
  确定能使工艺达到稳健（减少工艺的敏感性和变化）状态的输入参数水平。

DoE differs from the classical approach to experimentation, where only one parameter is varied while all others are held constant. This “one-factor-at-a-time” type of experimentation cannot determine process parameter interactions, where the effect of one parameter on a quality attribute differs depending on the level of the other parameters. The basic steps for the DoE approach are summarized below:
实验设计不同于传统的实验方法，传统的实验方法其中只有一个参数可变，而其他所有参数均保持

不变。这种传统的“一个因素一次”的实验不能确定工艺参数的相互作用，而单参数对质量属性的影响随其他参数的水平不同而不同。实验设计的基本步骤如下：

1. Determine the input parameters and output quality attributes to study.
   确定需要研究的输入参数和输出的质量属性。

   a. This is best done as part of a team approach to identify potential critical process parameters and quality attributes; in many cases, the process may be well-understood and the parameters and attributes for experimentation readily determined.
      最好的做法是将识别潜在关键工艺参数和质量属性作为分组法的一部分；这样在大多数情况下，工艺能被充分理解，同时需要进行实验的工艺参数和质量属性也会非常容易地被确定。

   b. If there are a large number of input parameters, an initial screening design, such as a fractional factorial or Plackett-Burman design, may be used (40). The purpose of a screening experiment is to identify the critical parameters that have the most important statistical effect on the quality attributes. Since screening designs do not always clearly identify interactions, the reduced number of parameters identified by the screening experiment will be included in further experiments.
      如果输入参数太多，可使用诸如：部分因子设计或正交设计等方法进行初步筛选（40）。筛选的目的是识别对质量属性有显著统计学影响的关键参数。由于筛选设计并不能总是清晰的识别因素间的相互作用，所以通过筛选实验而被减少的参数将被包含在进一步的实验中。

   c. If the change is to an existing process, it is often valuable to construct a Multi-Vari chart or SPC chart from current process data (41). A Multi-Vari chart can be used to identify if the biggest sources of variation are within-batch variation, between-batch variation, or positional variation (e.g., between fill heads on a multi-head filler). Variance components can also be calculated from the data to determine the largest component of variance. Process parameters that could be causing the largest sources of variation are then identified and included in subsequent experiments.
      如果对现有工艺做调整，那么对当前工艺数据进行多元变量图或控制图分析是非常有价值的。多元变量分析图可用于识别最大变化的来源（批内变化、批间变化或者是位置型变化）（如：一个多头填充器的多个填头之间的变化就属于位置型变化）。通过对数据计算方差分量也能确定最大变化的分量（该方法称为“方差分量估计”）。可能导致最大变化的工艺参数被识别后会被包含在随后的实验中。

For example, if within-batch variation appears to be the largest source of variation, then charge-in of components done once at the beginning of the batch is not likely to be a key contributor to this variation. Charge-in differences due to inadequate weighing, for example, could cause between-batch variation rather than, within-batch variation. This simple but powerful tool can sometimes discover important yet unsuspected critical parameters or “lurking variables” that contribute to process variation, even if they are not initially on the list of parameters.
例如，如果最大的变化是批内变化，那么在批次开始一次性投入的物料就不太可能是变化的主要因素。由于称量不足所造成的投料差异能够引起批间的变化而非批内的变化。该工具简单但有效，时常能发现重要但未知的关键参数或者会导致过程变化的 “潜在变量”（虽然它们最初并不在参数列表里）。

The same data may also be used to create SPC charts to determine if the process is in statistical control. Since a lack of statistical control will contribute to experimental error variation, it will be more difficult to understand the results of an experiment if the process is not in statistical control. Lack of statistical control may also mean that there are “lurking variables” not on the list of process parameters that are contributing to process variation.
也可以对相同的数据绘制控制图来判定工艺是否处于统计控制状态。由于缺乏统计控制将导致实验误差波动，所以如果工艺未处于统计控制状态，那么实验结果将会变得更加难以理解。

2. Conduct experiment(s) to determine which parameters have a significant main or interaction effect on the quality attributes.
   进行多次实验来确定哪些参数对质量属性有显著或交互影响。
   a. This will usually be a full factorial design for two to four parameters. A full 2-level factorial design has a low (–) and high (+) level selected for each factor (parameter). At least one experiment is run

at each combination of the factor levels. For two factors, 2^2 = 4 combinations exist; for three factors, 2^3 = 8 combinations exist; for four factors, 2^4 = 16 combinations exist. Full factorial designs are seldom used for more than four factors since so many experiments are required. Fractional factorial experiments, where only one-half or one-quarter of the combinations are used, are often done for four to six parameters.

b. a.对于 2 到 4 个参数，常用完全析因设计。一个 2 水平的完全析因设计表示每个因子(参数)都有低（-）和高（+）2 个水平供选择。所有因子水平的相互组合，对于其中每一种组合应至少进行一次实验。对于 2 个因子，就存在 2^2 = 4 中组合；对于 3 个因子，就存在 2^3 = 8 种组合；对于 4 个因子，就存在 2^4 = 16 种组合。当因子数超过 4 个时，很少采用完全析因设计，因为需要的实验次数太多。由于部分因子实验的实验次数仅仅需要组合数（所有因子水平的相互组合）的一半或四分之一，所以当参数数为 4 到 6 个时候，它常被应用。

c. If possible, control runs at the nominal midpoints (0) between the low (–) and high (+) levels of the factors should be included in the experimental design. Using control runs at the beginning and the end of the factorial experiment, and ideally also during the factorial experiment, will allow detection of any process drift during the experiments. Control runs at the beginning and end of experiments that do not give similar results indicate the presence of another uncontrolled variable. Replicate control runs at the nominal values also provide a true estimate of inherent process variation (called experimental error). In addition, these can serve as a basic check for a non-linear curvature effect between the parameters and quality attributes.

d. 如果可能，在实验设计时，应控制各因子在最高水平与最低水平的“中点”运行。在析因实验的开始和结束进行控制运行（理论上在实验中也需要）， 可检测出在实验中任何工艺参数的漂移。在实验开始和结束控制运行得出的结果不一致表明存在其他不受控制的变化。对标准值进行多次重复将得到工艺固有变化的准确估计值（称为“实验误差”）。此外，这可以作为输入参数和质量属性之间非线性曲率效应的一个基本检测。

e. If possible, the parameter effects on both the mean and variation of the quality attributes should be determined. Some parameters may affect the mean only, variation only, or both. This information can be used to minimize the variation while optimizing the mean, which results in a robust process. Standard DoE approaches may be used for this as well as the Taguchi method (42).
如果可能，过程参数对质量属性对平均值和变化的作用都应被检测到。一些参数只会对平均值/变化有影响，一些对两者均有影响。可以通过这些信息使变化最小化，同时优化平均值，以此使工艺达到稳健状态。可以使用标准的实验设计方法也可以用田口方法。

3. Optimize with response surface experiments and determine design space.
优化响应面并确定设计空间。

a. Occasionally, the science behind a process will be understood well enough to skip screening and 2-level factorial experiments and start with response surface experiments. If enough information is learned from 2-level factorial studies, no additional experiments will be required and this step can be skipped. However, it is often necessary to conduct more extensive experiments at three to five levels for the parameters identified as most important from earlier factorial experiments.
偶尔，工艺背后的科技被完全理解了，可直接跳过筛选和 2 水平析因实验，直接开始响应面实验。如果从 2 水平析因实验中得到了足够的信息，那么不需要进行额外实验，本步可以跳过。然而，如果在更早的析因实验中被认定为重要参数具有 3-5 水平，进行更广泛的实验是必须的。

The goal of response surface experiments is to develop an equation that accurately models the relationship between the input parameters and output quality attributes. This equation is then used to determine the design space region of the input parameters where the output quality attributes will meet specifications
响应面实验的目的是建立一个能精确模拟输入参数与输出质量属性之间的关系的方程式。然后利用这个方程式确定设计空间中输入参数的范围，使输出质量属性满足标准。

The most common response surface experimental designs are Box-Behnken, central composite, 3-level full factorial, and computer-generated D- and G-optimal designs (40). All of these have experiments where at least three levels of the parameters are included in order to estimate curvature (quadratic) effects. The Results are analyzed to determine regression equations to model

the process with such computer programs as Minitab, JMP, and SAS (41).
最常用的响应面分析法是 Box-Behnken 实验设计、中心复合实验设计、3 水平全因子分析和计算机生成的 D 最优设计和 G 最优设计。所有上述实验的参数都应至少具有 3 个水平以便估计曲率效应。 通过对结果的分析来确定回归方程，并用软件（如：Minitab、JMP、SAS）依据该回归方程对工艺进行模拟（41）。

b. Another aspect of optimization is to develop a robust process. The regression equations already developed can be used to locate input parameter settings that are "forgiving;" i.e., when the process is run at these settings, variation in the input parameters will not result in unacceptable variation in the quality attributes. The idea is to stay away from boundaries or areas in the parameter design space where variation in the parameter will result in rapid quality deterioration. This is accomplished by using the quadratic and interaction effects to minimize variation. The Taguchi method of experimental design mentioned earlier uses a slightly different approach to also develop robust processes.
优化的另一方面是建立稳健的工艺。利用已经建立的回归方程确定输入参数的设置是"宽容的"，即，当工艺在该设置下运行时，改变输入参数不会导致质量属性发生不可接受的变化。

c. The results may also be used to calculate the percent of total variation attributable to each parameter. This is called a variance components analysis. The input parameters contributing the most to the output quality attribute variation can be controlled the most tightly, made robust by running the process at a particular level of the other parameters, or improved by a process design change to reduce the impact of the parameter.
该结果也可用于计算每个参数对总变化作用的百分比。这种方法被称为方差组分分析。对质量属性作用最大的输入参数将被加严控制，通过保持其他参数在一个特殊的水平上或改变工艺设计降低该参数的影响使工艺达到稳健状态。

4. Confirm DoE results
确定实验设计结果

Once the design space region for the input parameters that results in quality attributes that meeting specifications is been determined, additional experiments can be used to confirm the expected DoE results. This may consist of running a few experiments at various parameter combinations to verify that the DoE equation adequately predicts the results. In some cases, where there is already good confidence in the DoE results, Stage 2 PPQ results may be used. For further information on DoE, see Montgomery (43) or Box, Hunter, and Hunter (44).
一旦设计空间中输入参数的范围（能产生符合规定的质量属性）被确定，随后的实验将确认实验设计的预期结果。这可能通过一系列实验（各种参数相互组合）来核实实验设计方程能充分预知结果。在某些情况下，如果在实验设计中有好的置信度，第 2 阶段 PPQ 的结果也可以被使用。关于实验设计进一步的信息，见 Montgomery (43) or Box, Hunter, and Hunter (44).

6.2.2 Statistical Process Control and Process Capability
统计过程控制和过程能力

Statistical Process Control (SPC) may be used to determine if a process is stable, predictable, and in statistical control. Process Capability is used to determine if the process is capable of consistently meeting specifications. A process is considered stable or "in statistical control" when only random variation around a stable process mean is observed, i.e., only natural, common causes of variation are present. **Figure 6.2.2-1** illustrates a stable process that is in classical statistical control. **Figure 6.2.2-2**shows a process that is not in statistical control and had a special cause of variation occur at lot 5.
统计过程控制可被用于判定工艺是否稳定、可预测、处于统计控制状态。过程能力分析被用于确定过程是否能够持续符合规定。一个过程被认为稳定或者"处于统计控制状态"是指该过程的观测值全部在"稳定过程均值"附近，也就是说此时只存在自然的常见原因的变化。**图 6.2.2-1** 给出了一个处于统计状态的稳定过程控制图。**图 6.2.2-2** 展示了一个不处于统计控制状态的控制图，其中第 5 批存在特殊原因。

Figure 6.2.2-1 Process in Classical Statistical Control; Common Cause Variation only
图 6.2.2-1 过程处于统计控制状态（只有常见原因变异）

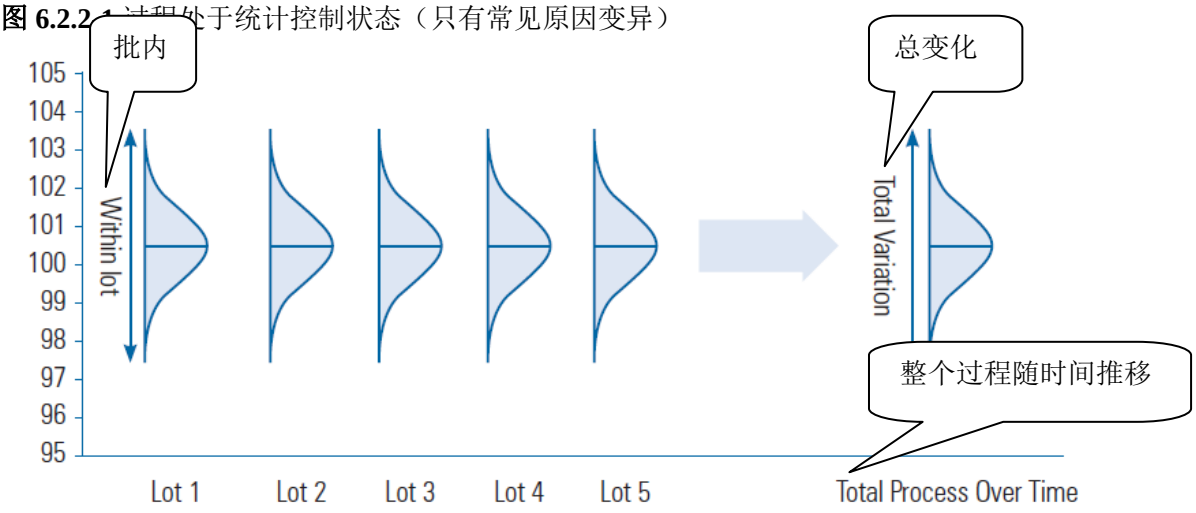
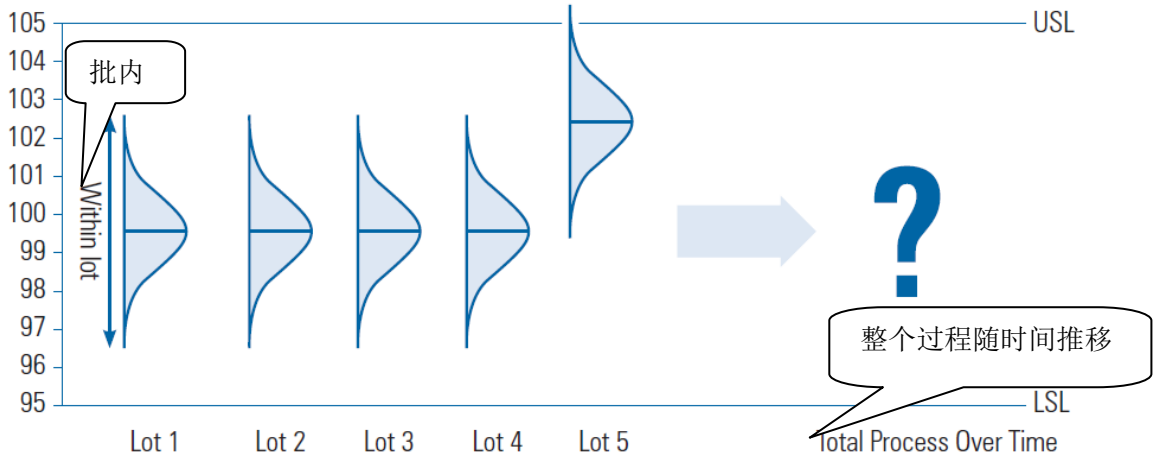
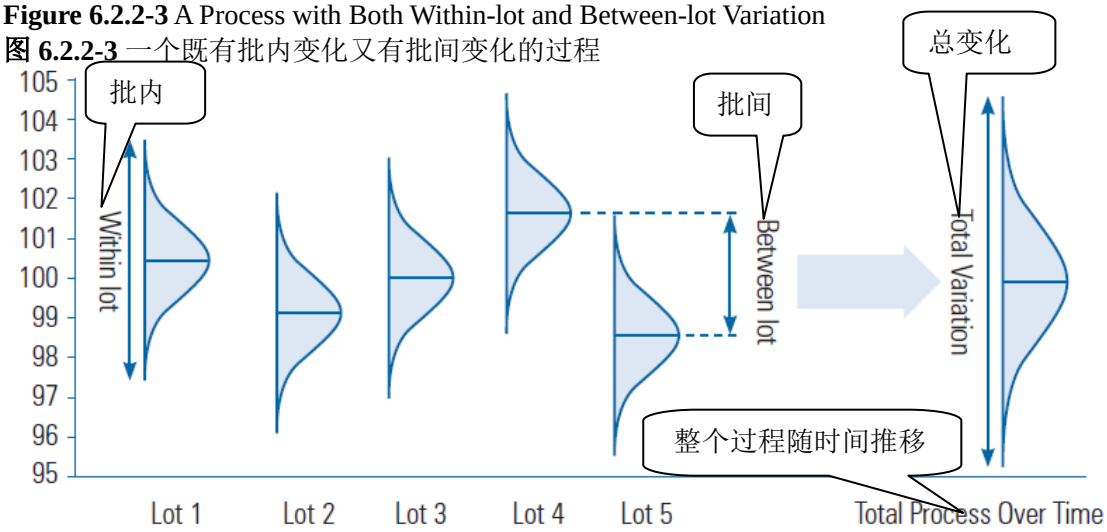


Figure 6.2.2-2 Process Not in Statistical Control -Special Cause Variation
图 6.2.2-2 过程不处于统计控制状态（有特殊变化存在）



A more complex form of a process that is also stable and in control is shown in **Figure 6.2.2-3.** This pattern is typical of many processes where there is variation both within and between lots, but the variation between lots is in control. One purpose of validation and CPV is to determine both within and between-lot variations.
一个更复杂的过程（稳定并处于统计控制状态）见**图 6.2.2-3**。该图是很多既有批内变化又有批间变化的过程的一个典型例子，但是批间变化处于控制状态。确定批内和批间的变化是验证和持续工艺确证的目的之一。

Figure 6.2.2-3 A Process with Both Within-lot and Between-lot Variation
图 6.2.2-3 一个既有批内变化又有批间变化的过程



6.2.2.1 Statistical Process Control Charts
控制图

Statistical process control charts are used to determine if a process is stable and in statistical control, or if there are special causes of variation present in the process. The basic procedure to construct a Statistical Process Control (SPC) chart to assess process stability is:
控制图常被用于判定过程是否稳定或处于统计控制状态，或被用于确定过程中是否存在特殊变化。通过绘制控制图（SPC）来评价过程能力的基本步骤是：

- Collect data from the process over time. Ideally, at least 20 subgroups should be collected, but preliminary limits may be made with less data and updated as more data become available (40). Other references, such as ASTM E2587 (45), have more detailed recommendations for the amount of data to collect initially. Plot the summary statistics from each subgroup over time, such as mean (Xbar), standard deviation (S), percent nonconforming, or individuals.
  从过程中收集资料（以时间序列）。理论上，应至少收集20个子组，但初期限制时，先使用较少数据，后续更新更多数据也是可行的。对于最初需要收集数据的量，其他参考文献如：ASTM E2587（45）有更详细的建议。以时间顺序绘制每个子组汇总的统计量，如：平均值（Xbar）、标准差（S）、不合格率或者单值。
- Draw centerlines at the grand average of the statistic being plotted.
  以总平均值为中心画中心线。
  Calculate the standard error of the plotted statistics and draw control limits at three standard errors on either side of the centerlines. These limits are called “3-sigma” control limits.
  计算绘图统计数据的标准差，画控制限（以中心线两侧3倍标准差为控制限）。该控制限常被称为“3西格玛”控制限。

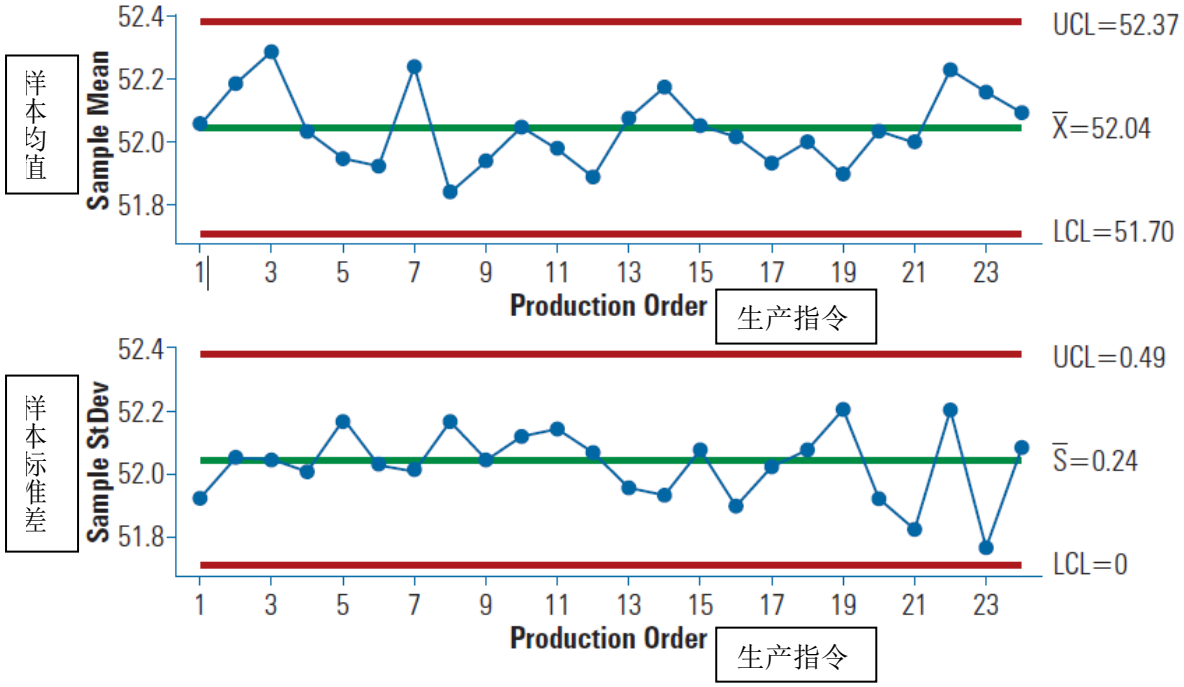
Values that fall outside the control limits indicate that special cause variation is likely present, and the causes for these excursions should be investigated. In addition to a single value beyond the 3-sigma limits, there are many other rules that may be used to check for process stability. Of these, the most commonly used are (40,41):
数据超出控制限表示极有可能存在特殊变化，超限的原因应调查。除此之外，如果数据在3西格玛控制限内，还需满足许多其他过程能力检查的准则。这些准则中最常用的如下（40,41）：

- 8 in a row above or below the mean;
  连续8点在中心线的同一侧；
- 2 out of 3 beyond 2-sigma limits;
  3点中有2点在2西格玛限外；
- 4 out of 5 beyond 1-sigma limits;
  5点中有4点在1西格玛限外；
- 6 in a row increasing or decreasing.

连续6点递增或递减。

Figure 6.2.2.1-1 shows an example of an Xbar/S chart for fill weight, where five vials from a singlehead filler were sampled every 15 minutes over a six hour production order or lot, for 24 samples. Both the mean and standard deviation appear to be stable, with no values exceeding the 3-sigma control limits. The process appears to be stable and in a reasonable state of statistical control.
图 6.2.2.1-1 是一个 Xbar-S 图（装量）的例子，其中在超过 6 小时或更长的生产指令中每隔 15 分钟对单灌装头取样一次，一次 5 小瓶，共计 24 组样本。均值和标准差都处于稳态，没有数据超出 3 西格玛控制限。过程呈现稳定且处于统计控制状态。

Figure 6.2.2.1-1 Xbar/S Control Chart for Fill Weight, n=5 per group
图 6.2.2.1-1 装量的 Xbar-S 图，子组大小 n=5



Control charts can be used during all three validation stages for within- or between-lot data. During Stages 1 and 2, they can be used to determine if the process is stable and in control in order to commence commercial production. Control charts are particularly useful during Stage 3 (CPV Stage). Special causes of variation affect almost every process at some point. Control charts help identify when such a special cause has occurred and when an investigation may be needed. As special causes are identified and corrective actions taken, process variability is reduced and quality improved. Control charts are easy to construct and can be used by operators for ongoing process control. They also create a common language for discussing process performance, and can prevent unnecessary adjustments and investigations. They encourage staff to be responsible for monitoring and improving their process, rather than just taking action when QC test results fail.
控制图能被用于分析工艺验证的三个阶段中批内或批间的数据。在第 1、2 阶段可以用它来确定工艺是否稳定受控以便决定是否开始商业生产。在第 3 阶段（持续工艺确证阶段）控制图特别有用。变化的特殊原因在某一个时刻几乎能影响到所有过程。控制图能帮助确定特殊原因何时会发生，何时需要对特殊原因进行调查。因为特殊原因被识别并采取了纠正措施，所以过程的可变性减少了，产品质量也就提高了。对于持续过程控制，操作员能够很容易的绘制和应用控制图。控制图为讨论过程能力建立了一种通用语言，并能避免不必要的调整和调查。控制图鼓励员工监控和改善他们的过程，而不是仅仅在 QC 检验失败后采取行动。

6.2.2.1.1 Factors to Consider in Designing a Control Chart
设计控制图时需要考虑的因素

There are many factors to take into consideration when designing control charts, including:
在设计控制图时，有许多因素需要考虑，包括：

- Characteristic(s) to chart
  控制图的特征
- Type of control chart to use
  需要使用的控制图类型
- Sample size and frequency of sampling
  样本大小和采样频率
- How quickly the chart will detect a problem of a given magnitude
  对于一个给定的量，控制图多快能发现问题
- Economic factors (costs of sampling and testing, costs associated with investigating out-of-control signals, costs of allowing defective units to reach the customer)
  经济因素（取样和测试的成本，对超过控制限调查的成本，允许发给客户的不合格品的成本）
- Production rate
  生产率

6.2.2.1.2 Types of Control Charts
控制图的种类

Control charts may be used for both variables and attributes data. Variables data are those that are measured quantitatively, such as potency, weight, and pH. Attributes data are those obtained by counting, such as number of rejected lots per month and percent of tablets rejected. For variables data, it is important to control both the process mean and variation, and both should be charted. A change in either indicates special causes acting on the process that should be investigated. For attributes data, such as percent nonconforming units or number of cosmetic flaws in 100 glass vials, only a single chart for the variable of interest might be kept. A separate chart for variation is not necessary because the variation of attributes data is related to the mean value; for example, the number of cosmetic flaws in 100 glass vials is usually modeled by the Poisson distribution, where the standard deviation is the square root of the mean.
控制图既可用于计量型数据也可用于属性数据。计量型数据指那些可以被测量的数据，如：效价、重量和 pH。属性数据指通过计数获得的数据，如：每月的拒收批次数和药片的拒收率。对于计量型数据，控制过程的均值和变化非常重要，因此 2 者均需要做控制图。过程中出现的任何变化都表明有特殊原因起了作用，应调查。对于属性数据（如：不合格率单位数或 100 个小玻璃瓶的表面缺陷数 ）可能仅需要一个关于变化的控制图就行。一个单独的变化图不是必需的，因为属性数据与均值有关；例如：100 个玻璃瓶的表面缺陷数通常符合泊松分布，其中泊松分布的标准差是均值的 0.5 次方。

When possible, it is preferable to use variables data rather than attributes data. A measured value contains more information than an attributes value, such as conforming/nonconforming. Control charts for variables data have more statistical power and can use smaller sample sizes than attributes data charts. Although the underlying theory for control charts assumes normally distributed and uncorrelated data, control charts are robust and generally work well even when these assumptions are not met (40). One exception is for attributes data with low values, which have a highly skewed non-normal distribution. Bioburden monitoring is an example of a process with low attributes data values, where many or most of the data are zeroes. Exact probability control limits use of the negative binomial, Poisson, or other suitable distribution that might be used to prevent too high of a false alarm rate; see “Understanding Statistical Process Control, 2nd ed. (42). Additional information on control charts is provided in Appendix 8.2, Types of Control Charts.
如果可能的话，尽量使用计量型数据而不使用属性数据。因为测量的数据比属性数据包含更多的信息，如：符合/不符合。计量型数据的控制图比属性数据控制图有更多的统计功效，因此样本量也相对较小。虽然控制图的基础理论假设数据随机且符合正态分布，但当数据不符合假设（数据随机且符合正态分布）时，控制图仍然是稳健的且普遍能很好地工作（40）。但较低值的属性数据是一个例外，因为它是一个高度倾斜的非正态分布。日常监测的微生物数据（其中大部分数据都是 0）就是这样的一个例子。准确的能力控制应使用负二项分布、泊松分布或其他合适的分布，这样可以避免较高的虚发警报；参见 Understanding Statistical Process Control, 2nd ed. (42)。关于控制图更多的信息在附录 8.2 控制图的类型中给出。

6.2.2.1.3 Process Capability
过程能力

Statistical process control charts answer the question, “Is the process stable and consistent?” Process capability statistics answer the question, “Is the process capable of meeting specifications?” Process capability is the ability of a process to manufacture product that meets pre-defined requirements. It can be assessed using a variety of tools, including histograms and process capability statistics. The two most common process capability statistics, Cp and Cpk, are shown in Figure 6.2.2.1.3-1. Cp measures the capability of a process to meet specifications if it is centered between the specification limits. Cpk assesses if the process is actually meeting specifications when any lack of centering is considered.

Examples of normally distributed processes with various values of Cp and Cpk are shown in **Figure6.2.2.1.3-2.**

控制图回答了“过程始终保持稳定吗？”。过程能力分析回答了“过程能够满足标准吗？”。过程能力是指一个过程能生产出符合预定要求的产品的能力。可以采用包括直方图和过程能力分析的多种工具对其进行评估。最常用的 2 个过程能力统计量 Cp 和 Cpk 见图 6.2.2.1.3-1. Cp 是衡量一个过程符合标准的能力（如果它处于标准限度之间的话）。Cpk 评估过程（当过程被认为缺少中心值时）是否真正符合规定。不同的 Cp 和 Cpk 对应的控制图（其数据均符合正态分布）见图 **6.2.2.1.3-2。**

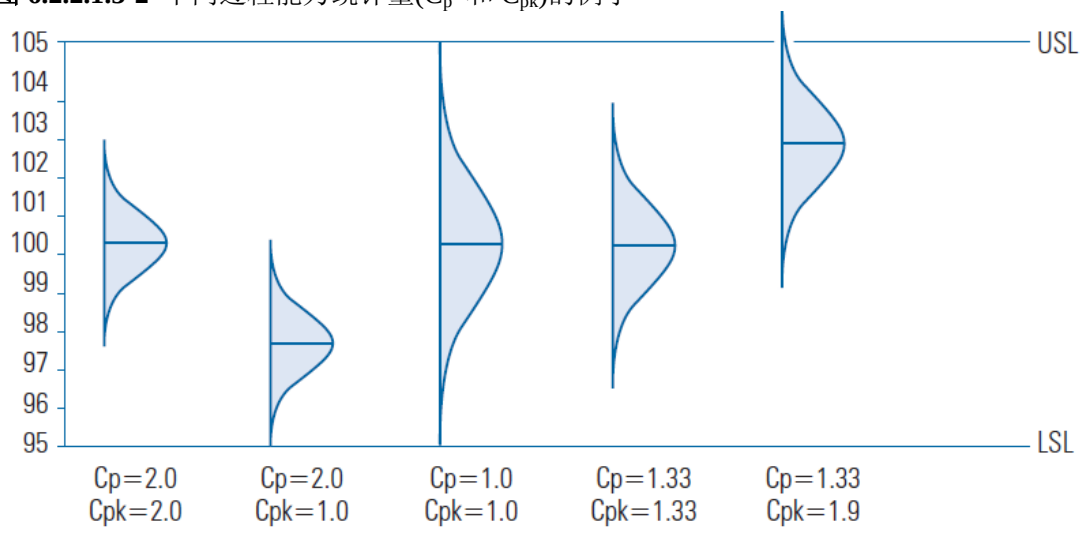
Figure 6.2.2.1.3-1 Process Capability Statistics C_p and C_{pk}
图 6.2.2.1.3-1 过程能力统计量 Cp 和 Cpk

$$C_p = \frac{(USL - LSL)}{6s}$$

$$C_{pk} = Min\left[\frac{(\bar{\bar{x}} - LSL)}{3s}, \frac{(USL - \bar{\bar{x}})}{3s}\right], \text{ where}$$

USL = Upper Specification Limit 控制上限
LSL = Lower Specification Limit 控制下限
$\bar{\bar{x}}$ = grand average of all the data 总平均值
s = standard deviation 标准差

Figure 6.2.2.1.3-2 Examples of Process Capability Statistics C_p and C_{pk}
图 6.2.2.1.3-2 不同过程能力统计量(C_p 和 C_{pk})的例子



If the process is in statistical control, the standard deviation (s) used to calculate Cp and Cpk in Figure

6.2.2.1.3-1 is usually based on estimates derived from the control chart for the standard deviation or range. These estimates of *s* will not include between-subgroup variation that may have occurred in the mean. For an individuals chart where n=1 per subgroup, the standard deviation is usually based on the moving range, which minimizes the effect of between-subgroup variation. If the standard deviation is calculated by the familiar equation $s = \sqrt{\sum (x_i - \bar{x})^2 / (n-1)}$ of all the data combined, this estimate will include between-subgroup variation, such as between-lot variation, and the indices are then called Pp and Ppk. If a process is in statistical control, there will be little difference between Cp and Pp or between Cpk and Ppk. If a process is not in statistical control, it is difficult to determine process capability because of the lack of process stability; see Figure 6.2.2-2. If a process is not in statistical control, Pp and Ppk are preferred as they include variation due to lack of stability. However, this practice is somewhat controversial; see "Introduction to Statistical Quality Control, 6th ed." (43)

如果过程处于统计控制状态，图 6.2.2.1.3-1 中被用于计算 Cp 和 Cpk 的标准差(s)通常用是基于控制图标准差或极差的估计值。对于单值图而言，每个子组的子组大小 n=1,此时标准差常用移动极差进行估计（子组间的差异被忽略了）。如果标准差采用的是最常见的公式 $s = \sqrt{\sum (x_i - \bar{x})^2 / (n-1)}$ 计算，那么该估计值包含了子组间的差异（如：批间差异），此时按图 6.2.2.1.3-1 公式计算出的指标我们称为 Pp 和 Ppk。如果过程处于统计控制状态，此时 Cp 和 Pp 或 Cpk 和 Ppk 之间有细微的不同。如果过程不处于统计控制状态，那么过程能力将很难确定（因为过程缺少稳定性），如图 6.2.2-2。如果过程不处于统计控制状态，那么计算 Pp 和 Ppk 是更合适的，因为他们包含了差异（由于缺少稳定性）。但是，这种做法是有争议的，参见《质量统计入门》第 6 版（43）。

Figure 6.2.2.1.3-2 shows the relationship between the process capability index Cpk and the probability the process output will be out of specification. The table assumes the process is in statistical control, normally distributed, and centered between the lower specification limits (LSL) and upper two-sided specification limits (USL). If the process is not normally distributed, process capability methods for non-normal distributions should be used.

图 6.2.2.1.3-2 展示了过程能力指数与过程输出值超限可能性之间的关系。这张表假定过程处于统计控制状态，数据符合正态分布且处于规定下限(LSL)与上限之间(USL)。如果过程数据不符合正态分布（符合其他分布），那么过程能力将采用其他分布计算。

Table 6.2.2.1.3-2 Relationship Between Capability and % or Per Million Nonconforming

表 6.2.2.1.3-2 过程能力和不合格数（%或每百万个不合格数）之间的关系

USL – LSL	±2σ	±3σ	±4σ	±5σ	±6σ
C_{pk}	0.67	1.00	1.33	1.67	2.00
Nonconforming	4.6%	0.27%	63 ppm	0.6 ppm	2 ppb
% of specification used (±3σ limits)	150	100	75	60	50

Acceptable values for Cpk depend on the criticality of the characteristic, but 1.0 and 1.33 are commonly selected minimum values. Six-sigma quality is usually defined as Cp≥ 2.0 and Cpk ≥ 1.5 for a normally distributed process in statistical control. See Wheeler (40) or Montgomery (43) for more complete treatments of SPC and process capability.

Cpk 的可接受值取决于特性的重要性，但 1.0 和 1.33 是最常用的最小值。6 西格玛质量管理通常解释为过程（数据符合正态分布且处于统计控制状态）的 Cp≥2.0 并且 Cpk≥1.5。

关于 SPC 和过程能力更完整的方法见 Wheeler (40) or Montgomery (43)。

6.2.3 Statistical Acceptance Sampling
统计验收抽样

Statistical acceptance sampling is another commonly used statistical tool for validation. The general

principle is that the sampling used for validation should provide higher confidence than sampling used during routine production. In validation, larger sample sizes, more replicates, and other such factors are typically used. Commonly used acceptance sampling plans for validation to ensure that a high percentage of individual units (e.g., tablets, vials) are conforming are:
统计验收抽样是另一个验证中常用的统计工具。其一般原则是验证取样应提供更高（相比于日常生产取）的置信度。在验证中，更大的样本量、更多的重复次数或其他类似的因素常被使用。在验证中为确保单项（如：药片、小瓶）具有较高符合要求的百分率常用的抽样方法有：

- Single sampling for attributes data
  属性数据的一次抽样法
- Double sampling for attributes data
  属性数据的二次抽样法
- Variables sampling for quantitative data
  数据的变量抽样法

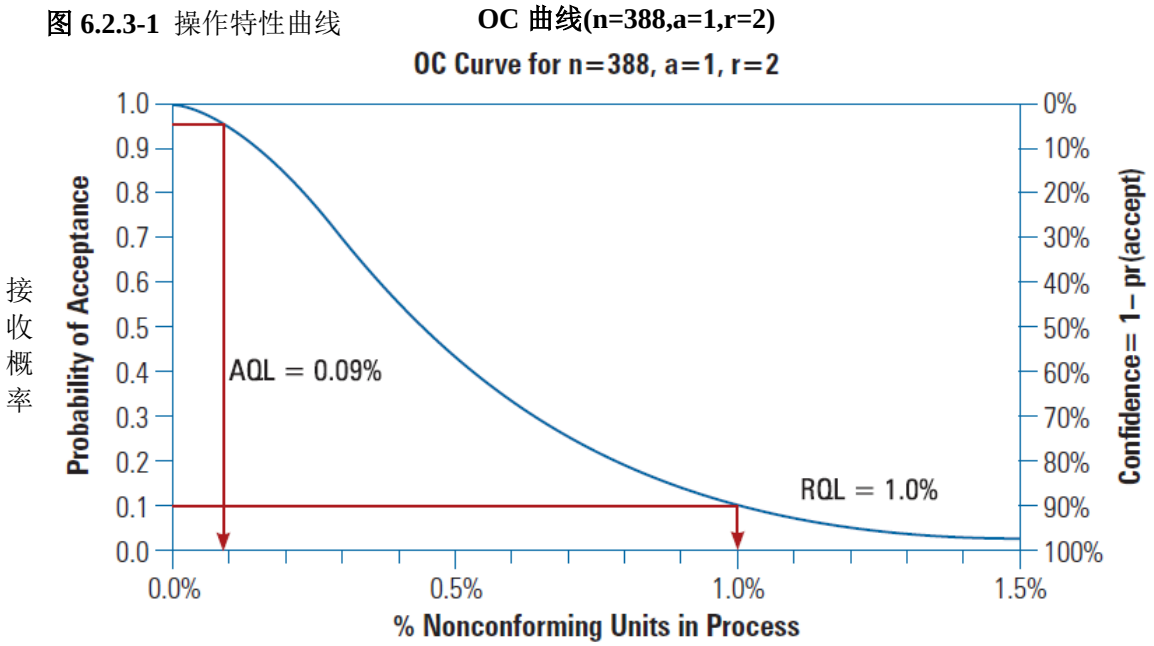
Samples should be representative of the entire population being sampled. Random, stratified, and periodic/systematic sampling are the most commonly used approaches. Targeted sampling to include suspected worst-case locations within the batch or process may be used when appropriate. For example, samples from the very beginning and end of the batch may be selected to assure that these potential trouble spots are included, while the rest of the required samples are randomly selected from throughout the batch.
样品应具有代表性。随机抽样、分层法和定期/系统抽样是常用的方法。在适当的时候可以采用针对性的抽样方法（包含批内或工艺中疑似最坏情况的位置）。例如：对一批产品在最开始和结束时进行取样以确保潜在的故障点都被包含其中，余下所需的样品可以从整个批次中随机选择。

Reaching at least 90% confidence at the end of PPQ is desirable when using statistical acceptance sampling for validation with little prior confidence. This means that the combined information from the PPQ runs shows that there is at least 90% confidence that the validation performance level has been met; 90% confidence is recommended as the minimum because it is the traditional confidence associated with detecting unacceptable quality levels (called the Rejection Quality Level [RQL], Lot Tolerance Percent Defective [LTPD], or Limiting Quality [LQ]) (46). Note that this use of the term ”confidence” is different than the traditional 95% confidence of acceptance associated with the Acceptance Quality Limit (AQL) in routine lot acceptance sampling. The AQL relates to the Type I error of incorrectly rejecting an acceptable lot, while the 90% minimum confidence recommended here refers to the Type II error of incorrectly accepting an unacceptable process.
验证时使用具有较小的置信度的用统计验收抽样后，在 PPQ 结束阶段，其置信度至少达到 90%。这表明验证性能水平符合规定的置信度至少有 90%。90%置信度是建议的最小值，因为它是传统检测不可接受质量水平的置信度（常称为“不良产品率”[RQL]，“批内允许次品率”[LTPD],或“极限品质”[LQ]）。需要注意的是这里的术语“置信度”不同于传统日常取样中与接受质量限度[AQL 相关的]95%“置信度”。接受质量限[AQL]中的“置信度”表示错误的拒绝了原本合格的批次（第 I 类错误），而这里所谓的 90%最小“置信度”表示错误的接受了原本不合格的工艺（第 II 错误）。

Single sampling for attributes is the simplest type of sampling. For example, a sampling plan of n=388 units, accept on 1 nonconformance, reject on 2, would detect a 1% nonconformance rate with 90% confidence. The statistical operating characteristic curve for this sampling plan is shown in **Figure 6.2.3-1.**

Figure 6.2.3-1 Example of an Operating Characteristic Curve

图 6.2.3-1 操作特性曲线



Double sampling plans for attributes may take a second set of samples depending on the results of the first set. For example, the double sampling plan n1=250, a1=0, r1=2; n2=250, a2=1, r2=2 will also detect a 1% nonconformance rate with 90% confidence. The values n1 and n2 are the stage 1 and stage 2 sample sizes; a1 and a2 are the accept numbers; r1 and r2 are the reject numbers. If a1（译注：个人认为是多余的）=0 nonconformances are found in the first set of n1=250 samples, the sampling plan is passed. If exactly 1 nonconformance is found in the first sample of n1=250 units, an additional n2=250 units are sampled.If the total number of nonconformances found in the combined 500 samples is no more than a2=1, the sampling plan is passed. If the total number of nonconformances found in the combined 500 samples is r2=2 or greater, the sampling plan is failed. One advantage of double sampling plans is that they often have lower false reject rates; i.e., good processes will not fail the sampling plan as often.

用于属性测定的二次抽样计划可能需要取第二组样品，这取决于第一组样品的结果。例如：这样一个检测 1%的不合格率抽样方案(90%的置信度)n1=250, a1=0, r1=2; n2=250, a2=1, r2=2。其中(n1、n2)，（a1、a2），（r1、r2）分别是第（1、2）次抽样的样本量，接受数，拒收数。

如果第 1 次抽样时 a1=0 且不合格数被抽到了。如果第 1 次抽样时不合格数恰好为 1，就需要进行第 2 次抽样。如果 2 次抽样的不合格总数不超过 a2=1，则取样计划通过。如果 2 次抽样的不合格总数≥ 2，则取样计划失败。二次抽样的优点是具有较低的假的拒绝率；也就是说好的工艺通常不会使抽样计划失效。

Several types of variables sampling plans may be used for validation, one of the most common being the normal tolerance interval. For example, one normal tolerance interval sampling plan for twosided specifications is n=30, k=3.17. If the average ± 3.17 standard deviation is contained within the specification limits, the sampling plan is passed. This plan also provides 90% confidence in detecting a 1% nonconformance rate. Variables sampling plans assume the data are normally distributed, and this assumption should be confirmed with a suitable normality test. An advantage of variables sampling plans is that they often are able to use much smaller sample sizes than attributes plans to provide the same confidence.

许多变量抽样法也可用于验证中，其中最常用的是正态容许区间。例如：对于一个具有两侧规格的正态容许区间（n=30,k=3.17），如果平均值±3.17 倍标准差包含在控制限内，则取样方案通过。该方案能检出 1%的不合格率（具有 90%的置信水平）。由于假设抽样方案中所有数据均符合正态分布，因此应对该假设进行正规检验。变量抽样法的优点是在相同置信水平的条件下需要的样本量更小（相比于属性抽样法）。

Example: The validation will show with 90% confidence that the process averages ≤0.1% leaking containers after simulated shipping. This requires an attributes sampling plan of n=2300, accept=0,

reject=1. Three lots will be used for the Stage 2 PPQ, so n = 2300/3 = 767 containers per lot will be inspected for leakage after simulated shipping. If no leakers are found in the combined n=2300 samples, the sampling plan is passed.
例如：要验证在模拟运输后容器泄漏率的平均值≤0.1%（90%的置信度）。属性取样方法需要 n=2300, 接受数=0, 拒收数=1。而工艺验证的第二阶段(PPQ) 需要进行 3 批 ，所以每一批都需要在模拟运输后对 n = 2300/3 = 767 个容器进行泄漏检测。如果在所有 2300 个样品中均未发现泄漏的，取样方案通过。

ANSI/ASQ Z1.4 "*Sampling Procedures and Tables for Inspection by Attributes*" and ANSI/ASQ Z1.9 "*Sampling Procedures and Tables for Inspection by Variables*" are commonly used sampling plans for routine production (47,48). They should be used with care for validation, since they may not provide a high enough level of confidence. For example, one Z1.4 tightened sampling plan for AQL 0.4% is n=315, a=2, r=3. If a validation lot has 2 nonconforming units in a sample of n=315, the validation lot would pass the sampling plan. (However, note that 2/315 = 0.63% is substantially larger than the AQL of 0.4%.) Finding 0.63% nonconforming units in a sample does not provide high confidence that the process is ≤0.4% nonconforming, if that was the goal of the PPQ. If Z1.4 and Z1.9 are used for validation, the Operating Characteristic curves in the standards should be consulted to verify that the desired confidence is achieved.
常用日常生产的取样方法见 ANSI/ASQ Z1.4 "*Sampling Procedures and Tables for Inspection by Attributes*" 和 ANSI/ASQ Z1.9 "*Sampling Procedures and Tables for Inspection by Variables*"（47,48）。在验证使用这些方法时应谨慎，因为他们无法提供更高的置信水平。例如：依据 Z1.4 中的加严取样法(AQL=0.4%,n=315,a=2,r=3).如果一个验证批次的样本中（样本量 n=315）不合格数是 2，该批验证将通过。（但是，注意到 2/315=0.63%大于 AQL=0.4%.）。在样品中发现 0.63%的不合格率并不能给出较高的置信度说明工艺符合要求（如果该工艺验证的目标是不合格率≤0.4%）。如果将 Z1.4 和 Z1.9 中的方法应用于验证中，那么应证明其 OC 曲线可以达到预期置信度。

Not all sampling plans used to make accept/reject decisions are for percent nonconforming units. For example, the USP test for content uniformity (of dosage units) is specified in terms of a two-stage sampling plan given in USP. In this case, validation sampling should provide confidence that the USP test can be passed with high confidence (49).
不是所有用于做接收/拒绝决策的取样方法都适合不合格百分数。例如：对于含量均匀度（单位剂量）USP 明确规定要采用二层抽样法。在这种情况下，验证取样应提供置信度以确保该测试能以较高的置信度通过。

Example: The sampling plan will show with 95% confidence that the routine USP content uniformity (of dosage units) test requirements can be met.
例如：抽样方法(具有 95％的置信度)表明常规 USP 含量均匀度（剂量单位）的测试可以满足要求。

6.2.4 Number of Lots for Stage 2 Process Performance Qualification (PPQ)
工艺验证第二阶段验（工艺性能确认）证所需批次数

The number of lots required for Stage 2 PPQ depends on the following:
工艺验证第二阶段所需批次数依赖于以下因素：

- Prior information about the process available from Stage 1 Process Design or quality history from similar processes. The more scientific evidence already available to establishes that the process is capable of consistently delivering quality product, the fewer the number of PPQ lots required.
  来自于第一阶段（工艺设计）或相似工艺质量历史的以前的信息。在建立工艺（能持续产出优质产品）时，采用现存的科学证据越多，PPQ阶段所需的验证批次也就越少。
- Risk factors, including criticality of the product characteristics and extent of in-process quality control (e.g., PAT,100% inspection)
  风险因素，包括关键产品质量特和工艺质量控制程度（如：PAT，100%全检）。
- Type of data: attributes (pass/fail) or variables (quantitative)
  数据类型：属性型数据（合格/不合格）或者数值型数据（数量值）
- Statistical confidence desired
  预期统计置信度

- Production rate (i.e., how often lots are produced). If only one commercial lot is produced per year, it will not be feasible to require a PPQ with a large number of lots.
  生产率（也就是多长时间生产一批）。如果每年仅仅进行1批商业生产，这是不可行的，因为PPQ需要大量的批次。

Depending on the prior information and/or risk involved, it may not be necessary to determine the number of PPQ lots using statistical methods. The less information and confidence at the transition to Stage 2 (PPQ), the more advisable it is to use statistical methods to help determine the number of PPQ lots where feasible and meaningful. See the Appendix 8.1, Statistical Methods for Determining the Number of Lots, for statistical approaches to determine the number of lots. Regardless of the number selected and acceptance criteria used, the data collected during PPQ should be statistically analyzed to help understand process stability, capability, and within (intra-) and between (inter-) lot variation. Lots produced during Stage 1 under similar conditions as the PPQ lots may potentially be used to reduce the number of lots required at PPQ. This can be done using Bayesian statistical methods or by
combining the Stage 1 data and Stage 2 PPQ results – if there are no significant differences in the data (50). The criteria for combining Stage 1 data and PPQ data should be specified before the PPQ lots are produced. These criteria would typically include such statistical comparisons as ANOVA (analysis of variance) to compare lot means, Levene/Brown-Forsythe or Bartlett's test to compare the lot standard deviations, SPC charts, and equivalence tests to demonstrate that Stage 1 and PPQ data are similar (51).
依据所涉及的现有信息和/或风险，可能没有必要采用统计学方法来确定 PPQ 的批次数。在信息较少、置信度较低的情况下过渡到第 2 阶段时，采用统计方法来确定 PPQ 的批次数是明智且有意义的。见附录 8.1，采用统计方法确定验证的批次数。无论选择的数量和使用的验收标准是多少，PPQ 阶段内收集的数据均应进行统计分析以帮助理解工艺的稳定性、性能和批内和批间的变化。在第 1 阶段生产的批次（与 PPQ 阶段相似的条件下生产的）可能被用来减少 PPQ 阶段所需要的批次，这可以通过贝叶斯统计理论或合并第 1、2 阶段的结果来（如果第 1、2 阶段的数据没有显著差异的话）实现。合并第 1、2 阶段数据的标准应在 PPQ 批次生产前规定。标准通常应包含一些统计比较（如：批次均值的方差分析、批次标准差的 Levene/Brown-Forsythe 或 Bartlett 检验、控制图和等效性实验）以证明第 1 阶段和 PPQ 阶段的数据是相似的。

6.3 Process Analytical Technology (PAT)
过程分析技术（PAT）

PAT is a method of process control, where the product or in-process material quality attributes are monitored and measured, and the process parameters and conditions are altered to maintain those quality attributes. PAT can provide high levels of product quality assurance through the analysis of material attributes, and the process adjustments. In that quality attributes do not vary outside of the prescribed ranges, product and material quality is maintained (52).
PAT 是一种过程控制方法，应用此方法可以监控或者测量产品属性或过程中的物料属性，并可（适当）改变一些工艺参数和条件以保持这些质量属性。通过分析物料属性并做适当的工艺调整，PAT 可以给予高水平的产品质量保证。由于质量属性不会超出规定的范围，产品和物料的质量便可以得到控制（52）。
PAT can provide an opportunity to enhance process analysis and process knowledge compared to traditional tests. It can support process validation whether it is a parallel activity (concurrent with process validation), reductive activity (reduces execution of existing tests), or replacement activity (alternative to traditional testing). Effective use of PAT to provide process control relies on the selection of correct quality attributes, process performance ranges, and methods for monitoring and reporting. It also relies on the proper design, use, and validation of the PAT monitoring, measurement, and control loop systems. The validation of the PAT system is based in part on the following principles:
与传统的检验相比，PAT 提供了一种机会可以更好地进行工艺分析并了解工艺知识。不论是同步的形式（与工艺同时进行），还是减少检验的形式（减少已有检验内容的执行量），还是替代的形式（替代传统的检验），PAT 均可用来支持工艺验证。PAT 在工艺控制中的有效应用取决于选择正确的质量属性、工艺参数范围以及监控和报告的方法。这也依赖于 PAT 监控、测量和控制环系统（control loop systems）恰当的设计、使用和验证：

1. Measurement of the correct product and in-process quality attributes

测量正确的产品和过程质量属性

2. Accuracy and understanding of the correlation between these quality attributes and the process parameters that will be adjusted
   准确知晓并了解这些质量属性和可以进行调节的各工艺参数之间的相关性
3. Reliability, suitability, capability, and accuracy of the monitoring, measurement, and process control loop or adjustment systems
   监控、测量和工艺控制环或调节系统的可靠性、适用性、工作能力和准确性
4. Acceptable performance of the PAT system throughout commercial manufacturing, including the ability to identify opportunities for process improvement.
   整个商业生产期间 PAT 系统的性能需符合要求，包括可以识别出工艺改进因素的能力。

6.3.1 Selection of PAT System
PAT系统的选择

PAT is an enabler to product and process understanding and an element of control strategy. Prior to the selection of the PAT system, the product and manufacturing process must be developed and well understood. Selecting the right PAT system should be based on fitness for purpose, system ruggedness, and vendor customer service. Selection criteria should include, but are not limited, to, specificity, sensitivity and accuracy, electronic integration requirements of information technology compatibility, data management, and communication. Table 6.3.3-1provides a partial list of PAT systems, each of which may provide information helpful to the understanding and validation of the respective drug manufacturing processes.

PAT 是一个可以推动对产品和工艺认识的使能器，并且也是控制策略的一个元素。在选择 PAT 系统之前，产品和生产工艺必须已经进行了研发并有了充分的了解。选择正确的 PAT 系统应基于合适的目的、系统的稳健性和供应商客户服务。标准的选择应包括但不限于，专属性、灵敏度和准确度、信息技术兼容性的电子集成需求、数据管理和通信。表 6.3.3-1 列出了 PAT 系统的一部分，每一项都可以为理解和验证各自药物制备工艺提供有用的信息。

Table 6.3.3-1 Examples of PAT Tools and Their Application
表 6.3.3-1 PAT 工具示例及其应用

PAT Tools PAT 工具	Process 工艺	Application 应用
Laser-based particle size analyzers 激光粒度分析仪	crystallization, granulation, milling 结晶、制粒、研磨	particle size, particle shape 粒径、粒子形状
FT-Infra-Red FT-红外	chemical reactions 化学反应	reaction progress and completion 反应过程和结束
	raw materials 原料药	Identification 鉴别
Nuclear Magnetic Resonance (NMR) 核磁共振光谱（NMR）	chemical reactions 化学反应	reaction progress and completion 反应进程和结束
Light induced fluorescence (LIF) 光激发荧光技术（LIF）	blending 混合	end point determination 终点测定
	compression 压片	content uniformity, assay 含量均匀度、含量测定
Near Infra-red spectroscopy (NIR) 近红外光谱（NIR）	blending, granulation 混合、制粒	end point determination 终点测定
	drying 干燥	water content 水分
	compression 压片	content uniformity, assay 含量均匀度、含量测定
	fermentation 发酵	nutrient content 营养物质含量
	raw materials 起始物料	Identification 鉴别
Raman spectroscopy 拉曼光谱	blending 混合	end point determination 终点测定
	granulation 制粒	water content, polymorphism 水分、多晶型
	compression 压片	content uniformity, assay 含量均匀度、含量测定
	raw materials 起始物料	Identification 鉴别
	lyophilization 冻干	water content, polymorphism 水分、多晶型
Refractive Index (RI) 折光率（RI）	blending or mixing 混合或搅拌	end point determination 终点测定
Turbidity 浊度	blending or mixing 混合或搅拌	end point determination 终点测定
Microwave 微波	blending, granulation 混合、制粒	end point determination, water content 终点测定、水分
Acoustic Absorption/Emission 吸音/发音	blending, granulation 混合、制粒	end point determination, water content 终点测定、水分
Effusivity 吸热系数	blending, granulation 混合、制粒	end point determination, water content 终点测定、水分

PAT Tools PAT 工具	Process 工艺	Application 应用
pH, Conductivity, Dissolved oxygen (DO), Oxidation-Reduction Potential (ORP) pH、电导率、溶解氧（DO）、氧化还原电位（ORP）	Fermentation 发酵	reaction progress, end point determination 反应进程，终点测定
Focused beam reflectance measurements (FBRM) 聚焦光束反射性测量法（FBRM）	Formulation of suspensions and emulsions 混悬剂和乳液制备	measure particles and droplets 测量颗粒和液滴
Rapid High-Performance Liquid Chromatography (Rapid HPLC) 快速高效液相色谱法（快速HPLC）	fermentation 发酵	nutrient content, reaction progress, end point determination 营养物质含量，反应进程，终点测定
	chemical reactions 化学反应	reaction progress and completion 反应进程和结束

6.3.2 Process Validation Considerations During the PAT System Design Stage
PAT系统设计阶段的工艺验证考虑要点

During PAT system design, information is developed to confirm that correct product and in-process quality attributes are being measured, and that the correlation between these quality attributes and the process parameters that will be adjusted is understood and accurate. During PAT system design, an understanding of how process parameter changes affect product attributes is established. Process monitoring and control systems are designed and linked to specific product attributes. Ranges of acceptable process parameter variation are determined. PAT design efforts should include: risk assessment, system feasibility and selection, in-process application development, and consideration of regulatory requirements.

在 PAT 系统设计时，需要开发出相关的信息以能够确认可以正确地测定产品和过程的质量属性，并且已充分知晓了质量属性和将会做调整的各工艺参数的相关性及其精确程度。在 PAT 系统设计时，必须要了解到工艺参数怎样改变会对产品属性产生影响。设计出工艺监控和控制系统并使其关联到指定的产品属性上。测定出可接受工艺参数的变化范围。PAT 设计的工作应包括：风险评估、系统可行性和选择性、过程中应用开发和对法规要求的考虑。

6.3.2.1 Risk Assessment
风险评估

The Risk Assessment should identify product and in-process quality attributes that have an effect on final product quality. The risk assessment should identify process steps and conditions that affect these attributes and can be measured and adjusted to assure product quality. Quality attributes, and corresponding process steps and conditions that are not monitored by the PAT system, may require other means to assure or validate performance. Having PAT systems is expected to lower the risk to product quality, by having additional controls, timely responses, increased detectability, increased understanding, and information (e.g., identification, measurement, control of CQAs). These features enable a more informed risk assessment decision. Tools for the assessment and evaluation of PAT processes and systems are discussed in Section 6.1,as well as PDA TR 54, ICH Q9 and other publications(12,13,30).

风险评估应能识别出会对终产品质量造成影响的产品和过程中的质量属性。风险评估应能识别出会影响到这些属性并且是为了保证产品质量是可测量和可调整的工艺步骤和条件。质量属性及其相应的不用 PAT 系统监控的工艺步骤和条件也需要其他手段来进行保证或验证其性能。采用 PAT 系统是期望于采取额外控制手段、及时响应、检出能力提高、理解加强和信息化（例如，鉴别、测量、CQAs 控制）等，而能够降低产品质量的风险。这些特性有利于在信息充分的情况下做出风险评估决策。在 PDA TR54、ICH Q9 和其他已发表刊物上对 PAT 工艺和系统的评估和评价工具进行了讨论（12,13,30）。

6.3.2.2 In-Process Application and Method Development
过程中应用和方法开发

The PAT methods for in-process product measurement and process adjustment should be selected and validated for specificity, linearity, range, accuracy, precision, repeatability, robustness, detection limit, and quantitation limit to ensure that the method is fit for purpose (13).
应适当选择用于中控产品测定和工艺调整的 PAT 方法并在专属性、线性、准确度、精密度、重复性、耐受性、检测限和定量限这些方面进行验证，以确保该方法适用于其目的（13）。

6.3.3 Process Qualification Considerations for PAT
PAT的工艺确认考虑要点

The Process Qualification Stage is where information is developed to confirm that the monitoring, measurement, and process control or adjustment systems are suitable, capable, accurate, and reliable. One key to effective PAT process control is the reliable operation of instruments and equipment. For implementation, an implementation and validation team should be assembled to categorize the validation requirements and propose acceptance criteria for each unit of operation, based on the application or intended use of the PAT system and method. These requirements and criteria will ultimately be included in a validation protocol and described in the validation report. The acceptance criteria should be aligned with the expected specification, protocol requirements, development experience, and manufacturing practice.
在工艺确认阶段，可开发获得信息来确认监控、测量以及工艺控制或调整系统是合适的、可胜任的、精确的以及可靠的。有效的 PAT 工艺控制的一个关键要素为仪器和设备的可操作性。为实现此方面，应成立一个执行和验证团队，以 PAT 系统和方法的应用或预期用途为基础，对每个操作单元的验证需求和可接受标准进行分类。这些需求和标准最后会包括在验证方案中，并在验证报告中进行描述。可接受标准应与预期的质量标准、方案要求、研发经验以及生产实践相一致。

Function and operation of the equipment and instrumentation used in the PAT system should be qualified to assure that it will monitor and control the process parameters accurately and reliably. Equipment and instruments used during the process should be qualified to verify that they are suitable for in-process use, including compatibility with process materials and conditions, accuracy, sensitivity, security, and reliability.
采用了 PAT 系统的设备和仪器的功能和操作应进行确认，以保证其监测和控制的工艺参数是精确的以及可靠的。生产期间采用的设备和仪器应进行确认，以证实它们适用其工艺目的，包括与工艺材料和条件的相容性、准确度、灵敏度、安全性以及可靠性。

6.3.4 Continued Process Verification Considerations for PAT
PAT的持续工艺确证考虑要点

The Continued Process Verification Stage is where information is obtained to confirm that the PAT system performs at an acceptable level throughout commercial manufacturing. It also determines where product and in-process quality attributes, or process parameters fall out of expected ranges; those that do are identified, investigated for cause, and addressed.
在持续工艺确证阶段，可获得信息来确认 PAT 系统在整个商业生产期间是在一个可接受的水平上保持运转。在这个阶段，还可测得产品和过程中质量属性或工艺参数是在什么地方落在了预期范围之外，将其识别、开展原因调查并处理。

By definition, PAT provides continuous process and product attribute verification. Stage 3 activities should therefore focus on accuracy and reliability of control methods, possible process control improvements, and process variables missed during process development and qualification. Evaluation of PAT and or in-process derived data should be part of the Quality System and review processes (11).Where data trending shows excursions in anticipated monitoring results, analysis of the cause of the excursion should be conducted to determine if changes to the control system are needed or opportunities for process improvement can be identified.
显然，PAT 可实现连续性的工艺和产品属性的确证。因此阶段 3 的活动应重点放在控制方法的精确性和可靠性、可能的工艺控制改进以及在工艺开发和确认阶段错过的工艺变量。PAT 和/或工艺过程中数据的评价应是质量系统和工艺回顾的一部分（11）。如果数据趋势显示有偏离预期监测结果的迹象，应进行偏离原因的分析，以确定是否需要对控制系统进行变更，或者识别出是否有工艺改进的可能性。

When variables are found that are not being monitored adequately, changes to the monitoring methods may be needed. All changes should be evaluated for impact on the process and product attributes. Changes should be evaluated and actions implemented to assure that residual risks do not adversely affect process performance or product quality. These actions may include steps to qualify the changed process and equipment.
当发现变量并没有被适当的监控时，则需要进行监控方法的变更。所有变更均应进行是否有工艺和产品属性造成影响的评价。应对变更进行评估并采取行动，以保证残留风险不会对工艺性能或产品质量带来不利影响。这些活动可能会包括几个阶段来确认变更后的工艺和设备。

6.4 Technology Transfer
技术转移

For a lifecycle approach to process validation to be effective, all information that is available to support the understanding of the process, including that from other sites and similar processes, should be considered. This information should be useful, accurate, and complete. The goal of technology transfer (TT) activities is to communicate product and process knowledge between development and manufacturing, and within or between manufacturing sites to achieve product realization. This information forms the basis for the manufacturing process, control strategy, process validation approach, and ongoing continual improvement (52).It also provides valuable insight into the development of the process, including process variables, process performance, and process control strategies.
为使工艺验证的生命周期方法能是有效的，所有获得的能支持对工艺理解的信息都应考虑在内，包括其他场所和类似工艺的信息。这一信息应是有用的、精确的以及完整的。技术转移（TT）活动的目标为实现研发与生产之间的产品和工艺知识的传达，在不同生产场所内或之间实现产品的生产。这一信息构成了生产工艺、变更策略、工艺验证方案和不断持续性改进的基础（52）。这也为工艺开发提供了非常有价值的洞察信息，包括工艺量、工艺性能和工艺控制策略。

Technology transfer is successful if process understanding has increased, and there is documented evidence that the recipient of the technology transfer can routinely reproduce the transferred product, process, or method against a predefined set of specifications from the sender. Process understanding and knowledge increase significantly during technology transfer, providing useful information for process control strategy design and process validation. Technology transfer can occur at different stages of the process validation lifecycle. If a new process is being transferred from research and development to commercial manufacturing, the technology transfer may occur between Stages 1 and 2. However, if it occurs after a product has been launched and it is in the commercial manufacturing phase, then transfer will occur during Stages 2 and 3. Refer to Table 6.4-1below for distribution of Technology Transfer Activities throughout the Product Lifecycle, which outlines the increasing knowledge and process understanding with each technology transfer.
如果是增进了对工艺的理解，则技术转移是成功的，并且有文件证明按照转移方预定好的系列质量标准，技术转移的接收方可以常规性的再现所转移的产品、工艺或方法。工艺理解与知识在技术转移期间会显示增加，这为工艺控制策略设计和工艺验证提供了非常有用的信息。技术转移可在工艺验证生命周期的不同阶段发生。如果是从研发到商业生产的新工艺，技术转移应在阶段 1 和 2 之间发生。但是，如果是发生在产品上市后并且产品处于商业生产阶段，则转移将在阶段 2 和 3 之间发生。参见下表 6.4-1，产品生命周期期间的技术转移活动分布，表中概要给出了伴随每次技术转移的持续增长的知识与工艺理解。

Table 6.4-1 Technology Transfer Activities throughout Product Lifecycle
表 6.4-1 产品生命周期期间的技术转移活动

Process Validation Lifecycle Stage **工艺验证生命周期阶段**	**Activities** **活动**	**Knowledge Development/Data** **知识开发/数据**	**Application** **应用**
Stage 1 阶段 1	Process Design provides product and process development knowledge and data for technology transfer. 工艺设计阶段提供用于技术转移的产品和工艺开发知识及数据。	Development Report: 开发报告： • Development history, including criticality assessments 开发历史，包括关键性评估 • and DoE with sources of variation 和包括变化来源的 DoE • Data and knowledge development from stability studies and development batches 来自稳定性研究和开发批次的数据和知识 • Rationale for specifications and methods 质量标准和方法的选择原因 • Critical Process Parameters (CPPs) 关键工艺参数（CPPs） • Critical Material Attributes (CMAs) 关键物料属性（CMAs） • Critical Quality Attributes (CQAs) 关键质量属性（CQAs） • KPPs, PARs, NORs KPPs、PARs、NORs • Manufacturing Process Description, Equipment Train 生产工艺描述，设备链	Technology Transfer Batches manufactured during Stage 1 are intended to establish comparability of product quality between sites and, develop filing/market authorization data. 阶段 1 期间的技术转移批次是为了确定生产场地之间产品质量的相似程度，并开发获得文件/市场许可数据。 Development Report summarizes activities from Stage 1. 开发报告总结了阶段 1 的活动。
Stage 2 阶段 2	Most technology transfer activities in a product lifecycle are carried out at Stage 2: 生命周期内绝大多数的技术转移活动是在阶段 2 内进行： • Development of Transfer Strategy	Technology Transfer Strategy: 技术转移策略： • Product and Process Description (as designed from Stage 1, and reported in the Development Report) 产品和工艺描述（如阶段 1 所设计的，在开发报告中有所报告） • Assessment of Site Change Requirements; e.g., PostApproval and,	Technology Transfer Batches manufactured during Stage 2 are intended to reproduce the manufacturing process, including components and

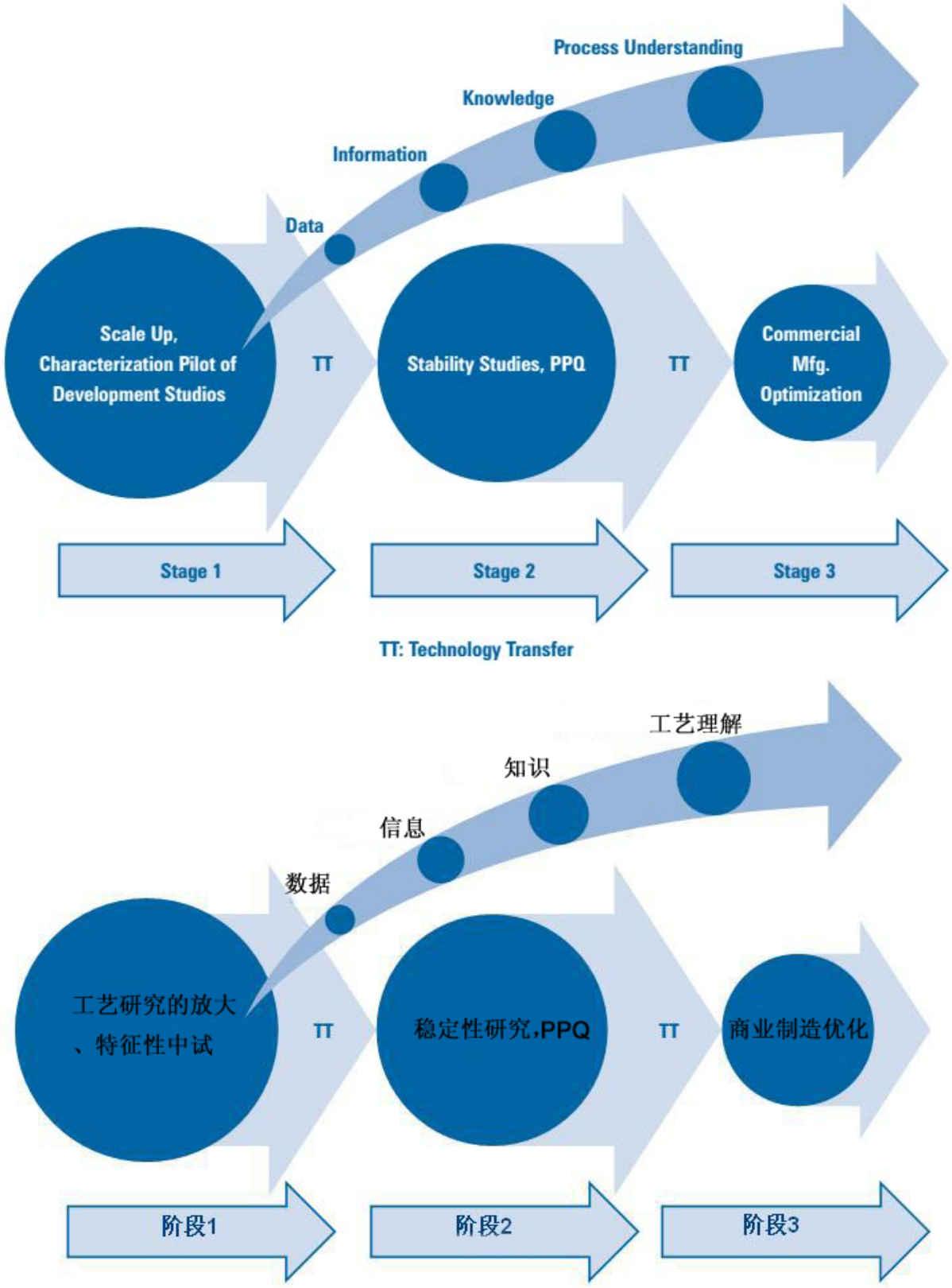
Process Validation Lifecycle Stage **工艺验证生命周期阶段**	**Activities** **活动**	**Knowledge Development/Data** **知识开发/数据**	**Application** **应用**
	转移策略开发 • Manufacturing of Commercial Scale PPQ Batches 商业规模 PPQ 批次生产 • Site Equivalency Analysis (from receiving to sending unit) 场地间等效性分析（从接收方到转移方） • Transfer and Validation of Analytical Methods 分析方法转移和验证 • Confirming CPPs at Commercial Scale 商业化规模下的 CPPs 确认 • Conducting Stability Studies at Commercial Scale under Commercial Package configurations 商业规模在市售包装条件下进行的稳定性研究 • Confirming Risk Assessments, Criticality Analysis 确定性风险评估，关键性分析 • Establish Sampling Plans and Statistical Methods at Commercial Scale 建立商业规模下的取样计划和统计学方法	Prior-Approval with rationale. Category under SUPAC guidelines, if applicable 场所变更需求评估，例如：批准后和批准前，说明原因。如适用，给出按照 SUPAC 指导原则确定的类别 • Number of batches required to meet transfer requirements, including validation/PPQ strategy/Matrix Approach 满足转移需求所需的批次数目，包括验证/PPQ 策略/矩阵方法 • Specifications and Methods Transfer Plan 质量标准和方法转移计划 • Validation Plan 验证计划 • Control Strategy 控制策略	composition configurations at the transfer site, and to conduct PPQ. 阶段 2 期间生产的技术转移批次是为了在转移场所再现生产工艺，包括组分和组成结构，并进行 PPQ。 Equivalency between sites is intended to compare equipment and facilities to assure that they are equivalent and qualified for commercial manufacturing 场所之间的等同性研究是为了对设备和设施进行比较，以保证这些设备和设施对于商业化生产是等同的，并且是经过了确认的。

Process Validation Lifecycle Stage **工艺验证生命周期阶段**	**Activities** **活动**	**Knowledge Development/Data** **知识开发/数据**	**Application** **应用**
	• Evaluation of Personnel Qualifications and Training 人员确认和培训评价		
Stage 3 阶段 3	Technology Transfer activities at Stage 3 are most likely carried out for products that have already been validated and are on the market. These are known as post-approval changes under the SUPAC guidelines (for small molecules), and apply to changes to alternate manufacturing sites within a company or to contract manufacturers. 阶段 3 的技术转移活动更像是已经完成了验证在市场上有销售的产品生产。这些活动在 SUPAC 指导原则（小分子）下作为批准后变更活动，可适用于公司内的或与合同生产商之间的生产场所的改变的变更。	Similar to activities in Stage 2, a Technology Transfer Strategy is recommended. The Strategy would include data listed under Stage 2 of this Table. For products at Stage 3, additional data and knowledge will be available. It should be considered and evaluated prior to starting technology transfer activities. 与阶段 2 的活动类似，推荐采取技术转移策略。策略中应包括该表格阶段 2 中所列出的数据。对于阶段 3 的产品而言，应能获得更多的数据和知识。在开始技术转移活动之前应对其做以考虑及评价。 At Stage 3, technology transfer activities may pose opportunities for process improvement at the receiving site using historical control and quality systems data. Valuable data to evaluate include: 在阶段 3，技术转移活动为接收场所采用历史变更和质量系统数据进行工艺改进提供了一定的机会。需评估的可用数据应包括： • Stage 2 Technology Transfer and Validation Reports 阶段 2 技术转移和验证报告 • Annual Product Reports, including Process Trending and Process Capability 年度产品报告，包括工艺趋势和工艺能力 • History of Investigations, CAPA, Change Control, OOS, Complaints Reports, Field Alerts, Stability Studies, Yield Variations 调查、CAPA、变更控制、OOS、投诉记录、场地警示报告（Field Alerts）、稳定性研究、收率变动的历史 • Executed Batch Records 批生产记录 • Sampling and Test Plans 取样和检验计划	Transfer to a new location within a manufacturing site, to an alternate site of the company, or to a contract manufacturer. Filing requirements are defined by SUPAC, as these have different implications from the regulatory standpoint. Validation requirements apply equally to any of the technology transfer scenarios. 在某一生产场所中转移到新的地点，转移至公司的另一个场所，或转移至合同生产商。SUPAC 定义了文件要求，因为在法规角度有不同的应用。几乎所有技术转移活动都有类似的验证需求。

Process Validation Lifecycle Stage **工艺验证生命周期阶段**	**Activities** **活动**	**Knowledge Development/Data** **知识开发/数据**	**Application** **应用**
		• Analytical Data 分析数据 • Conduct Gap Analysis at current vs. transfer site to assess risks and variations, including: 进行当前与转移场所之间的差异分析以评估风险和变化，包括： • Manufacturing Equipment Train design and operating principle, as well as qualification status 生产设备链设计和操作原理，以及确认状态 • Confirmation of CPPs, equipment operating ranges at new site CPP 确认，在新场所的设备操作范围 • Suppliers 供应商 • Personnel 人员 • New Site state of compliance 新场所的合规状态 Technology Transfer Strategy: 技术转移策略： • Product and Process Description (as designed from Stage 1,and reported in Development Report and Validation Reports) 产品和工艺描述（如阶段 1 所设计的，在开发报告和验证报告中有所报告） • Assessment of Site Change Regulatory Requirements: Post-Approval, with rationale 场所变更法规需求评估：批准后，并附理由 • Number of batches required to meet transfer requirements, including validation/PPQ strategy/Matrix Approach 满足转移需求所需的批次数目，包括验证/PPQ 策略/矩阵方法 • Specifications and Methods Transfer Plan	

Process Validation Lifecycle Stage **工艺验证生命周期阶段**	**Activities** **活动**	**Knowledge Development/Data** **知识开发/数据**	**Application** **应用**
		质量标准和方法转移计划 • Validation Plan & Control Strategy 验证计划和变更策略	

Figure 6.4-1 Distribution of Technology Transfer Activities throughout the Product Lifecycle
图 6.4-1 产品生命周期期间的技术转移活动分布



TT：技术转移

6.5 Knowledge Management
知识管理

The effective and efficient capture and analysis of process-related information is essential to process understanding and validation. Information that supports process validation should be identified, analyzed, communicated, maintained, and available. It is important to recognize that knowledge management is not just data collection. It involves a strategic, systemic, and methodical approach that should include the acquisition of data at pivotal process steps, rigorous data analysis, easy access, and controlled storage and dissemination of information about the product, process, and components. All desired or necessary activities should be included, for example:
有效果且有效率的获取和分析工艺相关信息对于工艺理解和验证是非常重要。可以支持工艺验证的信息应进行识别、分析、交流、保留并可获得。很重要的一点是需要意识到，知识管理不仅是数据采集。这是一种具有策略性、系统性以及有序性的方法，应包括在关键工艺步骤数据的采集、严谨的数据分析、容易获得以及产品、工艺和组方有关信息的受控保存和传发。所有要求的或必要的活动均应包括在内，例如：

- Technology transfers
  技术转移
- Process understanding
  工艺理解
- Product characterization
  产品特性

Knowledge management includes systems that capture review and feedback information in an effort to ensure correct decisions were made, and identify where process improvements can be implemented. Sources of knowledge include, but are not limited to:
知识管理包括了能捕获回顾和反馈性信息的各种系统，来努力保证决策的正确性，并可以识别出在哪些方面能够实现工艺改进。知识源包括但不限于：

- Prior knowledge (public domain or internally documented, such as similar processes)
  已有知识（公开发表的文献或内部文件，例如类似工艺）
- Pharmaceutical development studies
  药物开发研究
- Technology transfer activities
  技术转移活动
- Process validation studies over the product lifecycle
  产品生命周期内的工艺验证研究
- Manufacturing experience
  生产经验
- Risk assessments
  风险评估
- Continual improvement
  持续性改进
- Change management activities
  变更管理活动

The concept of sustainable and continually improved knowledge systems is essential to a lifecycle process

validation program. The flow of information from Stage 1 Process Design to Stage 2 Process Qualification and back from Stage 3 Continued Process Verification form the basis of the lifecycle approach.
可持续性以及不断改进的知识系统的概念对生命周期工艺验证计划非常重要。基于生命周期方法，信息流从阶段 1 工艺设计到阶段 2 工艺确认，再返回到阶段 3 持续性工艺确证。

Knowledge management systems should be designed, installed, used, and maintained. They play a pivotal role in finding problems and preventing process shifts by providing feedback for continuous improvement efforts (4).
知识管理系统应进行设计、建立、使用并进行维护。这些系统可对持续性改进工作提供反馈信息，在发现问题以及避免工艺漂移方面扮演着非常关键的角色（4）。

Appropriate information must be acquired, used, and archived. It should be accurate, timely, and useful. Information should also be properly interpreted and effectively communicated.
适宜的信息必须进行采集、使用并存档。信息应为精确的、及时的并且是有用的。信息也应做以适当的解释并进行有效的交流。

Information or knowledge is gained in Stages 2 and 3 that can improve the process should be communicated back to those responsible for process design and development. The information (including responsible individuals, sampling plans, and justification) should be communicated via an appropriate tool.
在阶段 2 和 3 期间获得的可改进工艺的信息或知识应反馈回给负责工艺设计和开发的负责人员。相关信息（包括责任人员、取样计划和理由）应采用适宜的工具进行沟通传达。

Information needed to support the process validation effort should also be communicated to those responsible for monitoring and providing feedback on commercial product manufacturing. A system should be in place to provide feedback to those responsible for process design and development, to confirm the accuracy of early process design assumptions, and to improve the process where possible.
需要用来给予工艺验证活动支持的信息也应与负责对商业产品生产监控和给予反馈的人员进行交流。该系统也应在适当情况下对负责工艺设计和研发的人员给予反馈，以此来确认早期工艺设计设想的精准程度，并在可能的情况下改进工艺。

When changes are made in Stages 2 and 3, they should be communicated to all affected parties in an efficient, accurate, and timely manner. Formal Change Control procedures are a recommended and required Quality System component (4).
阶段 2 和 3 出现的变更应与所有涉及的部门和人员进行交流，交流应是有效的、精确的并且是及时的。推荐应用正式的变更控制流程并需要有质量系统元素（4）。

Transparent interaction between teams collecting data, performing risk assessments, and transferring information is essential to the process validation effort. Joint reviews between teams responsible for process development, risk assessments, and data collection should be conducted throughout the lifecycle of the process. These reviews enable the effective transfer of information from scale-up through full-scale manufacturing batches, and help to ensure that the process operates in a reliable and predictable manner.
各团队之间在收集数据、执行风险评估以及传递信息这些方面的透明化互动对于工艺验证活动是非常重要的。在整个工艺生命周期期间，负责工艺研发、风险评估和数据采集的各团队之间应当进行

节点审核。这些审核可以促进从放大到正常规模商业批次之间的信息的有效转移，并有助于确保生产工艺是在一种可靠的并是可预见的模式下进行操作。

7.0 Examples

实例（暂缺）

7.1 Large Molecule (Biotech) 大分子药物（生物技术）

An example of the three stages of process validation for a humanized IgG1 is provided in **Table7.1-1** (Stage 1), **Table 7.1-2** (Stage 2), and **Table 7.1-3** (Stage 3).

表7.1-1（阶段1）、表7.1-2（阶段2）和表7.1-3（阶段3）提供了人源化IG1工艺验证三个阶段的示例。

Table 7.1-1 Stage 1: Process Design 阶段1：工艺设计

Category 类别	**Activities 活动**	**Outputs/ Deliverables 输出/结果**	**Rationale/Examples 原理/示例**
Process Development 工艺开发	Establish TPP & QTPP 建立目标产品概况和目标产品质量概况	Humanized IgG1; TPPs and QTPPs were established. 人源化IG1；已建立目标产品概况和目标产品质量概况。 • Immunological indication; MOA (mechanism of action) requires both CDC (complement depended cytotoxicity) and ADCC (antibody dependent cell-mediated cytotox) activity; IV administration at a fixed dosage; 免疫学适应症；作用机理（MOA）包括补体依赖细胞毒性（CDC）和抗体依赖细胞介导细胞毒性活动；定量静脉注射； • Liquid formulation with concentration at 20 mg/mL, iso-osmolar solution; material provided in a single use vial with a shelf life of at least 24 months at 2-8°C. 液体配方，浓度为20mg/ml，等渗溶液；包装于一次性瓶中，2-8°C储存有效期至少为24个月。	
	Identify Critical Quality Attributes 识别关键质量属性	Presumptive CQAs (inherent attributes from the molecule that provide desired activity, purity, and safety) were identified based on prior knowledge. 根据已有知识来识别假定的关键质量属性（分子的内在特性，决定了其作用、纯度和安全性） • Potential process parameters that impact the CQAs were identified for each unit operation based on platform information. 基于平台信息识别每一工序中可能影响关键质量属性的工艺参数。	Deamidation, Aggregate, Host Cell Protein, Residual DNA, etc. 脱酰胺、聚合、宿主细胞蛋白、残留DNA等

	Define Manufacturing Process 确定生产工艺	Prior knowledge, existing risk assessments for similar molecules, and early development data were used to define, unit operations: Seed train, bioreactor, harvest, Protein A, viral inactivation, column purification 2, column purification 3, viral filtration, UFDF. In addition: 以往知识、现有对类似分子的风险评估、早期开发数据可用来定义各操作工序：种子培养、生化反应器、收集、蛋白A、病毒灭活、柱层析2、柱层析3、病毒过滤、超滤/透析滤过。 还有： • Normal Operating Ranges identified 识别正常操作范围 • Raw materials identified 识别所用原料 • Cell line characterized to show free from adventitious agents. 对细胞株进行表征，证实未受到污染 • Master and working cell banks prepared and characterized. 制备并表征主细胞库和工作细胞库。 • Analytical method development was started. 开始分析方法的开发 • Initial formulation development (liquid or frozen) was initiated. Due to ease of control, frozen was initially selected while the liquid formulation was being developed in parallel. 启动初步处方开发（液体或冻干）。根据控制的难易程序，初步选择冻干处方，同步开发液体处方 • A Process Design Summary Report was created with preliminary process information. 根据初步工艺信息，起草工艺设计总结报告。	
Process Characterization 工艺表征		• Clinical Phase 1 & 2 manufacturing: 1阶段和2阶段临床药品的生产： o Material was produced for First-in-Human studies, in a GMP facility in a 2000L bioreactor facility, using a scaled-down version of the intended commercial process. Samples were put on stability to establish expiration times. 采用商业生产工艺的缩小批量，在GMP厂房的2000L生化反应器中生产用于首次人体试验的产品。	Upstream Process Parameters: 上游工艺参数： • Viable cell density 活细胞密度 • % Viability 存活率 • Temperature 温度 • pH pH • Dissolved Oxygen 溶解氧

		取样进行稳定性考察，以确定有效期。 o Material was produced for Phase 2 in a 2000L bioreactor process using the same GMP facility. Samples were taken and used for characterization studies in small-scale equipment (satellite studies) to define the eventual commercial process. Product was analyzed for the following (at a minimum): 在同一GMP厂房内的2000L生化反应器中生产阶段2临床产品。取样在小规模设备中进行表征研究（小型试验），以确定最终的商业生产工艺。产品应至少进行以下分析： • Appearance and identity 外观和鉴别 • Purity (IEC, SEC, CE SDS, endotoxin, bioburden, impurities 纯度（ IEC、 SEC、 CE SDS、内毒素、微生物负载、杂质） • Potency 效价 o Initial product acceptance criteria based on targets were set from other molecules and early development studies. Stability studies were initiated using a subset of the release testing assays 根据其他分子和早期开发研究，基于目标建立初步产品可接受标准。采用放行测试含量检查进行稳定性研究。 o Most of the analytical methods were qualified at this stage. 在该阶段对大多数分析方法进行确认。 • Clinical Phase 3 manufacturing was performed in a different 2000L bioreactor facility. Prior to the start of phase 3 material manufacture, some of the following activities were performed 3期临床生产在另一个2000L生化反应器厂房中进行。在3阶段产品生产开始前，完成以下部分活动： o Tech transfer process was conducted to transfer the process from the Phase 2 facility to a Phase 3 facility. 进行技术转移，将工艺由2阶段厂房转移至3阶段厂房。 o Comparability study (DS & DP) protocols were generated	Downstream Process Parameters: 下游工艺参数： • Protein load 蛋白载量 • Protein concentration 蛋白浓度 • Elution buffer pH 洗脱缓冲液pH • Viral inactivation pH 病毒灭活pH • Diafiltration volumes 透析体积 • A team of scientists led the tech transfer effort by performing facility fit, generating technical reports, training of operators, and transferring of manufacturing process and associated scale-down models. 由一组科学家团队领导技术转移工作，确定厂房符合性，制订技术报告，培训操作者，进行生产工艺和相关批量缩小模型的转移。

		制订一致性研究（原料药和制剂）方案 o Batch records were created 起草批记录 o Operator training was performed 进行操作者的培训 o Primary containers were finalized 确定内包材 • After Phase 3 material manufacture, the Process Design Summary Report was updated (e.g., CQAs and CPPs, unit operations) 在3阶段产品生产后，更新工艺设计总结报告（例如，关键质量属性和关键工艺参数、各工序）	
	Quality Risk Assessment 质量风险评估	A modified FMEA was used to perform Quality Risk Assessment (QRA). A template created for similar products was used as a starting material with appropriate modifications. 采用经调整的FMEA进行质量风险评估。可采用类似产品的模板，并进行适当修改。 Using the risk assessment process: 风险评估过程： • Initial categorization of process parameters was performed 完成工艺参数的初步分类 • Initial framework for control strategy was created based on high risks identified in the risk assessment 根据风险评估中确定的高风险，建立初步的控制策略框架 • Process characterization studies were designed based on prioritization developed from risks identified in the QRA. 基于质量风险评估中风险识别确定的优先级，设计工艺表征试验 • Statistical methods involving DoEs (screening designs to full factorial) were used to understand interactions of high-risk parameters and a design space developed wherever possible. 采用包括试验设计（从筛选设计到全因子试验）的统计方法，增加对高风险参数相互作用的理解，尽可能建立设计空间	• Downstream process determined that acidic variants impacted biological activity. 下游工艺决定了酸性变体影响生物活性。 Placed tighter controls on in-process hold times to control level of acidic variants. 对中间存放时间进行严格控制，以控制酸性变体的水平。 Updated Quality Risk Assessment and the Control Strategy. Increased the concentration of final bulk to save on storage capacity 更新质量风险评估和控制策略。提高最终溶液浓度以提高储存能力。

		• Scale-down models were created and tested; some required qualification (e.g., virus clearance). In these cases, protocols were created and approved by Quality. 建立并测试批量缩小模型；部分模型要求进行确认（如病毒去除）。这种情况下，应建立方案并由质量部门批准 • Based on characterization and small-scale model studies, operating ranges for process parameters were finalized. 基于表征和小批量模型研究，确定工艺参数的运行范围 • Acceptance ranges for performance parameters were established 建立性能参数的可接受范围	
	Finalize CQAs and CPPs 确定关键质量属性和关键工艺参数	• Based on process characterization and scale-down model studies, the QRA was updated, which in several cases required re-scoring. 基于工艺表征和批量缩小模型研究，更新质量风险评估报告，有时需要重新进行评分 • In a cross-functional team, the CQAs and CPPs were reviewed and finalized. The final CQAs and CPPs were subject to approval by the Health Authorities wherever applicable. 由多部门人员组成的小组，审核并确定关键质量属性和关键工艺参数。适当时，最终的关键质量属性和关键工艺参数应得到药监部门的批准 • The control strategy was updated based on the understanding of CQAs, CPPs, process controls, and detection capabilities. 基于对关键质量属性、关键工艺参数、工艺控制和检测能力的理解，更新控制策略	
	Documenting Process Design 工艺设计记录	• The Process Design Summary Report was updated (CQAs, CPPs, unit operations, operating ranges, specifications, and acceptance criteria and controls). 更新工艺设计总结报告（关键质量属性、关键工艺参数、单元操作、操作范围、标准、可接受标准和控制措施） • A commercial manufacturing was site was identified (12K bioreactor capacity), and a team of scientist and process engineers performed a facility fit analysis to identify any gaps in equipment capabilities.	

		确定商业生产地点（12K 生化反应器的产能），由科学家和工艺工程师组成的小组进行厂房适用性分析，以识别设备能力上的差距 • Tech transfer process was initiated to the commercial site. A tech transfer risk assessment was performed to understand the high risks. Scale-down model process transfer was also started in parallel. 启动向商业生产厂地的技术转移。进行技术转移的风险评估，以进一步理解高风险。同时开始批量缩小模型的工艺转移 • Around this time, the analytical method validation was completed. 在这一时间，已完成分析方法的验证	
	Process Validation Master Plan 工艺验证主计划	• Specific validation protocols were identified. 确定特定的验证方案 • The process validation strategy and ancillary studies were described in the plan. 在计划中描述工艺验证策略和辅助研究	
Process Qualification 工艺确认	Equipment, Utilities, and Facility Qualification 设备、设施和厂房确认	• The facility fit assessment identified the requirement of a larger scale centrifuge. 厂房适用性评估中发现需要较大的离心机 • Based on user requirements and design specifications, the new centrifuge was ordered. After FAT and SAT, the equipment was commissioned and qualified. To understand the control required, a risk assessment was performed. 基于用户需求和设计标准，订购新的离心机。在完成FAT和SAT后，进行了设备调试和确认。为了理解所需控制措施，进行了风险评估。	

Table 7.1-2 Stage 2: Process Qualification (Continued) 阶段 2：工艺确认（接前文）

Category 类别	**Activities 活动**	**Outputs/ Deliverables 输出/结果**	**Rationale/Examples 原理/示例**
Process Performance	Technology Transfer and Engineering	• The transfer process used engineering runs to demonstrate that the process worked and to fine-tune the operation set points.	

Qualification 工艺性能确认	Runs 技术转移和工程运行	转移过程采用工程运行试验来证明工艺符合要求，并对操作设置点进行微调 • Two engineering runs were performed using GMP materials with draft batch production records. These runs enabled training on the new process for the operators. 采用GMP物料进行2次工程运行试验，并记录在批记录草案中。这些运行试验可用于对操作者进行新工艺的培训 • The Process Design Summary Report was updated with any changes to process parameters. 对于任何工艺参数的变更，应更新工艺设计总结报告。	
	Process Performance Qualification Readiness Assessment 工艺性能确认准备情况评估	• A checklist was used to ensure that all the processes and procedures were in place to start the PPQ process. 采用检查清单来确保已建立所有工艺和程序，以启动工艺性能确认过程 • PPQ protocols were drafted and approved. 工艺性能确认方案已起草，并得到批准 • A sampling plan that described the sample points, number of samples, statistical justification, and analytical methods was created and approved. 已建立取样计划并得到批准，内容包括取样点、样品量、统计学依据以及分析方法 • A Continued Process Verification plan was created to identify the parameters and attributes to be tested and monitored during PPQ and Stage 3 (Continued Process Verification). 建立一个持续的工艺确认计划，以识别工艺性能确认和阶段3（持续工艺确证）中需测试和控制的参数和质量属性 Some of the elements included in the plan were justification of parameters, frequency of, statistical procedures used to determine state of control, and handling of excursions. 计划中包括的部分要素是参数、频次确定的依据、用于确定是否处于受控状态的统计方法，以及超限的处理。 • A qualitative decision tool was used to determine the number of PPQ runs. Some of the	

		factors considered were: 采用定性的决策工具，确定所需的工艺性能确认试验次数。需考虑的部分因素包括： o Process variability (e.g., novel and difficult scale-up unit operations, raw material variability, age of equipment and facility, level of commercial manufacturing experience of operators, clinical manufacturing experience, robustness of control strategy). 工艺变化（例如，新的和难的工艺放大操作、原料的变化、设备和厂房的已使用年限、操作者商业水平的生产经验、临床样品生产经验、控制策略的耐受性） • The tool suggested a range of 5-6 runs for the PPQ campaign. 该工具建议进行5-6次工艺性能试验。 • Discussions with the Health Authorities are helpful and generally a proposal is submitted for the number of runs. 有必要同药监部门协商，通常会提交一个试验次数的建议。 • A similar approach was taken for DP PPQ campaign. 制剂的工艺性能确定采用类似方法 • Materials generated during the DP PPQ campaign will likely expire before approval. Depending upon company practices, one may perform one run at full scale and others at reduced (approximately 10%) scale. 在制剂工艺性能确认阶段生产的物料可能会在批准前过期。根据公司操作要求，可在正常批量运行一次，其他则采用较小的批量（大约为正常批量的10%） • Cleaning validation that is specific for the new process was performed concurrently with the PPQ runs. 在进行工艺性能确认试验时，同步进行新工艺相关的清洁验证。 • Product and process comparability was initiated with approved protocols. 根据已批准方案，启动产品和工艺的一致性研究 • A comparability plan describes the actions to be taken in the event of significant process changes (including site change). The plan describes the testing program to be used to demonstrate comparability between the Phase 3 and the commercial processes.	

		一致性研究计划描述了在重大工艺变更（包括生产地址的变更）时应采取的行动。该计划描述了3阶段和商业生产工艺间一致性研究的测试计划。	
	PPQ campaign 工艺性能确认连续批次	• The qualification lots were scheduled in advance of the targeted submission date to allow for sufficient real-time stability data in the application. 在目标申报日期前计划好确认批次，以获得足够实时稳定性数据。 • PPQ campaign was conducted as per the protocols. 按照方案进行工艺性能确认连续批次的生产 • The PPQ was concluded to be successful after all the acceptance criteria were met. By meeting the statistically-derived acceptance criteria, the process was demonstrated to be in a preliminary state of control. The demonstration of state of control will continue into Stage 3. 当符合所有可接受标准，则工艺性能确认成功。符合基于统计学建立的可接受标准，证明工艺处于初步控制状态。处于受控状态的证明应持续至阶段3。 • The PPQ reports were generated and approved. 工艺性能确认报告起草和批准 • The Process Design Summary Report was updated appropriately. 适当更新工艺设计总结报告	In general, Health Authorities require 6 months of real-time stability data at the time of submission. 通常药监部门要求申报时提交6个月的稳定性数据 • Any excursions were handled according to the established procedures. 按照已建立的程序处理任何偏离 • Additional sampling is performed for all the runs in the event of an unforeseen incident, which would have compromised the initial PPQ runs. 当非预期时间可能对首次工艺性能确认产生不利影响时，应进行额外取样检测。
	Stability 稳定性	• Three lots of DS and DP from the PPQ campaign were put into the stability program. 工艺性能确认批次各取三批原料药和制剂进行稳定性考察 • Multiple freeze and thaw cycles of the DS were also included in this study. 原料药的多次冻融循环也应包括在该试验中。	• In addition to real-time testing and the designated storage temperature, stability at accelerated conditions is performed per ICH guidelines. 除了实时测试和指定储存温度，加速条件稳定性试验应按照ICH指南进行 • The stability program also includes a comprehensive study in which the DS is held at its longest expiry and then used to prepare DP vials, which will are also

			held for the entire expiry time. 稳定性计划还应全面研究：将原料药放至最长储存期，再用来生产制剂，制剂也应存放至最长有效期。 • In addition to the primary stability data obtained during the PPQ runs, supportive stability data acquired during clinical development is also used in the submission package. 除了工艺性能确认批次中获得的基本稳定性数据，在申报资料中还应包括临床开发获得的支持性稳定性数据。

Table 7.1-3 Stage 3: Continued Process Verification 阶段 3：持续工艺确证

Category 类别	**Activities 活动**	**Outputs/ Deliverables 输出/结果**	**Rationale/Examples 原理/示例**
Continued Process Verification 持续工艺确证	Process Monitoring 工艺监控	• The CPV plan that was developed prior to start of the PPQ was submitted to the Health Authorities. 在将工艺性能确认提交给药监部门前，建立持续工艺确证计划 • Testing and monitoring were performed during Stage 3 according to the CPV plan. 在阶段3，按照持续工艺确证计划进行测试和控制 • CPV data review was conducted as described in the CPV plan. 根据持续工艺确证计划审核持续工艺确证数据	• Preliminary control limits were established after 15 commercial batches (including PPQ batches) were manufactured. 在完成15批商业生产（包括工艺性能确认批次）后，建立初步控制限。 • Final control limits were established

		• The monitoring reports generated supplemented the Annual Product Review. 监控报告可作为年度产品回顾的补充 • The CPV plan was used throughout the product lifecycle and helped to ensure that the process was in a state of control. 在整个产品生命周期内，使用持续工艺确证计划，确保工艺处于受控状态。	after 30 commercial batches had been manufactured. 在完成30批商业批次生产后，建立最终控制限。
	Product Technical Teams 产品技术团队	• Each commercial product had a Product Technical Team (PTT) that helped to oversee the process for the remainder of the product lifetime. 每一产品都有个产品技术团队，协助产品剩余生命周期的工艺监管 • The PTT was also responsible for reviewing data from multiple production sites to ensure consistent process performance and product quality. 产品技术团队也负责审核多生产场地的数据，以保证一致的工艺性能和产品质量	• The PTT is cross-functional, including manufacturing, process development, analytical, quality, and statistics. The team is responsible for reviewing the processing data that accumulates during commercial production. 产品技术团队由多部门组成，包括生产、工艺开发、分析、质量和统计。该团队负责审核商业生产中收集的工艺数据。 • The PTT can recommend process changes and helps to ensure continuous improvement. 产品技术团队可建议工艺变更，帮助确保持续改进。
	Specification File 标准文件	• A manufacturing process specifications file was generated at the time of the license submission. 在提交注册申请的同时，建立标准文件 • The file was updated upon approval and contained the licensed parameters that had been agreed to by the agency. 注册申请批准后及时更新文件，并应包含监管部门批准的参数。	The file is maintained throughout the product lifetime and is be updated to include in process and specification changes that might occur. 在产品的生命周期内，对标准文件进行维护，在发生中间控制和工艺变更时及时修订。

7.2 Small Molecule (Parenteral) 小分子（注射用药物）

An example of the three stages of process validation for an organic, parenteral dosage form in **Table 7.2-1** (Stage 1), **Table 7.2-2** (Stage 2), and **Table 7.2-3** (Stage 3).
表7.2-1（阶段1）、表7.2-2（阶段2）和表7.2-3（阶段3）提供了一个有机注射剂的工艺验证三个阶段的示例。

Table 7.2-1 Stage 1: Process Design 阶段 1：工艺设计

Category 类别	**Activities 活动**	**Outputs/ Deliverables 输出/结果**	**Rationale/Examples 原理/示例**
Process Development 工艺开发	Establish TPP & QTPP 建立目标产品概况和目标产品质量概况	Parenteral drug solution dosage form:, sterile formulation in three multiple strengths, intended to comply with the USP compendial requirements for injection. Target shelf life at least 24 months at 25°C. 液体注射剂：3个规格的无菌处方，应符合USP对注射剂的要求。目标有效期至少为24个月（25°C）	The product development process had no clinical trials; therapeutic strength relied on bioequivalence. Thus, clinical manufacturing experience was minimal compared to a new chemical entity. 产品开发过程未进行临床试验；治疗规格依据生物等效性确定。因此同新化学体相比，临床生产经验很少。
	Identify Critical Quality Attributes 识别关键质量属性	Active collaboration took place between R&D, development, formulators, and analytical scientists to identify potential CQAs and methods for detection. Experience with past liquid dosage form manufacturing was vital in identifying CQAs. 研发、开发、处方研究人员和分析科学家积极协作，识别潜在的关键质量属性和检查方法。以往液体制剂生产经验在识别关键质量属性时的作用重大 Assays used to release product and test methods to release API were developed and verified at Stage 1 with the intention that they would be validated and transferred to the manufacturing site to support PPQ. 在阶段1建立并确认放行制剂的含量测定和放行原料药的测试方法，以便对其进行验证，并转移至生产厂，为工艺性能确认提供支持	
	Define Manufacturing Process 确定生产工艺	Development was based on experience with previous and existing processes, excipients, and capabilities at the company's current manufacturing sites. The lab scale formulation batches were produced using identical primary packaging material. All raw materials were in the company's	Samples from these pilot batches of 400 L were analyzed and tested to narrow down formulations based on compatibility and

		GMP system. 开发是基于生产厂以往和现有工艺、辅料、生产能力的相关经验。采用等同内包装材料生产实验室规模的产品。所有原料应符合公司GMP要求。 A DoE concluded that the DP was heat-sensitive, and therefore, would be manufactured aseptically and not terminally sterilized. Followed by lab feasibility / formulation batches, the pilot scale formulation stability batches (with at least three formulation pH levels) were prepared in an R&D Pilot Plant. The solution stability due to maximum temperature during compounding, filtration, filling and its impact on DP degradation rate and impurity profile was established. 进行试验设计，因为制剂对热敏感，所以采用无菌工艺生产而不是最终灭菌。在实验室规模的可行性/处方摸索批生产后，在研发中试厂房制备中试规模的稳定性试验批（至少应有3个不同pH水平）。建立了配料、过滤、灌装最大温度对溶液稳定性的数据，对制剂降解速度和杂质分布的影响 At least two API supplier batches were considered. Intentions were to use standard and familiar unit operations and minimize the time to develop the process. The process for the formulation studies performed at pilot scale (at least 10% of commercial scale) established knowledge on process variability, CPP, and CQAs. The process scale-up parameters, manufacturing specification, analytical, and biological specifications were established through pilot scale runs. 至少应考虑2个原料药供应商批次。目的是采用标准和类似的操作工序，并将工艺开发周期降至最低。中试（至少为商业批量的10%）时处方研究的过程提高了对工艺变量、关键质量参数、以及检验报告的认识。可通过中试批生产建立工艺放大参数、生产标准、分析方法，以生物学指标。	stability due to: 对中试批量400L进行取样、分析，基于一致性和稳定性筛选处方： • Light sensitivity, 光敏性 • Oxygen sensitivity, and 样灵敏性 • Formulation pH, 处方的pH • Container material incompatibility, 容器材质的不相容性 • Manufacturing material incompatibility, 生产物料的不兼容性 • Thermal stability, 热稳定性 • Color formation, and 成色 • Any anticipated stability-limiting factors. 任何预期的影响稳定性的因素 Solution temperature controls during mixing, filling, and storage were also followed as controls. 在混合、灌装溶液时温度的控制，储存也应进行控制
		• Scale-up models for unit operations were developed. R&D personnel provided justification for the models and documented the limitations through design and stage gate review processes. 建立各工序的放大模型。通过设计和阶段审核，研发人员提供模型建立依据，并记录各种限制。 • The Process Evaluation (PE) studies were initiated prior to manufacturing of the stability batch using the bracketing approach at the scale-up production GMP manufacturing site. A total of two	Tests of the Quality Attributes included: 质量属性的测试包括： • Appearance and identity 外观和鉴别 • Purity test 纯度 • Solution pH 溶液 pH • Osmolality 渗透压浓度

		scale-up batches of highest DP concentration using active product ingredient from two different suppliers were manufactured. To establish and understand all CPP and CQA, both batches were produced at full scale. The study design was based on risk assessment accompanied by an extended in-process control program defined in protocols and product- /batch-specific sampling plans. These studies established: 在生产稳定性试验批前，在放大生产的GMP厂房采用括弧法启动工艺评价研究。总共生产2批最高浓度的放大批次，并采用2个不同供应商的原料药。为了建立并理解所有关键工艺参数和关键质量属性，2批产品的生产应采用最大批量。研究方案的设计应基于风险评估，方案中确定的一个扩大的中间控制计划，以及特定产品/批次的取样计划。这些研究建立了： o drug dissolution profile 药物溶出曲线 o degradation over the manufacturing process 生产过程中的降解 o solution filter compatibility 溶液滤器相容性 o solution hold time 溶液暂存时间 o solution closure/container compatibility. 溶液和密封/容器的相容性 • Extensive sampling and specification evaluations were conducted. Characterization and comparisons among the batches for both active ingredient and finished product were performed. The data demonstrated that the DP met the finished product specification when produced using the worst case scenario. 进行全面取样和标准评价。完成了原料药和制剂生产批次的表征和比较。数据显示当采用最差条件生产时，制剂能够符合成品质量标准。 • Research personnel were primarily responsible for these batches, but manufacturing site personnel were also involved. 研发人员是这些批次的第一负责人，但生产人员也应参与。	• Dissolution profiles 溶出曲线 • Process impurities 工艺杂质 • Particulate matter 颗粒性物质 • Microbiological attributes 微生物特性 • Sterility assurance levels 无菌保证水平 These studies established CPPs: 这些研究建立了关键工艺参数： • RPM 转速 • Temperature 温度 • Dissolved oxygen 溶解氧 • Mixing time 混合时间 There were 10 sampling points throughout the PE batch of 2800 L during filling. These encompassed multiple (e.g., triplicate) samples at the beginning, middle, and end of the process step. This approach is patterned after other heterogeneous system sampling practices, such as the FDA's bulk powder blend sampling schemes. 在2800L灌装过程批次工艺评价中，有10个取样点。包括生产过程开始、中间和结束的多个样品（如一式三份样品）。这种方法是根据其他非均一系统取样操作（如FDA粉末混合取样计划）建立。
	Quality Risk Assessments	Formal risk assessments were performed during development. The scope was limited to the manufacturing risks of the product and processes. An approval of this document indicated that the	Risk Ranking and Filtering (RRF), which included severity and probability

	质量风险评估	residual risks and associated risk scores with development DOE activities were acceptable to process with an entry into the stability design phase. Well after Stage 2, other formal risk assessments were conducted during Stage 3 and during a long and successful commercial manufacturing phase. This included linking the worst case scenario for various operations, which aided in the development of the design space. 在开发时进行了正式的风险评估。评估范围限制在产品和工艺的制造风险上。该文件的批准表明开发试验设计活动的残留风险和相关的风险评分是可接受的，并进入稳定性设计阶段。在阶段2后，在阶段3以及后期商业生产中进行其他正式风险评估。这包括将最差条件与各操作相关联，这有助于建立设计空间。	components, was used. This is a simpler tool to understand; it enabled focusing on the most important factors. Other tools used were FMEAs and Cause and Effect diagrams. 采用风险排序和过滤，包括严重性和可能性。这是个更易理解的工具；它关注于最重要的因子。其他工具包括故障模式和影响分析、因果图。
Process Characterization 工艺表征		Unit operations were optimized to improve efficiency and robustness. Using experimental and scale-up studies, scientists were able to establish scale-up process parameters and perform evaluations prior to stability runs. 对各工序操作进行优化，提高效率和耐受性。采用试验和放大研究，科学家能够建立放大工艺参数，并在稳定性批次生产前进行评价。 Improvements in the process included enhancing immediate dissolution through solution mixing process optimization, in-tank solution pH, and a dissolved oxygen monitoring system. Process characterization or evaluation studies were designed using a DOE approach to minimize experiments. There were numerous research and scale-up / transfer reports, along with qualification and process understanding reports. Qualification of the most critical excipients from a different vendor was performed on the full-scale drug product. 工艺的改进包括优化溶液混合工艺、罐内溶液pH和溶解氧监控系统来促进快速溶解。采用实验设计方法进行工艺表征或评价研究的设计，以减少试验量。有无数研发和放大/转移报告，以及确认和工艺理解报告。采用正常批量制剂生产对来自不同供应商的最关键辅料进行确认。	Qualified excipients were those that impacted CQAs, such as the ones that controlled pH and osmolality. 需确认的辅料为那些影响关键质量属性，如控制pH和渗透压浓度的物料。
	Finalize CQAs and	• Issues with respect to API dissolution occurred during development and scale-up due to variations	CQAs were:关键质量属性是：

	CPPs 确定关键质量属性和关键工艺参数	in raw material particle size. The scale-up process parameters for agitation and solution temperature were modified and evaluated from model calculations. Manufacturing procedure specifications were modified and evaluated to confirm finished product CQA. 在开发和放大过程中，由于原料粒径的变化，导致了原料药溶出问题。通过模型计算，对放大工艺搅拌和溶液温度的工艺参数进行了调整和评价。对生产工艺进行了修订和评价，进一步确认成品的关键质量属性。 • CQAs for the solution product were identified early in development, refined during Stage 1, and implemented as final specification in the manufacturing procedure. These generally inherent attributes from the molecule and formulation provided desired activity, purity, and safety. The review and approval of the CQAs was performed by a dedicated team and documented in a formal report. The process parameters that impacted the CQAs were identified in PV protocols and their criticality determined from results of the PV studies. 液体产品的关键质量属性在开发阶段已进行了识别，在阶段1进行了改进，并作为生产程序中最终标准执行。这些分子和处方的内在属性提供了预期的活性、纯度和安全性。由指定团队进行关键质量属性的审核和批准，并有正式报告。在工艺验证方案中对影响关键质量属性的工艺参数进行了识别，并根据工艺验证研究结果确定了其关键程度。	• Solution pH 溶液 pH • Dissolved oxygen 溶解氧 • Drug dissolution and homogeneity 药物溶出和均一性 • Process (i.e., drug) impurities 工艺杂质 • Drug concentration (potency) 药物浓度（效价） • Osmolality 渗透压浓度 • Microbiological attributes 微生物特性 • Sterility assurance levels 无菌保证水平
	Documenting Process Design 工艺设计文件	• Analytical methods were not validated for PE/demonstration batches; however, they were validated and transferred from R&D to manufacturing sites prior to stability batch production at a GMP site. Factors included specificity, forced degradation, precision, linearity, LOD/LOQ, accuracy, and robustness. 对于工艺评价/示范批，不进行分析方法的验证；但是在稳定性批次生产前应进行验证并从研发转移至生产厂。内容包括专属性、强制降解、精密度、线性、检测限/定量限、准确度和耐受性。 • Scientists were encouraged to write technical reports that summarized different aspects of the process. In general, they focused on a single unit operation, describing changes and improvements. A technical review reference document was also prepared. It summarized all of the developmental reports covering methods, ranges, conditions, and knowledge of the entire process.	Analytical methods were dependable but not validated initially since: 分析方法是可靠的，但没有进行最初验证，因为： • The knowledge-gathering phase with experimental batches early in the lifecycle were carried out 在生命周期的早期已完成试验批的知识收集 • Draft specs were used and case changes made in the ranges

		鼓励科学家起草技术报告，总结工艺的不同方面。通常他们专注于单个一个工序，对变更和改进进行描述。还应起草技术审查的参考文件。它总结了所有开发报告，涵盖整个工艺的方法、范围、环境和知识。 • The documents are updated each time significant process changes occur. The technical review reference document and associated specifications and procedures are filed in a central archiving system, and are then used by manufacturing for generation of batch production records. 当重大工艺变更发生时，应对文件进行更新。技术审查参考文件、相关标准和程序集中归档，并用于批生产记录的制订。	采用草案标准，变更在范围内 • Saving on timeline of analytical method validation at this stage 节省了在该阶段方法验证的时间 Upon site transfer, lab analysts will be present for method validation according to internal SOPs. These will also meet ICH Q2, USP or other regulatory or compendial standards. 在方法转移时，实验室化验员需按照内部SOP进行方法学验证。也许符合ICH Q2、USP或其他法规/或药典标准
	Process Validation Master Plan 工艺验证主计划	Developed a detailed Validation Master Plan (VMP) that identified specific studies to be performed. Individual Process Validation protocols were written for each batch. The PPQ batches were completed just before the expected NDA approval. 建立详细的验证主计划，识别需进行的特定验证活动。各产品均起草相应的工艺验证方案。工艺性能确认批应刚好在预期的新药批准之前完成。 • In addition to new process validation studies, the plan identified studies and appropriate references that had been executed for other projects, but would be used to support this product. 除了新工艺的验证试验，主计划还识别了其他项目已采用的研究和适当参考，但能对这一产品提供支持。	The process validation plan was initiated prior to Stage 2 to identify supportive information needed from Stage 1. However, the formal Validation Master Plan was finalized during Stage 2, when all attributes, parameters, and systems were known. 工艺验证计划应在阶段2前起草，确定所需的来自阶段1的支持性信息。但正式的验证主计划在阶段2确定，这时已经知道了所有特性、参数和系统。

Table 7.2-2 Stage 2: Process Qualification 阶段 2：工艺确认

Category 类别	**Activities 活动**	**Outputs/ Deliverables 输出/结果**	**Rationale/Examples 原理/示例**

Process Qualification 工艺确认	Equipment, Utilities, and Facility Qualification 设备、设施和厂房确认	The extent of the qualification and verification of the equipment was based on risk assessment. The critical aspects (e.g., critical functions, controls, and attributes) and other system components or functions were verified to be fit for their intended use. Equipment and utilities had to be in qualified states of their own for any product used. This activity was carried out according to plant procedures to maintain a state of control. 设备确认和确证的范围应基于风险评估。关键方面（如关键功能、控制和特性）和其他系统组件或功能经证实符合预定用途。设备和设施应处于确认状态。这应根据工厂的程序进行，以保持受控状态。 Qualifications and calibrations were confirmed. Any system for which proper operation was fully ensured through routine calibration and/or preventive maintenance programs may not have required formal qualification. 对确认活动和校准进行确认。对于通过日常校准和/或预防维护计划确保正常运行的任何系统，可能不需要进行正式确认。	Qualification was performed for: 对以下进行确认： • Agitator mixing speeds 搅拌混合速度 • Sensors, such as level, volume, and temperature measurements 感应器如液位、体积和温度测量 • In-tank pH measurements 罐内pH测量 • Oxygen measurements 氧测量 • Solution filling system 溶液灌装系统 • Storage chambers (frozen). 冷冻储存箱
Process Performance Qualification 工艺性能确认	Technology Transfer and Engineering Runs 技术转移和工程运行	• Manufacturing, analytical, and biological procedure specs were transferred to the manufacturing site based on process evaluation batch results. 根据工艺评价批结果，将生产、分析和生物程序转移至生产厂 • Three stability batches of DP strength were produced at 10-15% of commercial batch volume. 以10-15%商业批量生产3批稳定性制剂 • Three different batches from various API suppliers were factored in (matrix approach) among all stability batches. One batch with the highest strength per API supplier was performed using the worst case scenario for CPP (e.g., solution hold-time). Stability studies were initiated using tank release, in-process testing, and finished product release testing assays. 所有稳定性批次需采用三批来自不同供应商的原料药（矩阵法）。其中规格最高的一批采用最差工艺条件（如，溶液暂存时间）生产。稳定性研究采用配液罐放行、中间控制测试和成品放行的含量测定。 • Analytical and microbiological methods were validated. Assays were performed by a dedicated stability operations group. Long term stability studies for the aforementioned batches at 2-8° C/60%	The demonstration batch included verifying: 验证批应确认： • Solution mixing process 溶液混合工艺 • Filling process 灌装工艺 • Sterilization process (as applicable) 灭菌工艺（适当时） • Packaging and confirmation of finished product meeting final specifications. 包装并确认成品符合最终质量标准 For the registration, the different suppliers provided matrix; everything else in the process remained the same. 注册时，采用矩阵法考察不同供应商的影响，其他均保持不变。

		RH; 30° C/65% RH and 40° C/75%RH were initiated. For one batch of each strength, stability data were generated for the products, which were stored in an inverted orientation. A formal stability plan was prepared prior to entering stability production, and was issued prior to submission. Formal stability production protocols were issued for each code prior to stability production. 对分析和微生物方法进行验证。含量测定由专门的稳定性检测小组完成。以上批次长期稳定性考察条件为 温度2-8° C/相对湿度60%；同时进行温度30° C/相对湿度65% 和温度40° C/相对湿度75%的试验。各产品的每一规格，应进行一批稳定性试验，并应将稳定性样品倒置存放。在进行稳定性生产前，制订正式的稳定性计划，并在提交申报资料前发布。在稳定性生产前，发布正式的稳定性考察方案。 • A full-scale commercial 'demo" batch was followed by multiple PPQ batches at a manufacturing facility for launch quantities 在正常商业批量的预验证批后，在生产厂进行多批工艺性能确认批上市产品的生产。	PPQ batches verified the same process parameters and quality attributes used in the demonstration (pre-validation) batch. 工艺性能确认批对示范批（预验证批）中相同工艺参数和质量属性进行了确认。
	Process Performance Qualification Readiness Assessment 工艺性能确认准备情况评估	• Sites for the commercial production process were identified in Stage 1. Readiness for PPQ was confirmed at 'Stage gate' meetings. 在阶段1确定商业生产场地。并在"阶段总结"会议上确认工艺性能确认的准备情况。 PPQs runs took place under nominal, routine conditions 工艺性能确认批在常规条件下生产。	Ensure finalization of: 最终确定： • Specifications 生产标准 • Previous reports (e.g., Formulation, PE) 以往报告（如处方、工艺评价） • Equipment and facility qualifications 设备和厂房确认 • Previous batches done at worst case scenario 最差条件生产的批次 • The readiness of other items, (e.g., labeling 其他事项（如贴签）的准备情况。
	PPQ campaign 工艺性能确认	Material requirements to support commercial runs determined the number of runs for the campaign. The DP PPQ campaign consisted of 5 runs, covering 3 batches with highest strength, 1 batch with mid-range strength, and 1 batch with the lowest strength of finished product made at the	• Solution Mixing step: Time, Temp., dissolve oxygen, agitator speed, solution homogeneity by drug assay, and pH–

		commercial production scale. Additional sampling was performed for all the runs. All runs that meet commercial release criteria could be used to support commercial supply. All PPQ batches were performed at nominal conditions. 商业生产用物料的要求决定了工艺性能确认的批次。制剂的工艺性能确认共有5批，包括最高规格的3批、中间规格的1批，以及最小规格的一批，均采用商业生产批量。所有批次都进行了额外取样。所有符合放行要求的批次都可上市供应。所有工艺性能确认批次都在正常条件下生产。 • Hold study was performed on one of the three highest strength product batches to establish and validate hold intervals for solution mix, fill, and hold prior to sterilization (as applicable). 用规格最大的1批进行暂存时间研究，以建立并验证溶液混合、灌装和灭菌前存放的时间间隔（适当时） • Data report of initial analysis of the variation of outputs such as quality and performance attributes in stages 1 and 2 对输出变量进行初步分析的数据报告，如阶段1和2中质量和性能特性 • Cleaning validation that was specific for the new process was performed concurrently with the PPQ runs. 特定新工艺的清洁验证与工艺性能确认同步进行。	mixing validation 溶液混合步骤：时间、温度、溶解氧、搅拌速度、通过含量测定确定的溶液均一性，以及pH-混合验证 • Sterile fill or terminally sterilized finished product testing: finished product assay, degradation and impurities, pH, particulate, microbial and sterility testing. 无菌灌装或最终灭菌产品的测试：成品含量检查、降解和杂质、pH、粒子、微生物和无菌测试 The number of batches in the entire process validation Stages 1 and 2 were: 整个阶段1和阶段2验证批次数量： • 3-6 feasibility batches 3-6批摸索批 • 3-6 formulation batches 3-6批处方筛选批 • 1-2 PE batches 1-2批工艺评价批 • 3 stability batches 3批稳定性批 • 5 PPQ batches 5批工艺性能确认批 Data were analyzed for the total of both stages. 对2个阶段的数据进行分析。 A slight variation in the number of development and PPQ batches can depend on dosage strengths, complexity of formulation and process, and results of PE and stability batches.

			根据产品规格、处方和工艺复杂程度以及工艺评价和稳定性批的结果，开发和工艺性能确认批次数可略做变动。 Five batches provided 3 at worst-case of most concentrated conditions. Lower concentrations were confirmed with 2 batches. 5批中有3批为高浓度（最差条件）。低浓度工艺采用2个批次进行确认。 Timing of PPQ batches were scheduled in advance of the targeted NDA submission date to allow for initial data in the application. In this case, 1 month of real-time and accelerated stability data was available. This led to the respective start of the DS and DP PPQ runs 12 and 9 months prior to the anticipated approval date. PPQ batches were thus able to be commercialized. 在预计新药申请提交日前做好工艺性能确认批的生产计划，确保申报中包含早期数据。这种情况下，有了1个月的长期和加速数据。这样可以在预期批准日前12和9个月分别开始原料药和制剂的工艺性能确认批生产。这样工艺性能确认批就可以上市销售了。
	Stability	All batches of DP from the PPQ campaign were put into the stability program. In addition to	

	稳定性	real-time testing and the designated storage temperature, stability at accelerated conditions was performed per ICH guidelines. In addition to the primary stability data obtained during the Stage 1 runs, supportive stability data acquired during PPQ runs was also used in the submission package on an as-needed basis. 工艺性能确认的所有制剂批次均进行稳定性考察。除了长期测试和指定储存温度外，还要按照ICH指南进行加速条件试验。除了阶段1获得的基本稳定性数据，需要时，在工艺性能确认中获得的支持性稳定性数据也用于申报资料中。	

Table 7.2-3 Stage 3: Continued Process Verification 阶段 3：持续工艺确证

Category 类别	**Activities 活动**	**Outputs/ Deliverables 输出/结果**	**Rationale/Examples 原理/示例**
Continued Process Verification 持续工艺确证	Process Monitoring 工艺监控	A process monitoring plan and trending were developed during the commercial phase. The monitoring plan was used during routine manufacturing to help ensure that the process remained in a state of control. The process capability metric and trend analysis were performed with positive outcomes. 在商业生产阶段，建立工艺监控计划并进行趋势分析。监控计划用于日常生产中确保工艺处于控制状态。过程能力指标和趋势分析结果良好。	• Performance metrics (e.g., yields, complaints, and deviations) continued during commercial production. 在商业生产阶段进行监控性能指标（如收率、投诉和偏差） • Process robustness contour plots are used when the number of data points is small (e.g., less than 20-25). Process performance capability indices, such as PpK and /or CpK, are used for 25 or greater data points. 当数据量少时（如低于20-25），采用工艺耐受等高线图。当数据量不低于25时，采用工艺性能能力指标，例如过程性能指数和/或过程能力指数。
	Product Technical	Each product has a Product Technical Team (PTT) that helps to oversee the process for the	Additional studies, including PAT, DOEs,

	Teams 产品技术团队	remainder of the product's lifetime. 每一产品有产品技术团队，协助对剩余产品生命周期的工艺进行监管。 The PTT is cross-functional, with representatives from manufacturing, process development, analytical, quality, and statistics. The team is responsible for reviewing the processing data that accumulates during commercial production. It can recommend process changes and help ensure continuous improvement. The PTT is also responsible for reviewing data from multiple production sites to ensure consistent process performance and product quality. 产品技术团队由多部门组成，包括生产工艺开发、分析、质量和统计部门的代表。该团队负责审核商业生产收集的工艺数据。对工艺变更提出建议，确保持续改进。产品技术团队也负责审核不同生产场地的数据，确保一致的工艺性能和产品质量。	continuous processing experiments, and clinical studies were carried out in a long Stage 3 to improve the product line. 在阶段3进行其他研究，包括过程分析技术、试验设计、持续工艺试验和临床研究，以改进生产线。
	Specification File/NDA Supplements 标准文件/新药补充申请	Numerous supplements to the registrations were made to add new manufacturing and testing facilities. Transfers and process validations were carried out during Stage 3. Manufacturing knowledge documentation files generated at the time of development are updated regularly with all pertinent studies. 增加新的生产和检验设施，对注册文件做了多次补充。在阶段3完成工艺转移和工艺验证。根据相关实验，定期更新开发时产生的生产知识文件。 Critical quality attributes and parameters have been agreed to by the development and quality organizations. The process understanding file is maintained throughout the product lifetime and is updated to include any process and/or specification changes. 开发和质量部门一起确定关键质量属性和参数。在整个产品生命周期内，对工艺理解文件进行维护、更新，以涵盖任何工艺和/或标准变更。	

8.0 Appendices
附件

8.1 Appendix 1: Statistical Methods for Determining the Number of Lots
附件 1：决定批数量的统计学方法

Listed below are statistical approaches used to determine the number of lots that may be required at the PPQ stage. Other approaches may also be suitable. As there is no standard industry approach to statistically determine the number of lots, multiple options are offered. This section will provide applied statistical methods for determining the number of lots. It will also stimulate further discussion on this issue. Regardless of the number of lots selected and the acceptance criteria used, the data collected during PPQ as well as CPV should be statistically analyzed to help understand process stability, capability, and within (intra-) and between-lot (inter-lot) variation.

下面列举的是在 PPQ 阶段用于决定批次数量的统计学方法。除此之外的方法当然也可能适用。因为行业中并没有从统计学上决定批次的数量的标准方法，所以其他多种方法同样可以提供。本章节将提供决定批次数量实用的统计学方法，并鼓励在这个方面更加深入的讨论。无论选择的批次数量以及采用的可接受标准是多少，PPQ 中收集的数据都应进行统计分析以帮助理解工艺的稳定性、工艺能力以及批内和批间的变化。

8.1.1 Average Run Length (ARL) to detect a p×100% lot failure rate
用以检测批失败率（p×100%）的平均运行长度（ARL）

The average number of lots until the first lot failure is ARL =1/p. where p is the lot failure rate that is important to detect.

直到出现第一批失败的平均批数量（ARL）=1/p,其中 p 为批失败率，检测出 p 是很重要的。

Example: A lot failure rate of 20% is deemed unacceptable for a given process. A lot failure rate of 20% would be detected on average in 1/0.2=5 lots.

例子：往往一个工艺出现20%的批失败率是被认为不可接受的。而20%的批失败率可以从平均1/0.2=5批中被检测出。

Common choices for p would be 25%, 20%, 10%, and 5%, depending on the other factors given earlier (e.g., prior knowledge, risk, production rate) Five (5%) would generally be the tightest value to consider since a process running right at the Acceptance Quality Limit is still expected to have a 5% lot rejection rate. If applicable, this approach can also be used to determine the number of lots to use with tightened sampling during CPV (continued process verification). It may be particularly useful when there are many quality attributes to assess. Rather than determine the number of lots required separately for each attribute, the PPQ stage is complete when all attributes pass for the required number of lots.

通常 p 的取值可以有 25%，20%，10%和 5%，其取决于早期的因素（比如已有的知识、风险、生产率）。一般 5%的 p 值被认为是最严格的取值，因为即使此工艺在可接受质量限度中运行正常，但其仍有 5%批的废品率。如果合适的话，这个方法也可以用于在 CPV（持续的工艺确证）中以决定加强取样的批次的数量，特别当工艺有许多质量属性可以评估时非常有用。当要求的数量的批次所有属性均通过时，PPQ 阶段才是完整的，而不是针对每一个属性来决定批次的数量。

8.1.2 **Range** of between-lot (inter-lot) variation expected to be covered in n_L lots

在 n_L 批中覆盖到的预期的批间变化的范围

Table 8.1.2-1 outlines the expected between-lot variation coverage in n_L lots.
表 8.1.2-1 简述在 n_L 批中预期批间变化覆盖范围

Table 8.1.2-1 Expected Between-Lot Variation Coverage in n_L lots

Expected Coverage **预期的覆盖范围**	**Number of lots n_L** **批次数量 n_L**
33%	2
50%	3
60%	4
67%	5
75%	7
80%	9
85%	12
90%	19
95%	39

Example: It is desired to represent two-thirds =67% of the between–lot variation during PPQ. The number of lots required is n_L =5 lots.
举例：如果在 PPQ 阶段要求 2/3（67%）的批间变化，那么要求的批次数量为 n_L=5 批

Expected coverage is calculated as $(n_L-1)/(n_L+1)$. This follows from the expected percentile of an order statistic being its rank divided by n+1 *(53)*. This approach does not require between-lot normality. The method may be modified to provide confidence levels of coverage instead of expected coverage. The approach may be used to determine "step-down sampling" during CPV. For example, highly tightened sampling may be used in PPQ for the first three lots until 50% coverage is reached. At that time, the PPQ is considered complete. Moderately tightened sampling for critical characteristics could continue into Stage 3 CPV for four more lots until 75% coverage is reached, at which point routine sampling begins.
期望的覆盖率计算公式为$(n_L-1)/(n_L+1)$。这公式由次序统计量百分点等级除以 n+1 推断得到。这种方法不需要批间正态。该方法可能会进行修订，即以规定覆盖率的置信水平来取代期望的覆盖率。该方法也可以用在 CPV 阶段决定"逐渐减少取样"。例如：PPQ 阶段的前 3 批需要更严格的取样直到 50%的覆盖率达到，此时，PPQ 就可以认为完成了。在阶段 3 CPV 4 批或更多批中只需要对关键特性进行中等程度的取样直到 75%的覆盖率达到，随后只需要进行日常取样。

8.1.3 Within and Between Lot Normal Tolerance Intervals
批内及批间正常公差区间

Statistical tolerance intervals are commonly used in validation. For example, a capping process may have a validation criterion of "demonstrate with 90% confidence that at least 99% of the removal torques for the lot are within specification limits." Tables of normal tolerance interval factors for variables data are widely available and also implemented in statistical software. Specialized software is available to optimally calculate the desired confidence statement. Normal tolerance intervals for the total process variation over time are more complicated; they include both within- and between-lot variation. Standard normal tolerance

interval factors assume that there is only one population in the data. However, most PPQs contain multiple populations since each lot is a separate population.
验证中普遍用到统计学公差区间。例如，轧盖工艺的一个验证标准是“证明至少 99%的批松开力矩均在标准限度且有 90%置信度”。计量型数据的普通公差区间因子在许多统计软件都可以查到并应用。可以使用专业的软件以优化计算出期望的置信区间。整个工艺变化的普通公差区间会越来越复杂，他们包括了批内以及批间的变化。标准普通公差区间因子假设数据中只有一个总体。然而，由于每一批都是一个单独的总体，因此大多数 PPQ 包括了多个总体。

If there are no significant differences between the lots, the simplest way to deal with multiple lots is to combine the data. ANOA may be used to compare lot means; within-lot variation may be compared with the Levene / Brown-Forsyth, Bartlett, Cochran, or Fmax tests (54-57). An omnibus test may also be used. If there are no significant differences between lots or if the between-lot variance component is not statistically, the standard normal tolerance interval for the combined data may be used. The sample size per lot and number of lots should be statistically determined to have adequate power to detect any between-lot variation.
如果批间无显著的差异，处理多个批次最简单的方法是合并数据。ANOA（方差分析）用于比较批均数。批内的差异用 Levene / Brown-Forsyth, Bartlett, Cochran, 或 Fmax 检验进行比较，也可以用多项混合测试。如果批间没有显著差异或批间方差分量没有统计学意义，那么就可以使用合并后数据的标准普通正常公差区间。每批的样本量以及批数量由统计学决定并足以检测到任何批间的变化。

Example: The specification for cap removal torque for a small volume parenteral (SVP) product is 8.0-12.0 inch-pounds. Limited data from Stage 1 showed a standard deviation of about 0.5. The production AQL (Acceptance Quality Limit) for removal torque is 1.0%. The acceptance criterion for the PPQ is to show with 90% confidence that at least 99% (1 minus the AQL) of the cap torques are within specifications.
举例：小容量注射剂产品的瓶盖松开力矩的标准是 8.0-12.0 英寸磅。阶段 1 有限的数据表明标准偏差在 0.5 左右。产品松开力矩的 AQL（可接受质量限度）为 1.0%。那么 PPQ 的可接受标准则为至少 99%（1 减去 AQL）的瓶盖松开力矩在指标内，置信度为 90%。

Three lots are included in the PPQ to evaluate the within- and between-lot variations. A sample size of 30 units per PPQ lot was tested to detect between-lot variation as large as the within-lot variation with 90% confidence (58). Samples were tested from throughout each of the three lots, and the acceptance criteria for each lot was met. An I/MR SPC chart indicated that the process was in control during each lot. Normality tests for each lot did not indicate significant non-normality. Since ANOVA and Levene's test showed no significant difference between the three lots, the data were combined. The 90 test results had a mean of 9.59 and standard deviation of 0.51.
PPQ 中用 3 个批次来评价批内以及批间的变化。每个 PPQ 批次用 30 个样本量来检测批间以及批内的变化，置信度为 90%（58）。取样测试始终贯穿 3 个 PPQ 批次的每一批，并且每一批都符合可接受标准。已使用 I/MR（单值-移动极差）统计过程控制（SPC）图表明每一批工艺均受控。每一批正态性检验表明没有明显的非正态性。由于 ANOVA 和 Levene 检验表明 3 批无显著差异,数据就可以合并在一起。90 个测试结果的平均值为 9.59，标准偏差为 0.51.

A 90% confidence normal tolerance interval for 99% of the population is 9.59±2.872 x 0.51=(8.13,11.05). This interval is within the specification limits of 8.0-12.0. Thus, the PPQ has shown with 90% confidence

that at least 99% of torque results are expected to meet specifications.
99%总体在90%置信度普通公差区间为9.59±2.872 × 0.51=(8.13,11.05).此区间在标准限度8.0-12.0 以内。因此，PPQ 显示至少99%的力矩有90%置信度是符合预期指标的。

If there are statistically significant differences between lots, the tolerance interval should be constructed with more advanced methods that take the between-lot variance component into account (56,57).
如果批间有着显著的统计学上的差异，应建立更先进的方法来建立公差区间，此方法应将批间的方差分量考虑在内。

8.1.4 Statistical Process Control Charts (45)
统计过程控制图（45）

Most SPC references suggest obtaining data from 20-30 time periods before calculating control limits to assess whether the process is in control. Samples could be taken at 30 time periods across three or more lots. For three lots, 10 sets of 'rational subgroup" samples could be selected from each lot. The SPC chart limits are then calculated and the process assessed for statistical control. The number of lots to use can be based on the power of the SPC chart to detect undesirable between-lot variation.
大多数的 SPC 参考文献都建议收集 20-30 组数据来计算控制限以评估工艺是否受控。可以从 3 批或更多批中取 30 组的样本。对于 3 批来说，可以将每批分为 10 组合理子群并取样。然后计算 SPC 图的限度并对工艺进行统计学控制评估。使用批次的数量就取决于 SPC 图检测到非期望的批间变化的能力。

A potential problem with the use of SPC charts, such as Xbar/S chart plotted across lots, is that they define a process as being in statistical control if there is no underlying lot-to-lot variation (**Figure 6.2.2.1-1**). This is often not the case, and some lot-to-lot variation is typical and expected, especially for lot means. In these cases, an I/MR chart for the mean and/or standard deviation or three-way between/within chart can be used to detect out-of-statistical–control between-lot variation.
SPC 图使用中会有一些问题，比如跨批用 Xbar/S 图，而该图定义了如果没有潜在的批与批变化工，那么艺处于统计学控制条件（**图 6.2.2.1-1**）。但这往往并非如此，一些批与批的变化是典型的并且是可以预料到的，特别对于批均数。对于这些情况，可以使用 I/MR 图对均值和/或标准偏差或三相间/内控制图进行统计以检测出批间不符合统计控制的变化。

If there is only one test result per lot, such as lot assay or pH of a tank of solution, the 20-30 time periods become 20-30 lots. This is seldom feasible for PPQ. An alternative is to select a smaller number of lots, perhaps 5-10, and construct a preliminary I/MR control chart. If it shows an in-control process, the PPQ would be complete and the control chart extended into Stage 3 to verify longer term statistical control during CPV.
如果每批只有 1 个测试结果，例如批含量或罐内溶液的 pH，那么 20-30 组就可以变为 20-30 批。这在 PPQ 中很少可行。另一种方法是选择小的批次数量，比如 5-10 批，然后建立初步的 I/MR 控制图。如果显示工艺受控，那么 PPQ 就是完整的并且将控制图延伸至阶段 3 以确认 CPV 中的长期统计控制。

8.1.5 P_{pk}, C_{pk} Process Capability Metrics (59)
P_{pk}, C_{pk} 工艺能力指标（59）

P_{pk} (see **Figure 6.2.2.1.3-1**) is the most common statistic used to assess long-term process capability.

Acceptable values of P_{pk} depend on the criticality of the characteristic, but 1.0 and 1.33 are commonly used. Smaller or larger values may be used depending on the risk factors involved. The P_{pk} acceptance criterion may be based on a point estimate or a one-sided lower confidence interval. If there is significant bewteen-lot variation, caution should be exercised in using confidence intervals for P_{pk} calculated by statistical software. Most statistical software programs do not take between-lot variation into account, and may provide optimistic confidence intervals that are too narrow.

在统计学上最常用 P_{pk}（见**图 6.2.2.1.3-1**）来评估长期工艺稳定性。P_{pk} 的可接受的值基于工艺特性的关键性，但一般使用 1.0 和 1.33。其他更小或更大的取值可以根据涉及到的风险因子来决定。P_{pk} 的可接受标准可以基于点估计（定值估计）或单侧较低的置信区间。如果批间有显著的变化，在用统计学软件计算 P_{pk} 使用置信区间时多加注意。大多数统计学软件程序并没有考虑批间的变化，并可能给出较宽松的置信区间，而这显然太过于狭隘了。

Example: Fill volume specification limits for a small-volume parenteral product are 98-102. PPQ acceptance criteria are that each lot's P_{pk}≥1.0; also, that the overall process P_{pk} is ≥1.0 with 95% confidence. To detect a between-lot standard deviation that is half of the within-lot standard deviation with 90% confidence, 33 units will need to be tested form across each of five PPQ lots.

举例：小容量注射剂产品的灌装体积标准限度为 98-102。PPQ 可接受标准为每次的 P_{pk}≥1.0，同时，总工艺的 P_{pk}≥1.0，置信度为 95%。为了检测出批间标准偏差，其为批内标准偏差的一半，置信度为 90%，需要从 5 个 PPQ 批次中每批取 33 个样本。

The data from the five lots were analyzed by control charts, histograms, normality tests, Levene's test, and ANOVA. These analyses indicated that the data from the five lots could be combined. Each of the five lots' P_{pk}s were >1.0. The calculated P_{pk} from the combined data was 1.14, with a lower 95% confidence interval of 1.03. Since each lot met its P_{pk} requirement and the lower confidence interval for the overall process, P_{pk} was above the acceptance limit of 1.0. Thus the PPQ acceptance criteria were met.

5 批中收集的数据使用控制图、直方图、正态性检验、Levene 检验以及 ANOVA 进行分析。这些分析表明 5 批的数据可以合并。5 批中每一批的 P_{pk} 均大于 1.0。合并后的数据计算出的 P_{pk} 为 1.14，95%下置信区间为 1.03。因为每一批均符合其 P_{pk} 要求且整个工艺的 P_{pk} 下置信区间在可接受限度 1.0 以上，所以该 PPQ 满足其可接受标准。

An alternative to calculating a parametric confidence interval for P_{pk} is to require four or five lots in a row to each meet the P_{pk} acceptance criteria. For example, four PPQ lots, each with P_{pk}≥1.0, provides over 90% confidence that the process median P_{pk} is ≥1.0. Five lots provide over 95% confidence.

另外一种计算参数 P_{pk} 置信区间的方法是要求连续 4 批或 5 批并且每一批均符合其 P_{pk} 可接受标准。例如，4 个 PPQ 批次，其中每一批 P_{pk} 均≥1.0，工艺中值 P_{pk}≥1.0 的置信度在 90%以上。5 批的置信度则在 95%以上。

8.1.6 Assure The Lot Conformance Rate is Above An Acceptable Rate With Specified Confidence 确保批合格率在可接受标准之上并具有规定的置信度

This approach demonstrates that the percent of lot conformance is acceptable. It identifies unacceptable variation due to either common or special causes. **Table 8.1.6-1** shows the required number of conforming lots. This method is sometimes called "confidence for reliability."

该方法证明批合格率是可接受的。其识别出由于常见或特定原因导致不可接受的变化。表 8.1.6-1 展示了需要的证明合格的批次数量。该方法有时也称为“可靠性置信度”。

Table 8.1.6-1 Number of lots to demonstrate confidence for lot conformance rate
表 8.1.6-1 证明批合格率置信度的批次数量

Confidence 置信度	Conformance Rate 合格率	Accept # 接受#	n 数量
50%	90%	0	7
	95%	0	14
	99%	0	69
90%	90%	0	22
	95%	0	45
	99%	0	230
95%	90%	0	29
	95%	0	59
	99%	0	299

Example: To demonstrate the process is acceptable, the PPQ acceptance criterion will be show with 90% confidence that the process lot conformance rate (the lot pass rate) is at least 90%. A total of 22 passing lots in a row will demonstrate this.
举例：为了证明工艺是可接受的，PPQ 的可接受标准必须要求工艺批合格率（批通过率）至少达到 90%，置信度为90%。那么连续 22 批合格批次即能证明这点。

Requiring such a large number of lots during PPQ to reach 90% or 95% confidence is difficult. An alternative is to use 50% confidence in PPQ and monitor the process further during CPV to reach the final desired confidence. Crossing the 50% confidence threshold is the point at which it is more likely that the selected lot conformance rate is met. For the example above, once 7 passing lots are reached, it is more likely that the conformance rate is greater than 90% rather than less than 90%, and the PPQ could be considered complete. An additional 15 lots during early CPV would reach the required 22 lots. This approach may be particularly useful when there are many quality attributes to assess. Rather than determine the number of lots required separately for each attribute, the PPQ stage is complete when all attributes pass for the required number of lots.
在 PPQ 中达到 90%的置信度需要大量的批次，但实际上是很困难的。另外一种方法是 PPQ 中使用 50%的置信度，在 CPV 中进行更进一步的监测并最终达到期望的置信度。置信度阈值若是 50%，那么所选批合格率更有可能满足。就上面来举例：一旦达到 7 批通过批次，批合格率更有可能大于 90%而不是低于 90%，那么 PPQ 就认为是完整了。在 CPV 早期阶段增加 15 批即达到了要求的 22 批。该方法可能特别适用于需要评估的质量属性有很多的情况。只有当要求数量的批次的所有质量属性均合格，PPQ 阶段才算是完整的，而不是对每一个属性进行单独的判定。

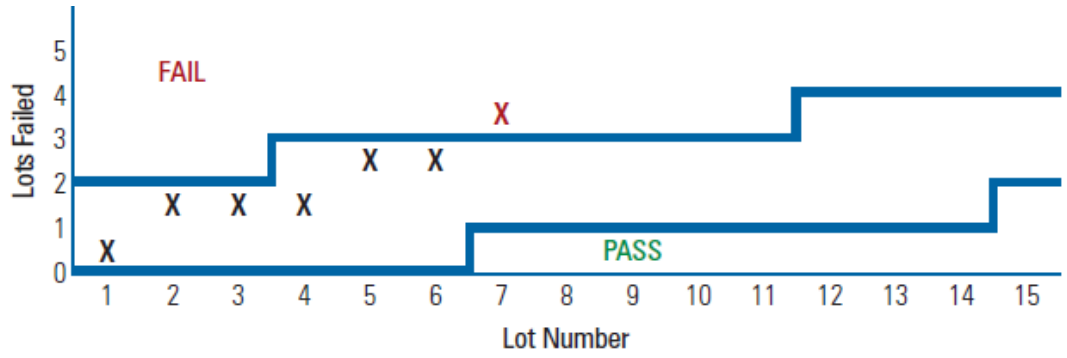
8.1.7 Wald Sequential Probability Ratio
瓦尔德序贯概率比

Wald's sequential probability ratio (SPR) test can be used to determine when a suitable number of PPQ lots have been made for decision-marking. No fixed number is specified in advance; the PPQ continues until either the failure or pass decision line is crossed. The SPR test is most often used for percent of passing units or lots, but it can also be used for other statistics as well as for CPV to determine when to revert to

normal sampling. An example is shown in **Figure 8.1.7-1.**
瓦尔德序贯概率比（SPR）检验可以用于决策时决定合适的 PPQ 批次数量。不事先规定总的抽样个数；PPQ 持续到超过失败或通过决策线。SPR 检验大多数用于合格单位或批次的百分比，但其同样也可用于其他统计学资料，比如在 CPV 中决定何时将取样强度恢复到普通。举例见图 8.1.7-1。

Example: A 5% lot failure rate is considered minimally acceptable, while a 25% lot failure rate is not acceptable. The SPR decision chart below was made using α=0.05, β=0.2, p_1=0.05, p_2=0.25. The failure decision line was crossed at lot 7; the PPQ failed due to too many lot (3 in 7) failures.
举例：5%的批失败率可以认为是最低可以接受的，而 25%的批失败率则是不能接受的。下面的 SPR 决策图中，α 取 0.05，β 取 0.2，p_1 取 0.05，p_2 取 0.25。第 7 批超过失败决策线。PPQ 失败，因为太多失败批次（7 批中有 3 批）。

Figure 8.1.7-1 Wald's Sequential Probability Ratio Example
图 8.1.7-1 瓦尔德序贯概率比举例



8.1.8 Narrow Limit Gauging
窄界限估计

Narrow limit gauging can be used to reduce the sample size or number of lots required in PPQ. The basic idea is to use narrowed pseudo-specification limits during PPQ to obtain more statistical power. An example is case in which the assay specification for an active ingredient in a solution is 95-105, and only one assay result is determined per lot. If five lots all are within narrowed limits of 97.5-102.5, this gives the same confidence as a larger number of lots being within the unadjusted 95-105 specification limits in detecting the lot nonconformance rate (see Farnuma and Stantona for calculation details) (57).
窄界限估计法可以用于在 PPQ 中减少样本大小或需要的批次数量。基本的想法是在 PPQ 中用窄的伪标准限度以获得更多的统计功效。一个实例是某个活性成分溶液的分析指标为 95-105，并且每批判定一个分析结果。如果 5 批均在窄限 97.5-102.5，那么这和在检测批不合格率中指标限在 95-105 的更大数量批次具有相同的置信度。（具体计算见 Farnuma and Stantona）（57）。

One form of narrow limit gauging is called PRE-Control. It is often used as a QC procedure for fill volume. If 5 units in a row fall in the middle 50% of the specification limit, then the lot is qualified for startup. This concept can be extended to quality characteristics (e.g., lot assay, pH)) where there is one result per lot. For an assay specification of 95-105 for an active ingredient, the PRE-Control narrow limits would be 97.5-102.5. If five PPQ lots in row meet the 50% narrow limits, then the PPQ is complete. Note that the narrow limits are not used to determine lot acceptance, but only to determine whether the PPQ acceptance criteria are met.

窄界估计另一种形式也叫预控制法。常用于 QC 规程中检查灌装量。如果连续 5 个单位均落在标准限度的中间 50%以内，那么该批就可以启动了。这个概念可以延伸至每批只有一个结果的质量特性（例如批含量、pH）。对于含量指标为 95-105 的活性成分，预控窄界限可以是 97.5-102.5。如果连续的 5 批 PPQ 批次符合 50%的窄界限，那么 PPQ 就完整了。注意，窄界限并不用于决定批可接受标准，只用于决定是否符合 PPQ 的质量标准。

8.1.9 Demonstrate Between-Lot Variation is Less Than Within-Lot Variation (Anova) (60)
证明批间变化少于批内变化（Anova 检验）（60）

Under the classical one-factor random effects variance components model, the total process standard deviation is calculated as $\sigma_t = \sqrt{\sigma^2_w + \sigma^2_b}$. Due to the squaring under the radical, if $\sigma_b < \sigma_w$, the impact of the between-lot variation σ_b on the total process variation decrease rapidly the smaller it is compared to the within-lot variation σ_w. **Table 8.1.9-1** shows this impact.

在经典的单因素随机效应方差分量模型中，总的工艺标准偏差按 $\sigma_t = \sqrt{\sigma^2_w + \sigma^2_b}$ 进行计算。因为根号下均是平方，如果 $\sigma_b < \sigma_w$，比批内变化 σ_w 越小，那么批间变化 σ_b 在总的工艺变化上的影响减小越快越小。表 8.1.9-1 显示了这种影响。

Table 8.1.9-1 Effect of between-lot variation on the total process variance
表 8.1.9-1 批间变化在总工艺方差上的影响

Within 批内 σ_W	Between 批间 σ_b	Total 总方差 σ_t	Total Variance 总方差 σ^2_t	Between as % of Total 批间占总方差% σ^2_b/σ^2_t
1.00	2.00	2.24	5.00	80%
1.00	1.50	1.80	3.25	69%
1.00	1.00	1.41	2.00	50%
1.00	0.75	1.25	1.56	36%
1.00	0.50	1.12	1.25	20%
1.00	0.25	1.03	1.06	6%

If the between-lot variation (σ_b) is half (50%) of the within-lot variation (σ_w), the former only accounts for 20% of total process variance. Reasonable PPQ acceptance criteria for between-lot variation would typically be 75%, 50%, or 25% of the within-lot variation. The sample size within lots and number of lots required may be determined by the statistical power to detect the differences of interest. Acceptance criteria could be based on point estimates of the variance components or confidence intervals.
如果批间变化(σ_b)为批内变化(σ_w),的一半（50%），那么前者仅视为总工艺方差的 20%。合理的 PPQ 中批间变化的可接受标准一般为批内变化的 75%，50%或 25%。批内的样本量以及需要的批次数量可以由统计功效决定以检测出感兴趣的差异。可接受标准可基于方差分量的点估计或置信区间。

8.1.10 Sample Size
样本量

Table **8.1.10-1** shows the sample n size required to estimate a standard deviation to within a specified % of its true value with 90% and 95% confidence (45,54). This method does not require a previous estimate or reference sigma since the error is expressed in relative rather than absolute terms.
表 8.1.10-1 列出了评价标准偏差在规定的真值百分比以内，且置信度为 90%和 95%所需的样本量 n（45,54）。这种方法不需要事先评估或参考 σ 因为此误差用相对而不是胜于绝对误差。

Table 8.1.10-1 Sample Size to estimate a standard deviation to within ±X% of true value
表 8.1.10-1 评价在真值±X%以内的标准偏差所需的样本量

Confidence 置信度	±% relative error ±%相对误差	n 样本量
90%	20%	35
90%	25%	23
90%	33%	14
95%	20%	49
95%	25%	32
95%	33%	18

Table 8.1.10-1 indicates that a minimum of 32 lots are required for the estimated between-lot standard deviation σ_b to be within ±25% of its true value σ_b with 95% confidence. Since the table assumes the lot

means are estimated exactly, more than 32 lots may be required if the sample size per lot is small or there is substantial within-lot variation. **Table 8.1.10-1** shows the difficulty in estimating a standard deviation: large sample sizes are required to obtain precise estimates. Again, a phased approach could be used where the PPQ is based on five lots, and additional data is collected during CPV to obtain a more precise estimate.
表 8.1.10-1 显示了评价批间标准偏差 σ_b 在其真值 σ_b±25%以内且置信度为 95%所需的最小批数量为 32 批。由于表中假设批均数为精确估算，所以如果每批的样本量较小或批内变化较多，那么可能需要多于 32 个批次。表 8.1.10-1 表明评价其标准偏差是困难的：精确的估算需要大量的样本。此外，当 PPQ 基于 5 个批次时可以用分阶段的方法，在 CPV 阶段可以收集额外的数据以获得更精确的评价。

8.1.11 Demonstrate the Between-Lot Standard Deviation $\sigma_b \leq$ Acceptable Value X
证明批间标准偏差 σ_b 不超过可接受值 X

It is generally easy to test enough samples to estimate the within-lot standard deviation σ_w with reasonable precision. Also, estimates of the within-lot variation are often available before PPQ from Stage 1 data or other similar production processes. The total process standard deviation is $\sigma_t = \sqrt{\sigma^2_w + \sigma^2_b}$. The PPQ acceptace criterion for σ_b may be selected to show that total process variation is **acceptable (e.g., 3-sigma capable or other desirable value).**
一般检验足够的样本很容易评价批内标准偏差 σ_w，并且有合理的精密度。同样，在 PPQ 之前的阶段 1 的数据或其他类似的生产工艺可以获得批内变化的估算。总工艺标准偏差计算公式为 $\sigma_t = \sigma^2_w + \sigma^2_b$ 。PPQ 中的 σ_b 可以选择以使总工艺变化达到可以接受的标准（例如 3σ 工艺能力或其他合适的值）。

8.1.12 Demonstrating equivalence between lots
批间等价证明

Differences between PPQ lots can be statistically detectable, but they might be small enough to consider the lots equivalent. To use this method, an equivalence test using multiple TOST (two one-sided tests) or other extension of the equivalence concept may be used. The number of lots required would be based on the statistical power for the equivalence procedure chosen (52).
PPQ 批次之间的差异可以用统计学检测出，但如果差异足够小就可以认为批次之间是等价的。如使用这种方法，需要用到多 TOST 等价测试（两次单侧检验）或其他等价概念拓展的方法。需要的批次基于所选等价程序的统计学功效（52）。