Technical Report No.65

Technology Transfer 技术转移

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1.0 introduction 简介

Pharmaceutical technology transfer consists of planned and controlled actions that are based on well defined acceptance criteria to convey a manufacturing process, analytical method, packaging component, or any other step or process along the pharmaceutical drug lifecycle from an originator site, known as a sending unit (SU), to a new site, the receiving unit (RU). 制药技术转移包含一些有计划的和受控的活动，这些活动根据规定好的可接受标准，从转出方（SU）传递生产工艺、分析方法、包装材料、或者其他任何与药品生命周期有关的步骤或者工艺到接收方（RU）。

1.1 purpose / 目的

The purpose of this technical report is to provide guidance and best practices for conducting technology transfer activities in the pharmaceutical industry. 这篇技术报告的目的是为制药工业进行药品技术转移活动提供指南和最佳实践。

1.2 scope /范围

The report provides an overview of the knowledge and skills used during a successful technology transfer project (TTP) along with references to consult, if necessary. The report includes practical examples of technology transfer activities. Rather than discuss a particular technology transfer topic, this report aims to provide a guide to safe TTP management. 本报告提供了一个成功的技术转移项目（TTP）使用的知识和技巧的概述，以及必要时可用的参考。本报告包括技术转移实例。不仅仅是讨论一个既定的技术转移主题，本报告也着眼于为保证的 TTP 管理提供指南。

This report does not address logistics and bridging stocks, which are comprehensively discussed in Technical Report No. 52: Guidance for Good Distribution Practices(GDPs)(1). 本报告不讨论物流和库存衔接，这个方面在第 52 号技术报告《良好分销实践指南 GDPs》中有广泛讨论。

The technology transfer organizational elements outlined in this technical report might not be appropriate for all companies. Established practices or the availability of personnel will dictate how firms conduct technology transfer activities. 这篇技术报告中列出的技术转移组织机构可能不适用于所有公司。各公司已有的实践和人员将决定公司如何管理技术转移活动。

2.0 Glossary of Terms 术语

Failure Mode Effects Analysis (FMEA) / 失败模式影响分析（FMEA）

A tool for analyzing processes or systems to evaluate all operating steps in order to identify and assess the risk associated with any potential failures(2). 用于分析过程或系统的一个工具，通过评估所有操作步骤来识别和评估任何潜在导致失败的风 险。

Planning Bill of Materials (BOM) / 物料计划清单（BOM）

A complete list of the raw material (chemicals, media, powders, resin, etc.) and consumables/ components (filters, bags, tubing, containers, etc.) that are required to manufacture the product. 一个生产产品所需的原料（化工品、媒介、粉末、树脂等）和耗材/组分（过滤器、袋子、管道、容器等）的完整清单。

Process Flow Diagram (PFD) / 工艺流程图（PFD）

A document, typically prepared by R&D, that describes the intended manufacturing process. The PFD includes all relevant information for the operation of the manufacturing process, organized by unit operation. The PFD serves as the source document for the initial development of the master production records and is locked down once development has determined that the process can be controlled. 一个描述计划使用的生产工艺的文件，通常由研发编写。PFD 通过单元操作来组织，包含了所有 生产工艺操作相关的信息。PFD 是初期起草主批生产记录的源文件，并且在确定工艺可控时，该 文件将被锁定。

Receiving Unit (RU) /转入方（RU）
Term for the internal or external recipient or site where the technology is being transferred to.
定义为内部或者外部接收技术的接收方或接收地。

Sending Unit (SU) /转出方（SU）
Term for the internal or external source or originator site of the technology to be transferred.
定义为内部或者外部转出技术的来源或始发地。

Work Breakdown Structure (WBS) /工作分解结构（WBS）
A hierarchical and incremental decomposition of a project into phases, deliverables, and work packages; commonly a tree structure that shows a subdivision of effort required to achieve an objective. 将一个项目按层级、按过程分解成阶段、可交付成果和工作包，通常是一个树状的结构展示了实现目标需要的各级努力。

Material Safety Data Sheet (MSDS) / 物料安全数据表（MSDS）
Information provided with chemicals and other materials intended to provide workers and emergency personnel with procedures for handling or working with that substance in a safe manner. 提供给化工品或其他物料的信息，用于指导工人和应急人员安全操作或使用该物质。
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3.0 Technology Transfer Project 技术转移项目

A technology transfer procedure is more of a project than a process, as described by the Project Management Body of Knowledge (PMBOK) Guide. The guide describes a project as a defined sum of non-repetitive activities that are designed to achieve a goal, are performed in a defined time range, employ defined resources, and are managed by a team. A process, by contrast, is the steps a given project follows (3). 根据项目管理知识指南(PMBOK)的描述，技术转移程序是一个项目而不仅仅是一个过程。该指南描述的项目是 一个各种非重复性活动的总和，这些活动是设计来实现一个目标、在规定的时间内实施、利用一定的资源、和 被一个团队管理的。一个过程，相比下，是一个特定项目按此进行的步骤。

A TTP typically provides governance for technology transfer by grouping similar activities together and moving them through each step. In this report, the technology being transferred is related directly or indirectly to a drug (small and large molecule) that is being developed or manufactured, and the manufacturing process, analytical testing, and/or other aspects of its processing and packaging are transferred either within the innovator organization or to a contract manufacture/packager/testing facility. Preservation of the product's quality and performance is a critical aspect of the TTP.
TTP 通常以工作归类和逐步实施的方式提供技术转移的管理。在这篇报告里，被转移的技术与药品（小分子和大分子）的开发或生产有直接或间接的关系，生产工艺、分析方法和与加工和包装相关的其他方面在研发机构内部转移，或者将这些转到合同加工/包装/检测场所。保证产品的质量和性能是 TTP 的关键内容。

Technology transfer can be applied to analytical methods and partial production steps (e.g., intermediates manufacturing, a filling or packaging step, or a cleaning procedure). Technology transfer procedures can also be applied to manage the transfer of individual analytical methods or process phases (e.g., filling, packaging, or manufacturing of specific intermediates). 技术转移可应用于分析方法和部分的生产步骤（如：中间体生产、灌装或包装步骤、或清洁程序）。技术转移程 序也可以应用于管理个别的分析方法或者工艺阶段（如：灌装、包装、或特定中间体的生产）的转移。

The transfer of individual process steps must be supported by stability data, validation of transport of intermediates, and a gap analysis of premises and equipment. The result of this type of technology transfer is generally an increase in manufacturing flexibility and capacity. 个别的工艺步骤转移必须有稳定性数据、中间体的运输验证、设施设备的差异分析的支持。这类转移的结果通 常是增加生产的灵活性和产能。

3.1 Technology Transfer Project Objectives / 技术转移项目目标

The objectives of TTP typically are to:
● Complete process performance qualification to demonstrate repeatability of manufacturing
● Demonstrate the similarity of the product produced at the end of the TTP at the RU
● Obtain licensing approval to manufacture and market the product
● Demonstrate robust manufacturing over a sufficiently large number of lots, including process, product, operations, and testing
● Comply with in-process intermediates and final product analytical specifications; process specifications (e.g., pH and temperature); expected yield; regulatory and quality requirements; and environment, health, and safety requirement TTP 的目标通常是：
● 完成工艺性能确认以证明生产的重复性
● 证明接收方在 TTP 的最后所生产出来的产品是相似的
● 获得生产和销售被转移产品的批文
● 通过足够多的批次，包括加工、产品、操作、和检测，证明生产的耐受性。
● 符合过程中间产物和成品质量标准，工艺标准（如，pH 和温度），期望收率，法规和质量要求，以及环境、健康和安全要求。

A successful TTP does not guarantee zero future rejects. Rather, it provides assurance that the process and the product knowledge is fully understood and properly transferred from the SU to the RU.
一个成功的 TTP 不能保证将来没有错误。更确切的说，TTP 为工艺和产品知识从 SU 到 RU 的充分理解和恰当传递提供了保证。

3.2 Types of Technology Transfer /技术转移的类型

TTPs can be classified into several groups. For example, for the transfer of a drug manufacturing process, types of approaches include:
TTP 可以分为多个类别。例如，对于药品生产工艺转移，方法可分为：

● Development to commercialization (intracompany): During the drug lifecycle, the product and the process through different phases, such as discovery, development, validation, registration, and commercialization. Transition between each phase requires a TTP for scale-up and activities management. The goal is to bring a process in a development phase to a robust and reproducible commercial process able to consistently guarantee the market supply. 从研发到商业生产（公司内）：在药品生命周期内，产品和工艺通过不同的阶段，如发现、开发、验证、注册、 商业化。阶段之间需要一个 TTP 来处理工艺放大和活动管理。目的是为了将研发阶段的工艺转化成具有耐受性 和再现性的可以持续保证市场供应的商业化工艺。

● Commercial to commercial (intercompany): Established processes can be transferred from one commercial site to another commercial site for business continuity or strategic reasons. 从商业生产到商业生产（公司间）：因为商业上的连续性或者战略性原因，一个已经建立的生产工艺可以从一个商业化生产场所转移到另一个商业化生产场所。

Development-to-commercialization, or intracompany, TTPs are usually easy to manage due to the existing relationship between the SU and RU. Since they are part of the same company, procedure, mindset, and governance are similar. 从研发到商业生产或公司内部的 TTP，由于 SU 和 RU 之间现成关系，通常容易管理。因为他们同属一个公 司，有相似的程序、理念、管理。

Commercial-to-commercial transfer generally presents some advantages:
商业化生产到商业化生产转移通常展现一些优点：

● Both sites have experience in regulatory authority inspections.
双方都有官方检查的经验。
● Quality systems are in place.
都有质量体系。
● Personnel are trained and experienced.
人员都经过培训且有经验。
● The product (e.g., intermediate or final) is well characterized.
产品（如中间体或最终产品）表征清楚。
● Product and process specifications are well established.
产品和工艺的标准已经明确建立
● The process is statistically under control.
工艺统计学受控。

The main disadvantage of commercial-to-commercial is that the development resides with SU and is usually not part of the information shared due to intellectual property concerns. A deep involvement of the R&D group, therefore, is required independently from the fact that the process under transfer is well-established, commercial process. A significant, initial milestone of a commercial-to-commercial TTP should be the establishment of governance suitable for both the
SU and RU.
商业化转移的主要缺点是，研发信息保存在 SU，处于知识产权考虑经常没有共享。因此即使被转移的工艺是一个成熟的商业化工艺的实事，转移仍单独需要深度包含一个研发小组。一个明显的、最初的里程碑的商业化转移 TTP 应该是适合 SU 和 RU 的管理方法。

3.3 TTP Oversight / TTP 监管

Managing TTPs, especially their organization and communication, is a challenge for any company. Teams must be created and motivated and project activities must be executed and monitored while the members still accomplish their routine work. In addition, interaction between different sites (often located in different countries) and external parties can be difficult.

管理 TTP，特别是组织和交流对任何公司都是一个挑战。必须建立小组并激发起来，项目活动在成员们仍然完成各自日常工作情况下必须得到执行和监管。另外，不同场地（通常位于不同的国家）之间以及外部合作方之间的互动可能是困难的。

Based on the potential complexity of the TTP, usually three groups are involved in successful technology transfer governance:
基于 TTP 潜在的复杂性，一个成功的技术转移的管理通常包括 3 个部分：

● Technology transfer unit/department
技术转移单位/部门
● Multidisciplinary technology transfer project team
多学科的技术转移项目小组
● Project committee
项目委员会

3.4 Multidisciplinary Technology Transfer Project Team /多学科的技术转移项目小组

Each pharmaceutical TTP requires the involvement of a well-trained, multidisciplinary team at both the SU and RU. The team needs such soft skills as leadership, effective communication, and pharmaceutical market access principle. The team also needs the following technical proficiencies to drive the team toward a positive outcome:
每个制药 TTP 都要求 SU 和 RU 双方有良好培训的、多学科的小组参与。这个小组要有这些软技术，如领导能力、有效沟通能力、懂得医药市场准入原则。为了达成好的结果，小组还需要以下技能：

● Quality assurance (QA)
● Quality control (QC)
● Manufacturing / 生产
● Engineering / 工程
● Finance / 财务
● Maintenance / 维护
● Environment, health, and safety / EHS
● Research and development / 研发
● Regulatory affairs / RA
● Legal issue / 法律事务
● Project management / 项目管理

The multidisciplinary technology transfer project team should be responsible for filing the relevant documentation for the transfer, including that exchanged between the SU and RU. The
team prepares the following key documents：
多学科技术转移项目小组应负责代表转移方递交转移文件，包括 SU 和 RU 之间的交换文件，小组应该准备以下关键文件：

● Project plan (includes project management documents, and tools, work breakdown structure, responsibility assignment matrix, and Gantt chart)
项目计划（包括项目管理文件、工具、工作分解结构、责任分配矩阵、甘特图）

● Technology transfer protocol
技术转移方案

● Technology transfer report
技术转移报告

The team is responsible for the transfer and implementation of the technology in a regulated context, such as a manufacturing facility, according to predefined acceptance criteria, such as process, intermediates, and finished product specifications. 小组负责在规范的背景下根据预定的标准，比如工艺，中间体和成品的标准传递和执行该技术，比如生产厂房。

Establishing two distinct teams and related team leaders is not uncommon. Assignment of more active role to the RU (e.g., management of its own team) should help lessen the impact of any resistance to the TTP. 建立两个不同的小组和相应的组长不是不常见的。安排 RU 一个更灵活角色（如，管理自己的小组）应能减少 对 TTP 阻力。

The essential functions to be included in TTPs are shown in Figure 3.4-1, although more may be required depending on the complexity of the project.
图 3.4-1 显示了 TTPs 应该包括的基本功能，但根据项目的复杂性，可能需要更多。

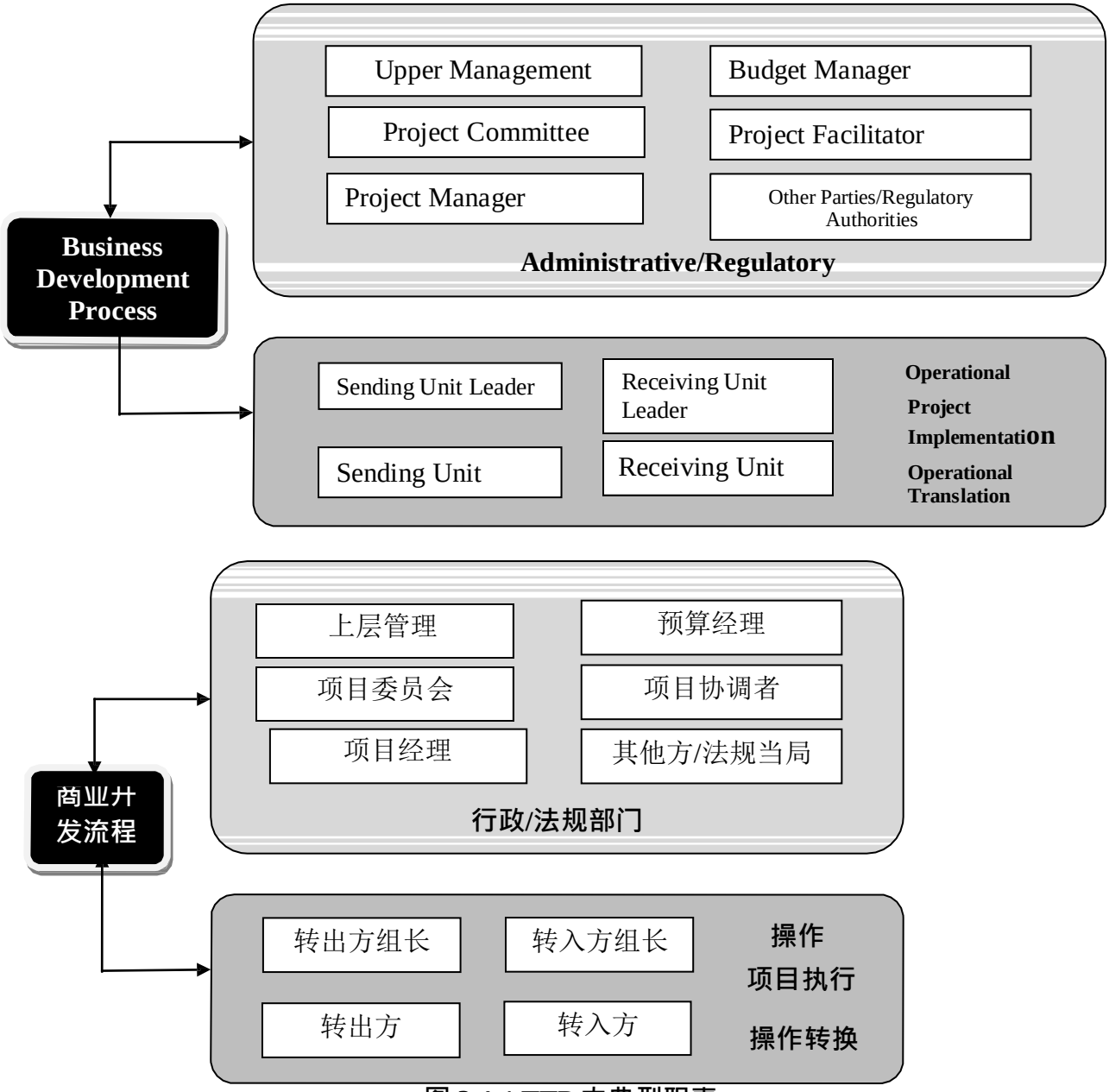


图 3.4-1 TTP 内典型职责

Depending on the size and organizational style of the firm, the roles outlined above and the responsibilities listed in Table 3.4-1 should be accounted for by, but not necessarily assigned to, individual personnel. Section 3.4.1 and 3.4.2 provide further detail regarding the administrative and regulatory functions and operational functions, respectively. 根据公司的大小和组织方式，表 3.4-1 列出的角色和责任应该指定到个人，但不是必须的。第 3.4.1 节和第 3.4.2 节分别进一步提供了关于行政管理职能和操作功能的细节。

表 3.4-1 技术转移组织构成

职能范围	具体职责
行政/法规	● 监控 TTP，提供建议和咨询 ● 在项目过程中代表上层管理者利益 ● 监控预算和投资 ● 作为和外部药监当局以及其他方的联络人
具体运营	● 转移和执行相关技术 ● 从转出方转移技术 ● 在转入方执行技术 ● 监控项目和项目合作 ● 计划和监控项目开发 ● 需要时提出整改行动建议 ● 确保计划活动顺利进行 ● 团队交流确保团队成员积极参与 ● 对管理层和其他相关人员更新项目进展 ● 确保符合质量要求

3.4.1 Administrative and Regulatory Functions /行政法规管理职能

3.4.1.1 Project Committee /项目委员会

Within the SU and RU, a dedicated project committee should be appointed and charged with monitoring the TTP. The members of the project committee must represent the interests of upper management during the project.
在 SU 和 RU 内部，应该指定专门的项目委员会并负责监督 TTP。在项目运行期间，项目委员会成员必须代表高层的利益。

The committee should provide advice and consultation and should act as the performance monitoring unit. The committee members should be well informed about the project and have authority to act in the case of events that could disrupt the TTP's critical path. A strong reporting procedure also needs to be in place. 委员会应该提供建议和咨询，应该作为项目实施的监管单位。委员会成员应该及时跟进目进展，当项目关键路 径受阻时有权利采取行动。一个强有力的汇报程序也要准备就绪。

Monthly meetings can be set up as part of project governance. In these meetings, the project committee members should review prior meeting minutes, management files, operating expense, and capital expense records. 月度会议可作为项目管理的一部分。在会议中，项目委员会成员应该回顾之前的会议纪要、管理文件、操作经 费、项目支出费用记录。

3.4.1.2 Project Manager / 项目经理

The project manager should have technical, relational, and managerial skills to fulfill the varied responsibilities of this position, described in Table 3.4-1 above. The use of typical tools of project management described in the PMBOK to plan and monitor the project activities strongly recommended (3). These tools can identify activities that could prolong the project unless they are properly controlled and monitored. 项目经理应该拥有技术、沟通、管理技巧来履行这个职位的各种职责，如上表 3.4-1 所述。强力建议使用 PMBOK 指南里描述的典型工具来计划和监管项目。这些工具可以识别出可能延长项目时间的活动，除非这些 活动被合适的控制和监控。

At an organizational level, the project manager should be able to mitigate any differences in a approach between R&D scientists and production/quality people even if R&D scientists were already involved in the scale-up and commercialization of the process. The various technology transfer personnel involved should advise the team leaders and mediate between manufacturing and R&D views. Reporting responsibilities are up to the project manager, as well. The technology transfer unit and project committee should be routinely updated on the status of the project. 在组织层面，即使工艺的放大试验和商业化生产已经包含了研发人员，项目经理应能减少研发的科学家和生产/ 质量人员之间的方式上的差异。各技术转移成员应建议组长和协调生产和研发之间的观念。汇报的职责也在于 项目经理。技术转移单位和项目委员会应当得到项目进展的日常更新。

3.4.1.3 Budget Manager / 预算经理

A budget manager should monitor the budget and investment expense forecasts.

预算经理应监管的预算和投资费用的预测。

3.4.1.4 Legal Office representative / 法律办公室代表

A legal office representative is required for any intercompany transfers regulated by legal contracts.
需要一个法律办公室代表，使用法律合同管理任何公司间的技术转移。

3.4.1.5 Project facilitator /项目协调人

A project facilitator should serve as a liaison with regulatory authorities and other parties involved in the process, (e.g., applicable engineering societies in foreign countries). 项目协调人应该作为和主管部门和参与本项目的其他方的联络人员，（例如，国外的应用工程团体）。

3.4.1.6 QA Leader /QA 负责人

The person who is responsible for QA should oversee process documentation and change control, quality risk management (QRM), and validation documentation.
QA 负责人应该总体管理工艺文件、变更控制、质量风险管理（QRM）和验证文件。

3.4.2 Operational Functions / 操作功能

3.4.2.1 Sending Unit (SU) and receiving unit (RU) / 转出方(SU)和转入方(RU)

Regardless of the context, technology transfer always involves an SU and an RU. The SU and RU are generally defined as the originator and the receiver of the technology, respectively. However, the composition of the units is varied and can be groups within a company, a specific site, or any other organization based on company needs. The responsibilities of the SU and RU are outlined in
Table 3.4.2.1-1
不管在什么情况下，技术转移总是包括一个 SU 和一个 RU。SU 和 RU 通常分别被定义为技术的来源方和接收方。但是，根据公司需求的不同，SU 和 RU 队伍的组成可以不同，可以是一个公司内的小组、一个专门的场地、或者任何其他的组织。SU 和 RU 的职责见表 3.4.2.1-1。

表 3.4.2.1-1

项目阶段	SU	RU
计划阶段	● 确认相关文件	● 落实 SU 提供的文件
准备完成阶段	● 将文件转让给 RU ● 审核 RU 落实的文件 ● 培训 RU 相关人员	● 组织验证和执行计划 ● 验证和执行受让的技术 ● 培训人员
执行和确认阶段	● 在验证，初次和后续阶段支持 RU 方 ● 对最初的失败或是差距支持 RU 进行分析和评估 ● 支持 RU 进行必要的改进和提高	● 进行初次生产，评估结果 ● 解决初次生产中发生的失败或偏差 ● 初次生产评估后进行潜在改进项目的确认
结束阶段	● 初次生产后续工作中对 RU 进行支持	● 连续确认和建立改进计划

The SU and RU leaders provide regular updates to the project manager about the progress of the activities, spending on the TTP, potential technical or financial concerns, and proposed corrective actions.
SU 和 RU 负责人定期地向项目经理汇报项目活动进展、TTP 花费、潜在的技术或财务问题、和建议的纠正措施。

The RU's functional routine is often disrupted by events unrelated to the TTP but are nonetheless necessary as part of their normal functions within their company. Assignment of a more active role to the RU (e.g., management of its own team) should help lessen the occurrence and effects of any internal or external resistance to the TTP. "Resistance events" can include:
RU 的日常职能经常会受到 TTP 之外的事件的影响，但是又是公司内他们必须要做的日常工作。安排 RU 一个更灵活角色（如，管理自己的小组）应该能减少内在的和外在的阻力对 TTP 的影响和发生率。"阻力事件"包括：

● Routine daily activities that don't include TTP activities Lack of experience with technology transfer and project management tools Different prioritization of project within the RU
不是 TTP 有关的日常活动；缺少项目转移经验和项目管理工具；在 RU 内不同的项目优先级别。

In general, the RU needs to review the technology transfer information provided by the SU to analyze possible gaps in training or experience of laboratory personnel. The RU then works with SU to describe possible training needs or additional information/questions regarding the process.
通常，RU 需要审核 SU 提供的技术转移信息，分析检测人员在培训和经验上可能的差异。然后 RU 和 SU 一起描述可能的培训需求或额外的工艺相关信息/问题。

3.4.2.2 Team Leaders / 组长

Each team in the RU and SU should be coordinated by a team leader who is the "owner" of the TTP and is responsible for implementing the technology at the RU or SU (e.g., manufacturing in the case of transfer of an industrial process)
在 RU 和 SU 的每个小组应该由一个组长协调，这个组长"拥有"这个 TTP，他负责在 RU 或者 SU 的执行技术（例如，转移一个工业工艺例子中的生产）。

The SU and RU technology team leaders should regularly update the project manager on the progress of the activities, budget use, potential technical or economic issues, and proposed corrective actions.
SU 和 RU 的技术小组组长应该定期向项目经理汇报项目活动进展、支出、潜在技术或财务问题、建议的纠正措施。

3.4.2.3 R&D Representative / 研发代表

R&D needs to be included whenever it is the SU or whenever preliminary tests of the technology at laboratory/pilot scale are foreseen.
可以预见的是，无论是在 SU 还是技术在实验规模或者小试规模的初步测试，R&D 都需要参与。

3.4.2.4 Combined Roles / 综合角色

Delegation of roles or combining different roles into a single function is a common practice for effective technology transfer. For example, the budget manager task could be assigned to the project manager or a team might not need a project facilitator. 将各种职责或者将不同的职责整合成一个职能是高效的技术转移中一种常见做法。比如，将预算经理的职责分　配给项目经理或者一个小组可能就不需要项目协调人。

3.4.3 Technology Transfer Unit / 技术转移单位

Companies conducting technology transfer should evaluate the need for a dedicated technology transfer unit. This could be a dedicated department or a group composed of personnel from the appropriate functional areas. Many companies eventually establish a technology transfer unit within a department at least. If a company chooses not to create a technology transfer unit or department, the company's engineering and R&D departments can dedicate select staff members to a TTP. 开展技术转移的公司应该评估是否需要一个专门的技术转移单位。这个单位可以是一个专门的部门或者一个由　各个其他合适职能领域的人员组合。很多公司实际上都至少建立了部门内的技术转移单位。如果一个公司选择　不建立技术转移单位或部门，那么该公司的工程和研发部门可以专门挑选人员进入 TTP。

Technology transfer units are responsible for the execution of the technology transfer projects and define the technology transfer policies for the company; they should have process and engineering competencies at a minimum，with the addition of R&D expertise as needed. Technology transfer units should leverage the expertise of their staff in support of the SU, the RU, the team leader, and the project manager, identifying best practices and gaps to be resolved. 技术转移单位负责执行技术转移项目和制定公司的技术转移政策；他们应该至少拥有工艺和工程的能力，需要　时还包含研发专家。技术转移单位应该利用他们的专家经验支持 SU 和 RU、组长和项目经理，识别最好的做法　和待解决的差距。

Based on experience and the results of the transfer, the technology transfer unit determines whether the technology transfer was successful or not and identifies corrective actions as appropriate. 根据经验和转移的结果，技术转移单位确定技术转移是否成功，合适时识别出纠正措施。

3.4.4 Organizational Model /组织模式

An organizational or governance model that identifies the people or groups responsible for each task must be developed and identify which matters are subject to risk-based decisions. The risk determination of the subjects will provide the group with the necessary awareness of risk. A policy for enterprise risk management should be in place at this stage. 必须建立一个组织或管理模式，识别要开展任务所需的人员或者团队的职责，识别那些需要基于风险的决定。根据风险决定的项目能给团队提供必要的风险意识。在这个阶段，应当有一个公司级的风险管理。

Regardless of the context of the TTP, technology transfer always involves an SU, an RU, and the key activities identified during the operational phase. From these pieces, a well-defined organizational set-up can be established. This set-up is implemented only after the project progresses to the operational phase, which is detailed further in Section 4.3: TTP Implementation and Qualification.
无论什么背景的 TTP，技术转移经常包括 SU、RU、在操作阶段识别出的关键活动。因此，可以建立一个成熟的组织机构。这个组织机构的建立只在项目进入操作阶段时进行，相关详细内容见第 4.3 节: TTP 的执行和确认。

Use of a light matrix organizational model can minimize of the impact of the transfer activities on the routine of the units activities involved in the transfer. Other approaches (e.g., hierarchical reports within a unit and within the transfer set-up or set-up roles engaged hierarchically in the transfer activities) may be appropriate, depending on the context and importance of the project. 使用一个简单的矩阵组织模式可以使转移活动对各转移相关单位的日常活动的影响降到最低。其他方法（在一 个单位内逐级报告或者设置逐级报告的转移工作）可能也合适，这决定于项目的背景和重要程度。

The following project relationships need to be determined:
需要确定以下项目关系：

- Project team internal dynamics / 项目小组内部的关系
- Dynamics between project team and external partners / 项目小组和外部合作方的关系
- Organizational dynamics that could affect the operational context / 可能影响实施作背景的组织机构的关系

3.4.5 Communications / 沟通

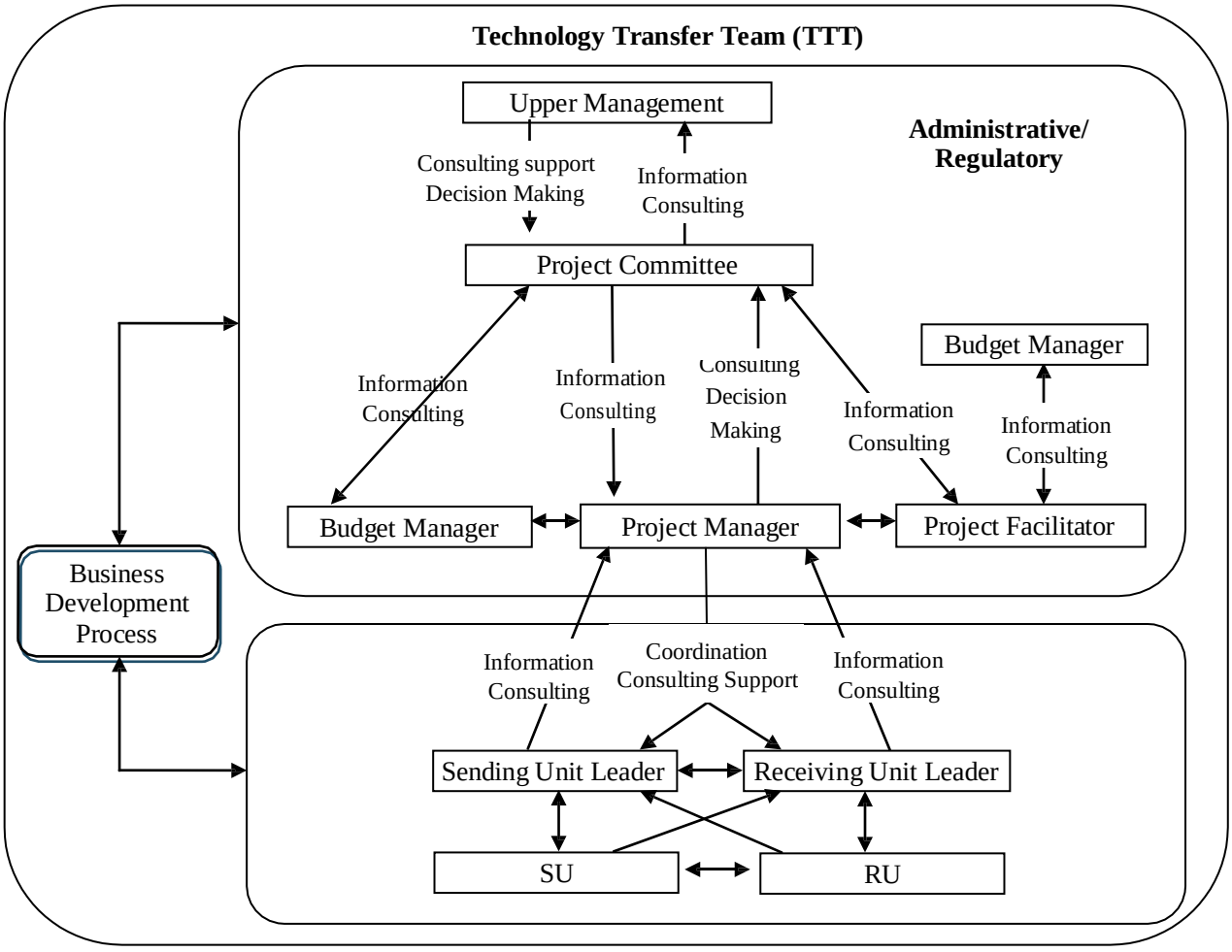
Knowledge management and transfer are key requirements of the TTP for preserving product quality and process performance after technology transfer. Because of the large amount of multidisciplinary information collected, evaluated, and elaborated during the TTP, a systematic approach to acquiring, analyzing, storing, and disseminating information related to the technology should be carefully regulated and conducted in accordance with company policies. 为了确保转移后产品的质量和工艺性能，知识的管理和传递是 TTP 的关键要求。由于在 TTP 时大量的多学科的 信息收集、评估和阐述，应当有一个系统性的方法用在获取、分析、储存、传播相关技术的信息，并在符合公 司的政策下仔细管理和执行。

During a TTP, communication should be carefully regulated and conducted in accordance with company policies. The success of TTP is related to the communication skills of and relationships between the technology transfer team members (described below). Open communication between team members, effective and timely communication, and direct communication between subject matter experts are key aspects to be considered and reinforced routinely by the project leader and sponsor.
在一个 TTP 中，根据公司的政策规定，沟通应该认真地管理和进行。TTP 的成功和转移小组成员的沟通技能和成员之间的联系有关（如下描述）。在成员之间公开沟通、有效和及时地沟通、相关专家之间的直接沟通是项目负责人和权利人需要考虑的关键点并在日常进行加强。

Communication between the teams should be both vertical (SU with SU leader, and RU with RU leader) and horizontal (SU with RU and RU leader). Technology transfer unit staff should communicate directly with the project as well as with the SU, RU, and respective leader. The project committee should interact primarily with the project manager, budget manager, and project facilitator. The project manager should act as a liaison between those responsible management functions (project committee, project facilitator, and budget manager) and those overseeing the technical functions (technology transfer team, team leaders, and technology transfer unit or department). The project manager and the project budget manager should remain in close communication with each other, other manager (e.g., project facilitator), and those responsible for technical components of the TTP (SU leader, RU leader, and technology unit or department).
小组之间的沟通可以是垂直的（SU 与 SU 领导，RU 与 RU 领导）也可以是横向的（SU 和 RU 以及 RU 领导）。技术转移小组人员应该直接联系项目负责人，也可以联系各自 SU 或 RU 负责人。项目委员会应该与项目经

理、预算经理、项目帮助人互动。项目经理应该作为行政管理职能之间（项目委员会、项目帮助人和预算经理）和操作职能团队之间（技术转移小组、组长和技术转移单位或部门）的联络员。项目经理和预算经理应该保持紧密联系，并和其他经理（如，项目帮助人）以及 TTP 其他组成人员（SU 领导、RU 领导和技术单位或部门）保持紧密联系。

To maintain project communication channels and avoid miscommunication, direct communication between team members and the project or budget managers should be avoided. The unit leaders should act as the primary liaison between team members and management (i.e., project facilitator, budget manager, and project manager). 为了保持项目沟通的通道和防止错误沟通，应避免小组成员直接与项目经理或预算经理的沟通。组长应该作为 成员之间和各管理人员（如：项目帮助人、预算经理、项目经理）之间的首要联络员。



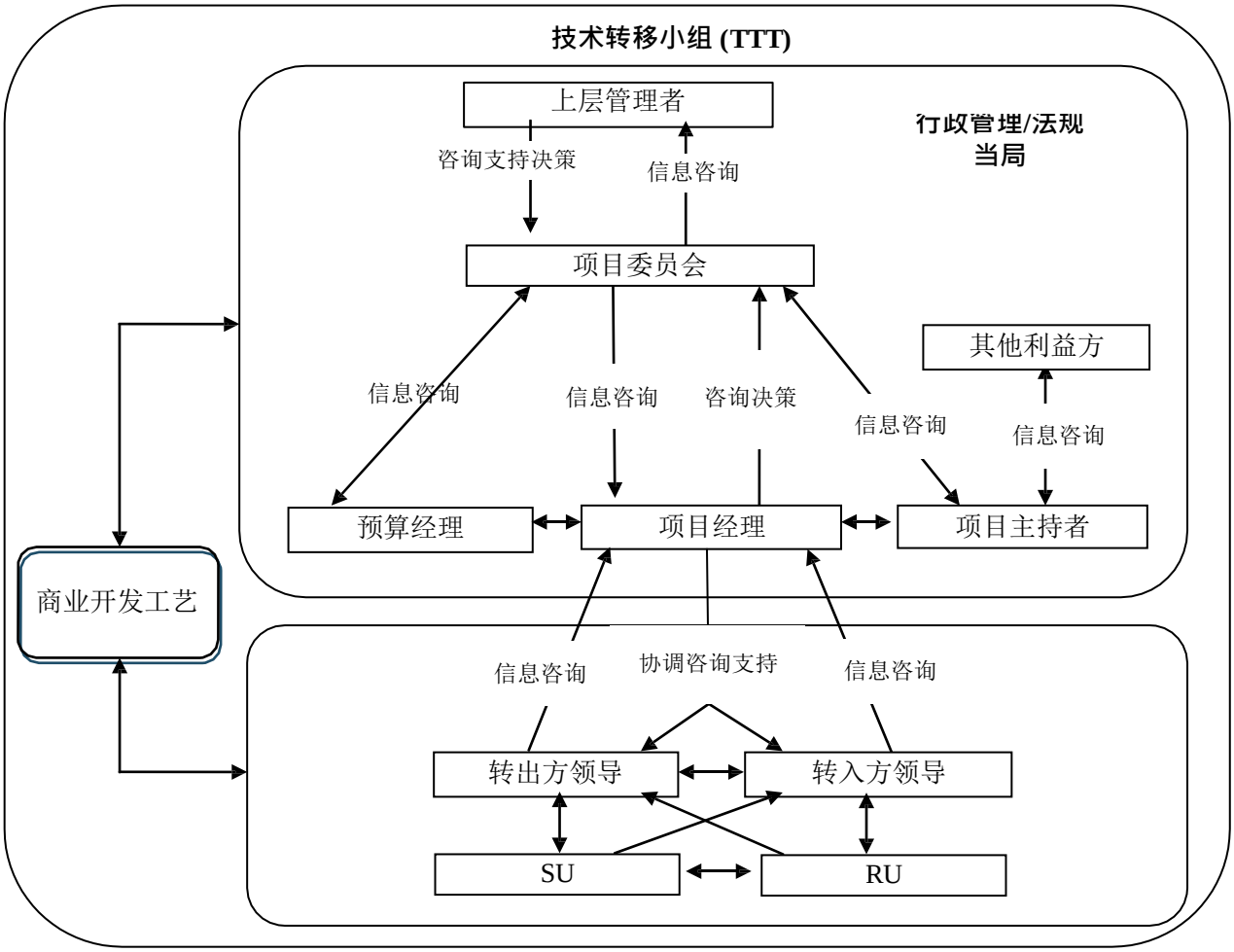


Figure 3.4.5-1 depicts this flow of communication.
图 3.4.5-1 描述了沟通的流程。

3.4.6 Document Management / 文件管理

The SU should provide all relevant documents to the RU.
SU 应该提供所有相关的文件给 RU。

3.4.6.1 Common Technology Transfer Documents / 常规技术转移文件

Documents related to the transfer of the process could include: 工艺转移
相关文件可包括：

- Batch records 批记录
- Planning bill of materials 计划的物料清单
- Item specifications and justifications 项目标准及其评价
- Summary of stability 稳定性概述
- Lists of potential impurities and degradants and typical levels. 列出潜在杂质和降解物，及其常见的水平
- Starting materials and material safety data sheets 起始物料和物料 MSDS
- Assay–related documents 分析相关文件
- Drug master file for active pharmaceutical ingredients (APIs) and excipients 原料药和辅料的 DMF
- Qualification of bioburden tests 微生物负载测试的确认
- Solubility profiles 溶解度情况
- Process flow diagram that provides a rationale for the selection of the synthesis, route, form, technology, equipment, clinical tests, and production composition 工艺流程图，提供合成、路线、形式、技术、设备、临床测试和生产组成的选择依据

● Vendor qualification (for transfers to contract manufacturing organizations[CMOs]) 供应商确认（给转移至合同生产组织[CMO]）
● Training protocols 培训方案
● Process validation report and master plan 工艺验证报告和主计划
● Cleaning validation protocols and reports 清洁验证方案和报告
● Project implementation plan 项目实施计划
● Risk assessments performed for the process or testing 对工艺和检验开展的风险评估

All documents generated during the project should be collected and filed by the RU together with the technical documents that are relevant to the project (e.g., know-how documentation). All documents related to the transfer should be collated in a comprehensive package and taken into account during approval inspections. The document package should be acknowledged by the RU, which generates its own process and validation documents (4). All documents associated with the technology transfer should be archived at the RU. Internal RU procedures for documentation handling and filing are necessary and routinely inspected by QA at the site.
项目进行期间产生的文件以及其他相关技术文件（例如，“知道何做”文件）应该由 RU 收集和归档。所有转移相关文件应该整理成整合包，为批准前检查做好准备。RU 应该认同文件整合包，起草自己的工艺和验证文件。所有技术转移相关文件都在 RU 归档。RU 内部程序必须规定文件处理和归档，需要现场 QA 进行日常检查。

3.4.6.2 Regulatory Documents / 法规文件

The project team must consider the TTP’s regulatory requirements and the potential impact of any step in the process on regulatory filings or authorizations. Some technology transfer documents can be filed for regulatory authorization and may be inspected during regulatory audits. For these reasons, document management has a very important role in each TTP step.
项目小组必须考虑 TTP 的法规要求，考虑转移过程的任何一步的对注册申报或主管机构造成的潜在影响。一些文件可以为注册资料进行申报，可能在官方检查时被查。由于这些原因，文件管理在 TTP 的每个步骤都很重要。

4.0 Technology Transfer Process 技术转移过程

A structured approach to the TTP is used to organize common activities into distinct stages and make the project's clear and logical progression evident to the team. Such an approach also provides defined points for review by senior leadership (stage gateway reviews). Stages are logical groupings of associated activities and tasks, and the stage gates are predefined review points for the governance team. The stages can reflect common project management approaches but are tailored for technology transfer.

TTP 的一种有组织的方法用于将通常的行为融入不同的阶段，并且能使项目的清楚且逻辑的进展对团队来说是明显的。这个方法也为高级管理层的提供了确定的审核点（阶段网关审核）。阶段是相关活动和任务的逻辑群体，而阶段网关是为管理团队预定的审核点。阶段能够反映一般项目的管理方法但专用于技术转移。

The stages are demonstrated on the chevron below and discussed in more detail in the following chapters.
阶段在下面的图中定义了，在之后的章节会详细介绍。

4.1 Stage 1: Planning 阶段 1：计划

During this preliminary stage, the SU and RU collaborate to develop a TTP plan that will govern the entire project. Critical inputs to the TTP include a regulatory strategy and a gap analysis (a comparison of the process, equipment, and facility between SU and RU; a risk assessment of the changes; and planned risk mitigation actions).
During the planning stage, requirements and constraints, goals and objectives, and key performance indicators (including the success criteria) must be determined and agreed upon. The technology transfer team should design a plan that takes into account cost (including materials and people), schedule (including supply of the product being transferred), scope, technology, and quality.
在初始阶段，SU和RU合作制定了TTP方案，这个方案会管理整个项目。TTP的关键输入内容包括法规策略和差距分析（SU和RU的工艺、设备和厂房的比较；变更的风险评估；计划的风险降低措施）。
在计划阶段，要求和限制、目的和目标、关键工艺指标（包括成功标准）必须被确定并同意。技术转移团队应该设计一个方案考虑到成本（包括材料和人员）、日程（包括被转移产品的供应）、范围、技术和质量。
Outputs of this stage include a finalized project plan detailing activities, resources, and schedule, and a risk assessment for the project. A gateway review by senior leadership is used to make visible the plans and risks and provides approval to move to the next stage.
这个阶段的输出内容包括最终形成的项目方案详细列明了活动、资源和日程、项目的风险评估。高层的网关审核用于使计划和风险可见，并批准进入下一个阶段。

4.1.1 Project Rationale 项目合理性

Technology transfer is generally aimed at introducing innovation (e.g., a new commercial product or new productions in existing plants) for the company, which, in turn, engages in TTPs for business opportunities.
The project rationale and project relationships (analytical/management/social) must be developed before the project starts. The rationale defines the project plan and the relationships define the "social intelligence." Both are fundamental to the success of a TTP.
技术转移一般目标在于为公司引入创新（例如，新的商业化产品或厂区内新的生产线），作为回报的是商业机会。项目的合理性和项目关联（分析/管理/社会）必须在项目开始前确定。合理性确定了项目计划，关联性确定了社交智能。这两者是一个TTP成功的基础。

4.1.2 Project Scope 项目范围

Applications of technology transfer must be GMP based and rely on well-documented knowledge. Specific acceptance criteria (objectives), batch sizes, and intended production capacity must be defined in advance. The scope of the TTP must be clearly stated and agreed upon by the TTP team.
技术转移的应用应该基于 GMP 并依赖于记录完善的知识。特定的可接受标准（目标）、批量、设计的生产能力必须提前定好。TTP 范围必须清晰的描述并且被 TTP 小组认同。

The knowledge (technology) to be transferred from SU to the RU should include:
准备从 SU 转移到 RU 的知识（技术）应包括：

- Product critical quality attributes (CQAs) 关键质量属性(CQA)
- Impurity profile 杂质档案
- Specifications (e.g., for drug substance; drug product; starting materials; raw materials; and auxiliary materials, such as filtration devices)质量标准（例如：API、制剂、起始物料、原料、辅助材料比比如过滤设备）
- Critical and noncritical process parameters and ranges and proven acceptable ranges
关键工艺参数和非关键工艺参数和参数范围和已证明的可接受范围
- Evaluation results for process and assay robustness 工艺和检测耐受性结果评估
- Manufacturing procedures 生产程序
- Procedures for process-related activities 工艺相关活动的程序
- Equipment management and maintenance procedures (if applicable) 设备管理和维护程序（合适的情况下）
- Technical description of the process and flows for raw and auxiliary materials, waste, personnel, starting materials, intermediates, drug substance, and drug product 原料、辅助材料、废弃物、人员、起始物料、中间体、API 和制剂的工艺和流程的技术说明
- Process flow charts with material balancing 有物料平衡的工艺流程图
- Validation documents, including process validation, cleaning validation, and equipment validation (if applicable) 验证文件，包括工艺验证，清洁验证，设备验证（适用时）
- Stability data 稳定性数据
- Product quality and performance history review and statistical analysis (is available)
产品质量和性能历史回顾和统计数据（如有）
- Safety precautions, material data safety sheets, and special material handling procedures
安全注意事项、MSDS、特殊物料处理程序
- Team member skills 小组成员技能
- Technical and instrumental resources and procedures 技能和仪器资源和程序
- Timelines 时限
- Finance/costs 财务/成本

As these activities occur, it is also necessary to transfer process knowledge, equipment, and material to the recipient facility in a timely and accurate manner. This will ensure that product quality, regulatory, and business needs are met. 当这些活动发生时，有必要及时地和准确地转移工艺知识、设备、物料到接收方。这会确保产品质量、法规和商业需求的达成。

4.1.2.1 Technology to be Transferred 待转移的技术

To aid in the assessment and development of a transfer strategy, a detailed description of the technology to be transferred (including the synthetic route, starting materials, reagents, and catalysts) needs to be prepared by the SU.
Depending on the stage of development, the information to be collected on the technology being transferred may differ. The requirements for transferring a Phase 3 process from one CMO to anther will differ significantly, for example, from the assessment performed when moving from an R&D environment into a manufacturing scale (scale-up) environment.
为了帮助转移策略的评价和制定，SU 需要详细的描述被转移的技术（包括合成路线、起始物料、中间体、试剂和分析人员）。
根据开发的阶段，收集的关于被转移的技术的信息可能不同。从一个 CMO 到另外一个转移一个阶段 3 的工艺的要求会有很大不同，例如当从研发转移到生产规模（放大）所进行的评估。

- Flow chart of the process with a description of each step

每一步都有说明的工艺流程图
● The amounts of materials/reagents and stoichiometry required
物料/试剂的投料量和要求的化学计算法
● Order of addition of reagents 试剂的投料顺序
● Specific conditions required (e.g., temperature, humidity, times, and pressures)
要求的特定条件（例如，温度、湿度、时间和压力）
● Yields of each reaction step 每一个反应步骤的收率
● Compound attributes (e.g., pH in solution, bulk physical properties, particle size and size distribution, moisture content and hygroscopic nature, partitioning coefficient, solubility profile, and degradation profiles)
配方的属性（如，溶液的 pH、大宗物料的物理属性、粒径大小和粒度分布、水分和吸湿性、分配系数、溶解性、降解情况）
● Historical process information 历史工艺信息
● Designation of registered starting material / 注册的起始物料的确定
- Depending on the stage of transfer, the registered starting material might be important. Steps prior to this material do not need to be performed under CGMPs, although the concepts discussed in this document could still be applied. 根据转移所处的阶段，注册的起始物料可能比较重要。起始物料之前的步骤不需要按照 CGMP 执行，然而这个 概念在这篇文章可能依然适用。
● Designation of CQAs CQA 的确定
● Allowable variations in scheme and permitted ranges based on historical information or quality-by-design information
基于历史信息或者 QBD 建立的允许的参数变化范围

4.1.2.2 Scale-up of Production level 生产水平的放大

When a process is transferred from a development facility to a manufacturing facility, the level of production is probably scaled up along with the process transfer. In such cases, either equipment modification or installation of new equipment is probably required to accommodate the increased manufacturing scale.
Therefore, the scale-up philosophy chosen will influence the equipment used in production. Once a scale-up philosophy has been identified for each unit operation, it should be documented in the technology transfer plan or in the individual technology transfer study protocol/report.
当一个工艺从研发厂房转移到生产厂房时，生产的水平可能与工艺转移一起放大规模。在这样的情况下，设备修改或者新设备的安装可能被要求以适应增加的生产规模。
因此，选择的放大方法将会影响到生产用的设备。一旦确定了每一单元的放大方法，那它应该记录在技术转移方案或者单个的技术转移研发方案/报告中。
Along with a formal development of scale-up and control philosophies, the technology transfer team should define requirements for:
随着放大和控制原则的正式开发，技术转移小组应明确以下内容的要求：

● Data gathering: the appropriate requirements are specified for the data historian
数据收集： 合适的要求在数据历史学有特别规定
● Criticality of instruments: may be based on the criticality of the corresponding process parameter
仪器的关键性：可能基于相关工艺参数的关键性
● Tolerances for instruments: may be based on control requirements (e.g., pH)
仪器的公差：可能基于控制需求（如 pH）
● Alarming requirements: may be based on the criticality classification of the process parameters
报警要求：可能基于工艺参数的关键性类别

After a formal assessment of equipment, instruments, and control needs, the technology transfer team can incorporate the scale-up or design philosophy requirements into a set of user requirement specifications (URSs). In practical, the URS are general documents containing environment, health and safety, GMP, and other requirements. The URS will form the basis for the design/fabrication/procurement of the equipment. Simultaneously, functional and design specifications may be defined for any equipment used in the process.

For example, a production bioreactor or fermentor might be scaled up. While the vessel volume is scaled up, some factors, such as the volumetric oxygen mass transfer coefficient (kLa) or power input per unit volume of bioreactor, might be able to remain constant. If the kLa is to be kept constant across scales, then the fermentor's gas supply capability may need to be upgraded. In either case, a different type of reactor modification may be required based on the scale-up philosophy chosen (5).
在经过正式的设备、仪器和控制需求的评估后，技术转移团队可以把放大或设计方案要求融入一系列的URS中。在实践中，URSs是包含了环境、健康和安全、GMP和其它要求的总体文件。URS将形成设备设计/制造/采购的基础。同时，生产中用到的任何设备得功能和设计标准可能确定。
例如，一个生产生化反应器或发酵罐可能被放大。当管路体积放大时，一些因素，比如体积氧传质系数（kLa）或生化反应器每单位体积的电源输入，可能仍然能够保持不变。如果kLa在各个批量时保持不变，那么需要升级发酵罐的气体供应能力。如果电源输入要保持不变，那么发酵罐的搅拌系统可能需要升级。在任一种情况下，不同类型的反应器的修改可能基于选择的放大方法而被要求。

4.1.2.3 Control Philosophy / 控制原则

Like a scale-up philosophy, a control philosophy needs be identified for each of the major pieces of equipment that will be used in the process.
和工艺放大原则一样，工艺中的每一个的重要设备的控制原则需要确定。

In a fermentor, for example, the dissolved oxygen (DO) used may be process specific and may need to be calibrated and optimized for specific operation. Control of DO may be affected by cascade control whereby a change in the agitator speed is the first change in response to a DO change. This agitator control loop is a "slave" to the "master" DO control loop. An alternative to cascade control is a simple increase in air or oxygen sparge rate. A similar discussion may also be given for the trans-membrane pressure control of tangential flow filtration unit operations employed in many bioprocesses. 对于发酵器，比如，使用的溶解氧（DO）可能跟工艺有关，而且对于特定操作需要校正和优化。DO 的控制可 能通过串级控制来影响，搅拌速度的改变是响应 DO 改变的第一个变化。搅拌器的控制在流程上是"从属"于"主 人"DO 控制流程的。串级控制的另一个方式是简单的提高空气或氧气的喷射率。类似供讨论的例子可以是很多 生物过程使用的切向流过滤单元操作时横跨膜压差的控制。

4.1.3 Control Strategy / 控制策略

As defined by ICH, Q10 control strategy is: 如 ICH Q10 定义，控制策略是：

> A planned set of controls, derived from current product and process understanding that 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(6).
> 源自于现行产品和工艺理解的一组规划过的控制，用于保证工艺性能和产品质量。这些控制可包括与原料药和药用物质及组分，设施和设备运行条件，过程控制，成品质量标准，和监控与控制的关联方法与频次相关的参数与属性（6）。

Control strategy provides critical governance throughout the product lifecycle. The control strategy evolving as the product moves through development, technical transfer, commercial production, and discontinuation. Although the strategy varies at different stages, the core purpose of the control strategy remains the same: to ensure process performance and product quality. The principles of QRM can be applied to identify the control strategy. 控制策略为整个产品生命周期提供了关键的管理方法。控制策略参与了产品从研发、技术转移、商业生产到停 止上市的整个过程。虽然不同阶段控制策略会不相同，但是核心目标是一样的：确保工艺性能和产品质量。可 以将风险管理的原理用于确定控制策略。

From a control strategy management perspective, the application of risk analysis and human/ technical/economic resources management tools should also be taken into consideration. 从控制策略管理观点，也应该考虑风险的应用和人/技术/经济资源管理工具的应用。

A general analysis of production feasibility, using risk management principles, should be conducted prior to beginning transfer activities. The feasibility reviews are used to create and update the process risk assessment (described in the following sections) and identify potential manufacturing challenges. They also provide recommendations for process modifications needed to address manufacturing constraints and/or desired utilization strategies (e.g., yield or process time targets). 使用风险评估原理对生产可行性进行的常规分析应该在转移开始之前进行。可行性回顾用于建立和更新工艺风

险评估（以下章节介绍）和识别潜在生产挑战。风险分析也提供了工艺改进的建议，需要在生产限制和/或期望的利用策略中考虑（如，收率或工艺时间目标）。

Fishbone (Ishikawa) analysis is commonly used in risk assessment to identify the risks by laying out causes and effects (Figure 4.1.3-1)
鱼骨图（石川图）分析经常用于风险评估，通过展出原因和影响的方式来识别风险，(图 4.1.3-1)。

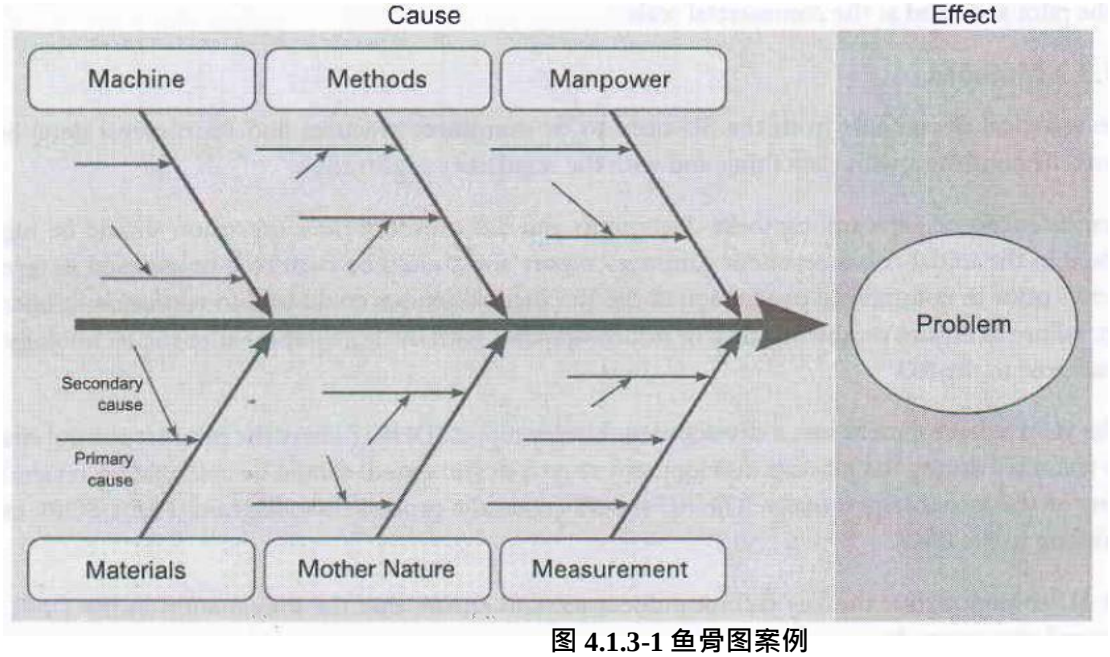


图 4.1.3-1 鱼骨图案例

The principles of fishbone analysis can be applied to identify the control strategy. The effect would be adverse effects on product quality, which are defined by CQAs. The causes can be laid out according to six main components (the six M's in an Ishikawa, or fishbone, diagram) (7, 8):
鱼骨图原理可以用于确定控制策略。鱼骨图中的影响产品质量，来自 CQA 定义，将是负面的。鱼骨图中的原因可分为 6 个主要成分（6 个 M）(7,8)：

1. Machine (equipment) 机器（设备）
2. Methods (documentation) 方法（文件）
3. Material 物料
4. Manpower 人
5. Measurement 测量
6. Mother nature (environment) 环境

The six Ms are described in detail bellow. 6 个 M 在下面详细介绍。

4.1.3.1 Machine 机器

The technical transfer team needs to identify the key sets of equipment used to control the CPPs. The operating ranges of the key equipment at the RU need to be checked, and their capability to achieve the critical process parameter (CPP) range needs to be evaluated. Any gaps revealed during the evaluation are documented as part of the risk assessment.

Equipment operational qualification should be performed as a prerequisite of process validation at the RU. Preventive maintenance programs should be established at the RU, and the SU's project management program can be referenced for consistency.

If the technology is transferred from a development site to a commercial site, the scalability of the equipment needs to be evaluated. The CPPs developed at laboratory or pilot scale may be scale dependence.

The CPP ranges at the receiving commercial scale should be corrected to account for the scale-up factors. For example, if the agitation rpm of a crystallizer is chosen as a CPP based on the development-scale models, the appropriate range of rpm at the commercial scale needs to be established. This should be based on a comparison of factors, such as mixing and shear stress between the crystallizers, at the pilot scale and at the commercial scale. 商业规模的接收方应该考虑

4.1.3.2 Methods 方法(文件)

The technical documents from SU need to be examined; practices and instructions described should be consistent with each other and with regulatory registration.

Inconsistencies or gaps among these documents and difficulties in their execution should be highlighted in the initial risk assessment summary report and should be corrected or assessed in terms of risks prior to commercial production at the RU. Inconsistencies could lead to confusion in operation, failure to ensure product quality, or noncompliance with the registration after the technology is transferred to the RU.
If the SU is a development site, a development history report (DHR) (where the product control strategy identified during the product development stage is documented) should be available for review as a part of the technology transfer. The RU should create the process flow diagram (PFD), SOPs, etc. according to the DHR.
The SU should review the key technical documents to ensure that the information in the DHR is captured appropriately.

4.1.3.3 Material 物料

The SU needs to provide the raw material specifications. If an API process with multiple intermediate products is transferred, all intermediate product specifications need to be provided by the SU.
The SU needs to ensure that the specifications listed in the local documents are consistent with the registered specifications. The RU is responsible for qualifying the raw material suppliers (unless the agreement between the two units states otherwise).
If the process is transferred from a development site to a commercial site, the suppliers' sustainable capacity needs to be examined during the suppler qualification. The storage conditions of the raw materials (including the intermediate products) should be specified, and associated hold times (or expiry dates or reevaluation periods) should be available to the RU. The constraints of transporting raw materials across different regions or countries should be considered. Delays in obtaining these materials as a result of customs clearance procedures may occur, and the storage conditions might therefore change temporarily. The impact of delays and temporary storage condition changes on intermediate product quality should be assessed.

4.1.3.4 Manpower 人

The RU should clearly define the roles and responsibility of each technology transfer team member and ensure adequate operation and supporting staffing for commercial production at its facility. A training or personnel qualification should be established at the RU. Proof of training completion for each person is needed prior to process validation.

4.1.3.5 measurement 测量

Analytical methods should be validated prior to the process validation at the RU, regardless of whether the methods have been validated at the SU. The analytical methods to be validated include those for both routine samples, such as intermediate products and buffers, and for nonroutine samples, such as samples for process-related impurities. The sampling plan, including sample location, size, frequency, method, and handling, should be clearly defined. The instruments used to measure in-process parameters should be qualified. The measurement uncertainty for CPPs needs to be calculated at the RU.
This information is used to set the operation targets to ensure that the true CPP values are within the predefined limits when instrument measurement uncertainty is considered.

4.1.3.6 Mother Nature 环境

Whether the RU is prone to nature disasters and how well it is designed to minimize their impact should be evaluated. This may have been done when the RU's facility was built. If the RU and SU have a dramatic climate difference, temperature and moisture control would need additional consideration, particularly for raw material storage and transportation.

4.1.3.7 Feasibility Reviews 可行性审核

Regardless of the knowledge and different type of TTP (e.g., inter-or intracompany transfer of a manufacturing process from a multi-purpose department to a dedicated department), the feasibility analysis and the six Ms described above in this section have to be accounted for by both SU and RU teams.

The preliminary feasibility study should consist of at least a gap analysis that compares the SU's manufacturing plant/department to the RU's manufacturing plant/department. It should identify potential differences that could make the process/product fail the set specifications and identify corrective actions. The results of this analysis should be recorded in a controlled document and be approved by the SU and RU as well as the project manager. This document should officially state the suitability of the RU to reproduce the process to be transferred.
4.1.3.1 机器
技术转移团队需要确定用于控制 CPPs 的一组关键设备。RU 处的关键设备的操作范围需要被核对，并且他们实现 CPP 范围的能力需要被评价。评价过程中发现的任何差距都要记录作为风险评估的一部分。
在 RU 设备运行确认应作为工艺验证的预要求。RU 处应确认预防性维护项目，并且可以参考 SU 的工程管理项目来确认一致性。
如果技术是从一个研发地转移到商业生产地，那么要评估设备的可扩展性。实验室或中试批开发的 CPPs 可能是跟规模相关的。
商业规模时的 CPP 范围应该修正以对放大因素负责。例如，如果基于研发规模模型，结晶设备的转速被选做 CPP，那么需要确定商业规模的转速的范围。这需要基于中试批和商业批的因素的比较，例如不同结晶设备的混合和剪切应力。
4.1.3.2 方法
需要检查来自 SU 的技术文件；描述的操作和说明应该彼此一致并与法规注册内容一致。
这些文件中的不一致性或差距，以及执行过程中的困难应该在最初的风险评估摘要报告中进行评估，并且需要在 RU 处的商业生产之前已风险的形式修正或评估。在技术转移到 RU 后，不一致性可能导致操作的困惑。无法保证产品直来那个或不符合注册内容。
如果 SU 是研发地点，作为技术转移的一部分，一份开发历史报告（产品开发阶段识别的产品控制策略需要在此被记录）应该可以用于审核。RU 需要根据 DHR 创建工艺流程图（PFD），SOPs 等。
SU 应审核关键技术文件以保证 DHR 中的信息被合适的抓到了。
4.1.3.3 物料
SU 需要提供原料标准。如果一个具有多种中间体的 API 被转移，那么 SU 需要提供所有的中间体的标准。
SU 需要保证本地文件列出的标准与注册标准一致。RU 需要确认原料供应商（除非两个部门另有协议）。
如果工艺从研发地点转移到商业生产地，那么在供应商确认过程中需要检查供应商的持续能力。原材料的存储条件（包括中间体）需要明确，同时相关的存放时间（或失效期或复测期）需要对 RU 可用。要考虑跨区域或国家运输原材料的限制。由于海关放行程序可能延迟获得这些无聊，那么存储条件可能暂时变化。需要评估中

间产品延迟和暂时储存条件变化的影响。
4.1.3.4 人力
RU 需要清楚的确定每个技术转移团队成员的角色和职责，并要保证厂区的商业生产所需的足够的操作和支持人员。RU 需要确立培训或人员确认。在工艺验证之前需要证明每个人培训的完成。
4.1.3.5 测量
RU 的工艺验证之前需要验证分析方法，无论 SU 处是否验证了该方法。需要验证的分析你方法既需要包括常规样品，例如中间产品和缓冲液，还包括非常规样品，例如工艺相关杂质样品。取样方案，包括取样地点、取样量、频率、方法和处理都需要明确。检测过程中参数的仪器需要确认。RU 处的 CPPs 的测量不确定性需要计算。当考虑到仪器测量不确定性，这个信息可用于设定操作目标以保证真实的 CPP 值在预定的范围内。
4.1.3.6 环境
应该评估 RU 是否易于导致自然灾难以及它们减少影响的设计如何。这个可能在 RU 厂房建设好了时已经完成。如果 RU 和 SU 有很大的温度差别，温度和湿度控制需要进行额外考虑，尤其是原材料的储存和运输。
4.1.3.7 可行性审核
不考虑 TTP 的知识和不同类型（例如，生产工艺从多目的部门到专门部门的公司内部或外部的转移），SU 和 RU 团队都要进行可行性分析和之前描述的 6Ms。
预先的可行性研究应该至少包括差距分析，要比较 SU 生产车间/部门和 RU 生产车间/部门的不同。需要确定可能导致工艺/产品不符合设定标准的潜在的差别，并要确定改正措施。分析的结果需要记录在控制文件中并被 SU 和 RU 以及项目经理批准。文件需要正式的声明 RU 的适用性以重现被转移的工艺。

4.1.4 Facility Design/Layout considerations 厂房设计/布局考虑

It is very common to design and develop the manufacturing technology in a non-GMP facility, which allows for flexibility and is more cost effective than performing these activities under GMP conditions. As a result, the process may be transferred from a non-GMP to a GMP facility.
在非GMP车间设计和开发生产技术很常见，它有灵活性并且比在GMP条件下更节省成本。结果，需要将工艺从非GMP车间转移到GMP车间。

4.1.4.1 Transfer from Non-GMP to GMP Facilities 从非 GMP 设施转移到 GMP 设施

Per regulatory guidelines, all GMP facilities must maintain certain standards for facility layout, design, and controls (e.g., temperature, air pressure, and humidity) in addition to the basic elements of facility design (e.g., animal and pest control and environmental monitoring)(9).
The process development work may have been performed using non-GMP utilities (e.g., plant steam instead of process steam or plant air instead of clean air). When such a process is transferred from the development facility to a GMP facility, the technology transfer team should examine the use of the appropriate utilities at appropriate stages in the process. The RU might have general policies guiding the use of GMP and non-GMP utilities for various activities (e.g., use of plant steam for steaming non-product contact small parts as part of cleaning). Any dedicated/special equipment used for the process may be outside the scope of the facility guidelines, so the technology transfer team may need to determine the appropriate type of utilities to be used for those pieces of equipment.
每个监管指南，所有的GMP厂房必须维持厂房设计的基本元素（例如，动物和昆虫控制、环境监控）之外，还要维持厂房不具、设计和控制的一定标准（例如，温度，压差和湿度）。
工艺开发工作可能使用了非GMP设施进行（例如，厂用蒸汽替代工艺蒸汽或者厂用气体替代洁净气体）。当这种工艺充开发厂房到GMP厂房时，技术转移团队需要确认在工艺中的合适的阶段使用了合适的设施。
RU可能需要有整体方针来指导GMP和非GMP设施用于各种行动（例如，使用厂房蒸汽来用蒸汽处理非产品接触的小件来作为清洁的一部分）。任何用于工艺的专用的/特别的设备可能在厂房指南的范围之外，那么技术转移团队需要确定适用于这些设备的设施的合适的类型。

4.1.4.2 New Facility Construction 新厂房建设

If the transfer activity involves the construction of a new facility, the RU should generate a user requirement-like document that describes the facility characteristics needed to meet the process/ product specifications, which in turn drive the engineering development of the facility. The transfer of the process can sometimes be conducted using the transferred documents to define the requirement. It is well understood that this approach could lead to mistakes due to incomplete evaluation of all variables; therefore, a common solution is to define the requirements starting from the transferred information, proceed with a deep gap analysis, and then determine whether the documents are sufficient to support those requirements.
如果转移活动包括了新设施建设，RU 应该起草一个类似于 URS 的文件，这个文件描述了满足工艺/产品质量标准的设施的特性，这个文件进而推动了设施的工程开发。有时候工艺转移，可以使用转移的文件来确定需求。这种方法通常会由于不完整的评估各种情况导致错误，因此，一个普遍的解决办法是从信息转移开始，经过深度地差距分析，然后决定这些文件是否足以支持那些需求。

4.1.5 Facility Fit Report 厂房适用性报告

Facility fit reports (FFRs) are a key deliverable in steps 2 and 3 to aid in the transfer of the late-phase development and commercial processes to the commercial facility. These reports translate the process description details into an operational map of how the process is to be executed at the site.
场地合适性报告（FFR）是在第 2 步和第三步中的关键可交付成果，该成果有助于开发后期工艺和商业化工艺到商业化场地的转移。这些报告将工艺说明细节转化成工艺如何在现场执行的一个操作图。

Process ranges, buffer volumes, column volumes, tank assignments, and step durations are examples of the type of information included in these reports. These reports are typically authored by the RU process subject matter experts (e.g., commercial technical support personnel) and reviewed and approved by SU process subject matter experts (e.g., manufacturing, facilities, supply chain, and quality personnel). 工艺范围、缓冲体积、柱体积、储罐分配、步骤持续时间是这些报告所包含的信息类型的例子。这些报告通常 是由 RU 项目主题专家（比如商业化技术支持人员）起草，由 SU 项目主题专家（如生产、设施、供应链和质 量人员）审核和批准。

These reports govern the transfer of process details into manufacturing batch records and solution preparation records and serve as a guide for the flow of the process through the facility. FFRs may include summaries of process risks, raw material safety risks, and action items resulting from fit-to-plant exercises. 这些报告管理工艺的细节转成批记录和溶液配制记录和作为工艺在设施内的流向指南。FFR 可能包括工艺风险 概述、原料安全风险、以及工厂化运用结果的行动项目。

Other information typically found in the FFR includes: FFR 通常含有的其他信息：

● Detailed process descriptions by unit operations and associated process flow diagrams that reflect the commercial scale of operations and fit considerations 通过单位操作和相关的工艺流程图详细描述的工艺，反映了商业规模的操作和合适性考虑

● Process sample plan with in-process control limits, where appropriate
带有中控标准的取样计划，合适的时候

● Comprehensive list of raw materials and components used in the process
工艺用到的原料和组分的综合清单

● Gap/risk analyses related to process fit, including new capital equipment or modifications of capital equipment required, equipment/facility gaps, clean-in-place/steam-in-place flow path utilization, new materials or manufacturing supplies needed, and/or automation gaps 关于工艺合适性方面的差距/风险分析，包括新的主要设备或主要设备需要的改造，设备/设施的差距，管道在线 清洁和在线灭菌的使用，新的物料或生产供应商，和/或自动化差异。

4.1.5.1 Environmental Variables 环境变量

Environmental variables are normally controlled within set tolerances at given facilities. However, an assessment should cover the potential that, even though both facilities operate within given tolerances, facility differences may have an impact on the product or the tests to be performed. The assessment should be based on the available process information or analytical tests performed and their susceptibility to environmental factors.
在既定的厂房中，环境变量通常控制在设定的范围内。然而，评估应该包括这个可能性：即使两个厂房运行都在给定的范围内，但是厂房的差异可能对产品或进行的分析测试产生影响。评估应该给予可用的工艺信息或执行的分析测试，以及对环境因素的敏感性。

The following are examples of some environmental condition that, even if properly controlled within set tolerances, may have impact on product production or testing: 以下是一些关于环境条件的例子，即使控制在设定误差内，也可能影响产品生产或检测：

● **Humidity and Temperature**: Humidity and temperature are controlled in most facilities, but they should be assessed to determine whether potential differences could affect product production or testing. This testing may involve evaluating trends over a year in addition to the allowed range. 湿度和温度：大部分厂房都有温湿度控制，但是应该评估确定两地潜在的差异是否能影响产品的生产和测试。 这个测试可包括超过一年的趋势以及允许的范围。

● **Light**： The source and type of lighting should be evaluated. Particular attention should be given to possible source of natural light due to their impact on photosensitive compounds when these sources are compared to the lighting of the RU. 光：光的来源和类型应该评估。应该特别关注自然光的可能来源并比较 RU 的光源，因为他们会影响有光敏感性的化合物。

● **Pressure**: Pressure does not to be controlled, but it may have undesirable consequences for final dosage forms that are liquids, ointments, or creams that are filled in flexible containers. A light-density polyethylene bottle filled at a plant at 3,000 m altitude could be aesthetically affected, for example, when marketed at sea level and vice versa. 压力：
压力一般不需要被控制，但是它可能对最终的制剂产品产生不希望的后果，如被装进不同容器的液体、药膏、油脂。例如一个在3000m海拔的工厂灌装的光密度聚乙烯瓶到海平面高度的市场上可能影响其外观，反之亦然 。

4.1.5.2 Viral Segregation 病毒隔离

Transfer of processes for biotechnology-derived products expressed in animal cells (e.g., monoclonal antibodies from Chinese hamster ovary [CHO] cells) requires consideration of the impact of viral segregation on facility design/layout. CHO cells are known to endogenously express retrovirus-like particles. Although dedicated steps for virus clearance (i.e., inactivation and removal) are built into the purification scheme, these steps may not occur until midway through the purification process. In such cases, an effort should be made to segregate virus-related" process streams from non-virus-treated process streams, especially if open processing is used. The technology transfer team should consider initiating specific clearance steps prior to exposing the treated and nontreated process steams if physical segregation or completely closed processing is not feasible. 表达于动物细胞的生物技术产生的产品（如来自于 CHO 细胞的单抗）的工艺的转移要求考虑病毒分离对厂房设计/布局的影响。CHO 细胞是内源性表达的类似逆转录酶病毒的粒子。尽管专门的病毒清除步骤（即灭活和去除）设计在纯化计划中，但是这些步骤可能直到纯化工艺中间才可能会发生。在这样的情况下，应尽力使未处理病毒的工艺流与处理过病毒的工艺流分开，特别是使用开放工艺的。当物理隔离或者完全密闭的工艺无法实现时，那么工艺转移团队在暴露处理和未处理过的工艺流之前应考虑启动专门的清理步骤。

4.1.5.3 Support Laboratory 支持实验室

Finally, using an on-site support laboratory (which can be non-GMP) to help with troubleshooting and routine support for the production facility can also be considered. Performing scale-independent technology transfer studies in an on-site development laboratory will help share knowledge between production and support personnel. 最后，也可考虑使用一个在现场支持的实验室（可以是非 GMP 的）用来帮助解决问题和对于生产场所的日常 支持。在支持实验室开展与批量无关的技术转移研究可以帮助生产的和支持人员之间知识共享。

An example of such support work is evaluation or generation of worst-case soil for use in facility cleaning validation studies. If the philosophy used for cleaning validation is to use worst-case process soils to demonstrate the efficacy of clean-in-place cycles, this material can be generated from the on-site support laboratory. Generation of this material in the support laboratory early during technology transfer (instead of generating this material at scale in the production facility) allows sufficient time for experimentation/development of cleaning cycles.
这类支持工作的一个例子是评估或产生用于厂房清洁验证研究的最差条件。如果用于清洁验证的理论是用最差条件来证明在线清洗循环的效力，那么这种材料可以产生于现场的支持实验室。在技术转移早期产生于支持实验室的这种物料允许有足够的时间用于清洁循环的试验/研发。

4.1.6 Transfer of Documents 文件的转移

Technology transfer presents challenges relating to the documentation provided by the SU and its implementation by the RU, especially in the transfer from R&D to manufacturing due to the nature of the project step.
技术转移在 SU 提供的文件以及该文件在 RU 的实施提出了挑战，由于项目步骤的特点，特别是从 R&D 到生产场所的转移。

Specifically in these cases but applicable to all technology transfer projects, the documents transferred by the R&D unit should include at least the following:
特别是在这些情况下,但适用于所有技术转让项目，文件从 R&D 转出应该至少包括如下：

- Product CQAs 产品关键质量属性
- Impurity profile 杂质概况
- Specifications (at least for drug substance/product and packaging components) 质量标准（至少是原料药/产品和包装材料）
- Critical and noncritical process parameters along with ranges and proven acceptable ranges 关键和非关键参数范围和被证明的可接受范围
- Manufacturing instructions 生产指令
- Procedures for process-related activities 工艺相关活动的程序
- Raw and auxiliary materials 原料和辅助材料
- Cleaning procedures 清洁程序
- Available stability data 已有的稳定性数据
- Validation documents (at least aseptic process and pathogen clearance validation reports) 验证文件（至少无菌工艺和病原体清除验证报告）
- Analytical method SOPs 分析方法 SOP
- Process development documents (e.g., key technical reports and process development history reports) 工艺开发报告（如，关键技术报告和工艺开发历史报告）
- Previous regulatory filing 先前的法规注册
- Manufacturing process flow and instructions 生产工艺流程图和说明
- Analytical methods and procedures 分析方法和程序
- Development report 开发报告

The following information might also need to be provided to the new product producer:
以下信息可能也需要提供给新的产品生产者：

- Clearance of process impurities 工艺杂质的去除

● Virus clearance 病毒的清除
● Hold times of the process steps 工艺步骤的保留时间
● Mix times of the solutions and the product 溶液和产品的混合时间
● Chromatography, filter, and membrane lifetimes 层析、过滤器和膜的寿命
● Container closure study descriptions 包装系统的研究描述
● Reprocessing or rework data 返工或重加工数据
● Stability of raw materials, APIs, or cell lines 原料、API 和细胞系的稳定性
● Polymer materials that have direct contact with the product (compatibility/leakage) 和产品直接接触的聚合物材料（相容性/泄漏）
● Annual product review for trending 产品年度回顾中的趋势

4.1.7 Technology Transfer Protocol 技术转移方案

A road map must be designed from the very beginning of the project to ensure comprehensive project management. The SU and RU should jointly develop a TTP plan that will govern the entire project. Critical inputs to the technology transfer plan include a regulatory strategy and a gap analysis (described in Section 5.7). Outputs of this stage include a finalized project plan describing the activities, resources, schedule, and project risk assessment. 应该在项目的一开始设计一个路线图以保证项目的综合管理。SU 和 RU 应联合起草管理整个项目的 TTP 计划。 TTP 计划的关键输入包括一个法规策略和一个差距分析（第 5.7 节）。这个阶段的输出包括一个最终的项目计 划，该计划描述了活动、资源、日程表和项目风险评估。

The TTP plan should drive the overall process and define the strategic approach by describing:
TTP 计划应驱动整个过程并通过以下内容的描述来确定策略方法：

● The manufacturing process being transferred 被转移的生产工艺
- Sampling and testing steps 取样和检测步骤
● Roles and responsibilities of the SU and RU SU 和 RU 的角色和职责
● RU’s equipment and facilities RU 的设备和设施
- If the transfer is from one manufacturing facility to another, a description of both sites that includes gaps and/or differences 如果是从一个生产场所到另一个生产场所的转移，一个含有两地差异和/或不同的说明
● Documentation requirements 文件需求
● Project schedule, including roles and responsibilities of personnel (a Gantt chart is helpful here) 项目日程表，包括人员的角色和职责（甘特图在这里是有帮助的）
● Technology transfer tools, including templates 技术转移工具，包括模板
● Backup plans for critical tasks to avoid delaying or stopping the project due to unforeseen events 关键任务的备份计划以防项目因为不可预见的事故而延迟或者停止
● Status monitoring 状态监控
● Correlations to previous and subsequent tasks 前后任务的相关性

The technology transfer protocol must establish context for the TTP, including internal and external contextual factors and which risk-management tools to use. The external context might include competitive, financial, regulatory, legal, environmental, and cultural aspects. The internal context can involve company policies and procedures, systems, operational objectives, personnel training and knowledge, available resources, and culture.
技术转移方案必须建立 TTP 的背景，包括内部的和外部的背景因素和哪个使用风险管理工具。外部环境可能包括竞争、财务、法规、法律、环境和文化方面。内部环境包括公司的政策和程序、系统、运营目标、人员培训和知识、可用的资源和文化。

All personnel with management roles in the transfer, including the two team leaders, should agree to and sign the project plan. The exception is the project committee, which functions primarily as a consultant. A gateway review by senior leadership is used to make visible the plans and risks and provides approval to move to the next stage. 转移中，所有管理人员包括两个组长，应该同意并在项目计划上签字。项目转移委员会除外，其功能主要是顾 问。一个上一级领导的节点审核用于显示这个阶段的计划和风险，提供可以进入下一个阶段的批准。

4.2 Stage 2: Process Readiness 阶段 2：工艺准备

The goal of this stage is to achieve readiness of the process, equipment, automation, facility, operations, and assays to successfully execute process performance qualification (PPQ) lots. Shakedown activities culminate in the production of engineering lots that provide conformation that all systems are sufficiently ready to perform PPQ lots. Training at the RU is a key goal of this stage. A gateway review is used to highlight the rationale for proceeding to the next stage and should include a discussion of the potential risks to the successful execution of PPQ lots. 这个阶段的目标是实现工艺、设备、自动化、设施、操作、检测的准备工作，以成功的执行工艺性能确认（PPQ）批次。工程批生产积累的临时活动给所有系统提供了确认，都已经充分准备好执行 PPQ 批次了。在 RU 的培训是这个阶段的关键任务。节点审核用于强调进入下一个阶段的依据，节点审核应包括成功实施 PPQ 批次的潜在风险的讨论。

At the end of the assessment and planning phases and before the start of the TTP implementation, the technology transfer team sets up a stage/gateway step. The purpose of this step is to confirm that the process is ready, that all critical aspects of the project have been deeply analyzed, and that the potential associated risks have been identified and properly mitigated.
在评估和计划阶段的最后，在 TTP 实施前，技术转移小组队设置一个阶段/节点步骤。这个步骤的目的是确认工艺是否准备就绪，所有的关键项目都已经深入分析过，潜在的相关风险已经得到识别和适当的降低。

The formalization of the assessment and appropriate training of personnel impacted by the transfer are critical. Thus, the proper procedures have to be in place in the RU and SU. 评估的正式化和受转移活动影响的人员的合适培训是关键的。因此，RU 和 SU 现场需要有合适的程序。

4.2.1 Process Changes 工艺变更

The RU should manage the transfer via its change control procedure, and a general risk management analysis should be performed to evaluate the impact of the process on the affected departments.
RU 应通过自己的变更程序管理转移，一个常规的风险管理分析应执行以评估工艺的对受影响部门的影响。

The RU should then translate the R&D information and procedures (e.g., specific activities and batch records) and adapt the process flow to fit the designated department through creation of specific procedures. Analysis of raw and auxiliary materials should be performed to identify and qualify suitable suppliers and materials. A risk management approach should also be applied to classify and evaluate the impact of process changes aimed at optimizing the process itself. 然后，RU 应转化研发信息和程序（如详细的活动和批记录），吸收工艺流程并指定合适的部门建立相关程序。开展原料和辅助材料的检测以识别和确认合适的供应商和物料。风险管理方法也要应用到分类和评估工艺变更的影响，致力于优化工艺自身。

In the course of scale-up, process parameters and equipment may be subjected to change. Procedures should be in place at the RU to efficiently manage any changes while maintaining traceability. The procedures must take into account any documents submitted to regulatory authorities and the possibility of the need for amendments. Affected processes and equipment include:
在放大过程中，工艺参数和设备可能要变更。RU 需要有个程序来高效管理任何变更并保持可追溯性。程序必须考虑任何递交到监管当局的文件，需要修订的可能性。受影响的工艺和设备包括：

- Filtration areas 过滤区域
- Media 媒介
- Operating pressures and flow rates 操作压力和流速
- Process hold times 工艺持续时间
- Cleaning solutions/procedures and rinse volumes 清洁溶液/程序和淋洗体积
- Devices (e.g., changing from housing to a filter-press for depth filtration) 器材（如深度过滤时压滤罩的变更）
- Disposable versus stainless steel containers 一次性容器相对于不锈钢容器

Process development reports should detail the rationale to support any changes. The application of good documentation practices and design of experiment (DoE) techniques during process development are fundamental to support these changes and the application of GMPs during clinical manufacturing. Insertion of new steps into, or modification of, the process flow should be carefully evaluated from quality and regulatory points of view. In the event of a substantial process modification, the transfer should be put on hold and feasibility studies should be performed again.

工艺开发报告应详述理论依据来支持任何变更。良好文件体系规范的应用和在工艺研发期间的实验设计（DoE）技术是支持这些变更的基础，是 GMP 应用于临床生产的基础。插入新的步骤，或者修改工艺流程应该从质量和注册的观点仔细评估。当工艺重大修改时，转移应该暂停，转移可实施性研究应该再次执行。

4.2.2 Training 培训

Based on an evaluation of the RU's experience, the SU should provide hands-on training for specific steps in the process as needed. This training may be performed either at the SU or the RU facility. The type and the amount of training vary depending on the complexity of the steps and the experience of the RU personnel in performing the specific steps. 根据对 RU 现有的经验进行的评估，必要时，SU 应该提供工艺中特定步骤的手把手的培训。这个培训可能在 SU 设施也可在 RU 设施进行。培训的类型和量根据步骤的复杂性和 RU 人员在特定步骤的操作经验而不同。

Training should be divided into two steps:
培训应分成两步：

1. The RU technology transfer team members managing the TTP (e.g., RU leader, manufacturing department head, plant maintenance head, and engineers) and other key personnel (e.g., head of shift for manufacturing or maintenance departments) should be trained in the process at the SU (i.e., on-the-job training, training the trainer).
RU 技术转移小组中管理 TTP 的成员（如 RU 负责人，生产部负责人，公司维护部门负责人，工程师）和其他关键人员（如生产的班组长或者维护部门的班组长）应该在 SU 处进行时培训（如在岗学习、培训培训师）。

2. Trained personnel should draft the process-related procedures for the RU and for training the operating personnel.
已受培训人员应该为 RU 起草工艺相关的程序并给操作人员做培训。

4.2.3 Development Data on Process Management 工艺管理的开发数据

Development Data are the data captured during the R&D phase of creating a new product. This may consist of data from quality of design, the CQAs, the specifications, and the assurance of product and process consistency. The data relay how the process performs; whether it can perform consistently; and whether it ensures the purity, quality, safety, and efficacy of the drug product or drug substance.
开发数据是在 R&D 创造新产品期间获得的数据。这可能包括从质量源于设计、CQA、质量标准、确保产品和工艺一致性来的数据。这些数据传递工艺该如何实施；实施是否能连贯统一；是否能确保药品或 API 的纯度、质量、安全性和有效性。

Development data are derived from analytical methods, testing of the product during the R&D phase, and scale-up of the process. Process management during the development phase is critical in light of compressed time-to-market expectations. As a result, development strategies and milestone dates for chemistry, manufacturing, and control activities needs to support requirements for product development and should be described in development plans. During process development, it is important to understand the production environment, the equipment, the parameters that need to be developed, and the operations to be used.
开发数据是从分析方法、产品在 R&D 期间的检测、工艺的放大中获得的。由于紧缩的上市时间要求，在研发期间的工艺管理是非常关键的。事实上，化学、生产、控制活动的开发战略和里程碑日期需要支持产品开发和应该在开发计划中说明。在工艺开发期间，理解产品背景、设备、需要开发的参数、将运用的操作是重要的。

The development phase data are critical because they verify that the safety and efficacy of the product align with the specification and ensure consistency from development to manufacturing. The data from the development phase are part of the TTP from R&D through production as the ranges are refined throughout the process. 开发阶段数据是关键的，因为这些数据证明药品的安全性和疗效与质量标准一致和确保研发和生产的一致性。 从研发阶段来的数据是 TTP 从 R&D 到生产的一部分，随着 TTP 开展，数据的范围会更新。

Critical process parameters should be defined during development. These parameters establish criteria that are consistent with process stability. The key is to characterize the range that will result in producing a product that meets certain CQAs or proven acceptable ranges while keeping other parameters constant, as defined in ICH Q8 (R2). Many organizations also establish normal operating ranges that are tighter and can identify the need for investigation (2). 关键工艺参数应该在开发期间确定。这些参数标准和工艺稳定性是一致的。关键是确定参数范围，就像在 ICH Q8 里（R2）介绍的，在这个范围内生产一个产品将导致产品符合特定的 CQA 或者已证明的可接受范围（当保 持其他参数不变时）。很多组织也建立正常操作范围，这些范围更窄和能识别调查的需要。

To assess risks and establish critical process parameters, a top-down approach, such as a fault tree analysis, can be used to identify critical subprocesses within the overall process. The subprocesses identified can then be assessed through a failure mode and effects analysis (FMEA)-based approach to identify root causes and critical manufacturing steps. 评估风险和建立关键工艺参数，自上而下分析法如失败树分析，可用于识别整个工艺中的关键子工艺。识别出 的子工艺再通过 FMEA 识别根本原因和关键生产步骤。

4.3 Stage 3: TTP Implementation and Qualification 阶段 3：TTP 实施和确认

During TTP implementation, equipment is installed and qualified, preliminary laboratory or manufacturing trials are conducted, and the PPQ lots are manufactured to satisfy the requirements for demonstrating reliable manufacturing. A gateway review is used to critically evaluate the performance of the PPQ lots, including stability data when applicable and any risks posed to the successful licensure of the facility.
在 TTP 实施期间，设备已经安装和确认，早期的实验室和车间生产试验已经实施，PPQ 批次已经生产以证明生产的可靠。节点审核被用于批判性评估 PPQ 批次的性能，包括场所被成功批准所带来的风险，必要时包括稳定性数据。

As discussed previously, the design of the plant and process is crucial to the success of the technology transfer and should be monitored closely by the appropriate transfer team members. Moreover, the transferred know-how should be the basis for scale-up evaluations or established process transfer and to organize the new plant and process to meet product specifications and process requirements. R&D scientists should be involved in such activities. 正如前面讨论的，工厂和工艺的设计对转移的成功是至关重要的，应该由合适的技术转移小组队成员密切地管 理。此外，已转移的“知道怎么做”应该作为放大批量的评估或者已建立的工艺转移的基础，可组织新工厂和工 艺以满足产品标准和工艺需求。R&D 科学家应参与这类活动。

4.3.1 Manufacturability Reviews 可生产性审核

Upon completion of each cycle of process development, detailed facility and process fit assessments and manufacturing information reviews are conducted prior to creation of manufacturing batch records. These represent a key deliverable for this step in the TTP. 在每一个工艺开发周期结束时，详细的设施、工艺适合性评估和生产信息要在生成批生产记录前被审核。这代 表了这一 TTP 步骤的一个关键可交付结果。

Manufacturability reviews are an end-to-end product review of the proposed late-phase development and commercial processes to be manufactured at the commercial site. These reviews are facilitated by the RU and conducted jointly by the SU and RU process subject matter experts (SMEs; e.g., commercial technical support and process development personnel) in collaboration with unit SMEs (e.g., facilities and engineering personnel). 可生产性审核是一个研发阶段后期和在商业化生产场所进行商业化生产初期的首尾交接审核。这些审核由 RU 促进，由 SU 和 RU 项目主题专家（SME，如商业技术支持和工艺开发人员）联合 SME 单位（如设施和工程人 员）共同进行。

Key outcomes of the manufacturability review at the early stages of the TTP are facility and equipment gaps and recommendations for process changes. Preliminary reviews may be needed for more complex processes to identify equipment and facility modifications requiring long lead times.
可生产性审核在 TTP 早期的关键输出是设施设备差距分析和工艺变更的建议。复杂的工艺可能需要初步审核，以便识别交付时间长的设备和设施的改造。

Another key output of manufacturability reviews is the plan of record. This document describes stage-appropriate assumptions approved by both the RU and SU. It also lists the process targets planned by the SU and the facility modifications and schedule planned by the RU. For example, this document lists the commercial titer to be targeted for the production bioreactor, the number and size of chromatography columns, and the cycle time for the bioreactor. 另一个可生产性审核的关键输出是记录的计划。这个文件描述了适当阶段的 SU 和 RU 共同批准的假设。可生 产性审核文件也列出了 SU 计划的工艺目标和 RU 计划的设施改造和日程表。例如，这个文件列出了生产用生 物反应器要达到的商业化浓度，色谱柱的次数和大小，生物反应器的周期时间。

4.3.2 Transfer of Analytical Test Methods 分析方法转移

Analytical test methods are well defined and are used for QC of raw materials, intermediates,

APIs, or final drug products. The analytical control methods should be transferred before the manufacturing process to ensure proper testing of the products.
分析方法是良好建立的，被 QC 应用于检测原料、中间体、API 或最终药品。分析控制方法应该在生产工艺前转移以确保产品的适当检测。

The SU should prepare the following information for evaluation to conduct a risk assessment of the analytical test methods:
SU 应该准备以下信息来评估开展分析方法的风险分析：

- Detailed description of the test method procedure 分析方法程序的详细描述
- Method validation report 分析方法验证报告
- Prior method transfer data 之前的方法转移数据
- Historical method performance information 历史的方法性能信息
- Detailed description of instrumentation used 用到的仪器的详细说明
- Examples of generated data (e.g., spectra and chromatographic plots) 已产生的数据的例子（例如，谱图和色谱图）

The RU should review this information and evaluate it for possible gaps (e.g., lack of experience in method type or differences in instrumentation to be used). Any gaps identified should be assessed for risk of failure by both the SU and the RU.
RU 应该审核这些信息并评估可能的差距（如，缺少该类型方法的经验或者使用的仪器不同）。任何已识别的差距应由 SU 和 RU 评估失败的风险。

After the initial assessments of the methods, a pre-approved protocol will be prepared to describe the experiments to be performed. There are a number of ways in which the transfer may be performed. 在最初的方法评估之后，一个预先批准的方案将会准备好来描述要进行的实验。转移开展的方式有很多种。

Examples of the types of approaches described in USP <1224> are shown below, but other transfer designs may be acceptable. The approach used should be justified and evaluated during the risk assessment (10).
USP 第 1224 章描述的方式类型的例子如下，但其他转移方式是可以接受的。使用的方法应该在风险评估期间被证明和评估（10）。

- **Comparative Testing**: The RU and SU both analyze a predetermined set of samples and perform a comparative analysis of the results generated. 对比测试：RU 和 SU 共同对预先设定的一组样品进行分析，并对得到的结果进行综合分析。
- **Covalidation between two or more laboratories**: The SU includes the RU in the validation team for the validation exercise to obtain data on reproducibility. 两个或更多实验室之间联合验证： SU 把 RU 包括在验证小组内以取得实验数据的重复性。
- **Revalidation**: The RU can perform a revalidation or partial validation of the method. 再验证：RU 可以对方法开展再验证或部分验证。
- **Transfer Waiver**: During the assessment, the given method does not require official transfer. The USP chapter contains examples of this situation, such as compendial methods, which do not need to be transferred between the SU and RU. However, the RU would need to perform method verification testing as defined in USP<1225> (11). 免予转移：在评估时，给定的方法不要求正式转移。USP 章节包括了这种情况的例子，比如药典方法不要求从 SU 转移到 RU。然而，RU 要根据 USP 第 1225 章开展方法确认测试。

Other study designs for method transfers are provided in PDA Technical Report No.57: Analytical Method Validation and Transfer for Biotechnology Products. Ultimately, the approach chosen should be based on the results of the risk assessment for the methods and this choice should be justified in writing (12).
方法转移的其他研究设计由 PDA 技术报告第 57 号提供：生物技术产品的分析方法验证和转移。最终选择的方式应当根据方法的风险评估结果，并且这个选择应当有书面的合理性评价（12）。

As part of the assessment of the transfer, the actual tests to be performed for the transfer need to be evaluated. The tests performed may depend on the experience of the laboratory, any gaps determined during the assessment, and the nature of the method to be transferred. 作为转移的一部分，用于转移而开展的实际检测需要被评估。开展的检测可能取决于实验室的经验、评估时决 定的任何差距以及要转移的方法的本质。

4.3.3 Monitoring 监控

4.3.3.1 Microbial Monitoring 微生物监控

Depending on the transfer phase and the type of product being transferred, an assessment will need to be performed of the applicability of microbial control and monitoring. The type and extent of microbial control and monitoring (e.g., sterility, endotoxins, bioburden, or container/closure integrity testing) will depend on the manufacturing process assessment and the probability of microbial contamination along with the final product's ability to support microbial growth. 根据转移阶段和要转移的产品类型，微生物控制和监控的适用性要进行评估。微生物控制和监控的类型和范围
（如，无菌、内毒素、微生物负载或容器/封闭完整性测试），取决于生产工艺评估和微生物污染可能性，以及最终产品支持微生物生长的能力。

If microbial monitoring methods are required, these methods should be transferred from the SU to the RU by on-site validation of the methods. Assessments should be performed of the RU facility's ability to support microbial testing or appropriately outsource the work to a third party. For implementation of compendia microbial monitoring methods, the USP contains descriptions of the necessary steps to perform the required verifications/validations. 如果要求微生物监控方法，那么这些方法应当通过现场方法验证从 SU 转移到 RU。要对 RU 设施支持稳定性检 测的能力或恰当的外包工作给第三方进行评估。对于药典微生物监控方法的执行，USP 描述了必要的开展要求 的确认/验证的步骤。

4.3.3.2 In-Process Monitoring 中间过程监控

The assessment of the manufacturing process should include the need for in-process analytical testing. Most steps are likely to be well defined and controlled, whereas other steps may require monitoring to ensure completion of reaction or maintenance of specific process tolerances (e.g., moisture content, extent of reaction, and pH). In-process methods may be continuous monitoring of a key attribute (e.g., pH), or may be performed at a single time intervals (e.g., moisture content or extent of reaction). The need and type of in-process method should be based on the results of the overall assessment of the process. 生产工艺的评估应当包括过程分析测试的需求。大部分步骤可能是明确的和受控的，然而有些步骤可能要求监 控来确认反应完成或维持特定的工艺限度（如，水分、反应程度和 pH）。过程方法可能是连续监控关键属性的
（如，pH），或者可能是单个时间间隔开展的（如，水分或反应程度）。过程方法的需求和类型应该根据整体工艺评估的结果而定。

For the selected in-process analytical methods, the level of information to be provided and the requirements for transfer will vary. The assessment should determine the difficulty of the method as applied and the criticality of the method. Methods determined to be more complex and critical may require additional information and evaluation during the transfer process. The information should include a sufficiently detailed description for performance of the method. Additional information may be required for more complex methods (e.g., chromatographic analysis). 对选定的过程控制分析方法，需提供的信息和转移的要求会是不同的。评估应当确定要应用的方法的难度和关 键性。确定更为复杂和关键的方法在转移过程中可能要求额外的信息和评估。信息应包括执行方法的足够详细 的描述。对更复杂的方法可能要求额外信息（如，色谱分析）。

In-process analytical methods do not require the rigorous level of transfer that is required for QC analytical methods, but the principles used for QC methods may be applied to the in-process methods. It may be useful to rank each of the methods to determine the extent of transfer required using the following criteria:
过程控制分析方法不像转移 QC 分析方法那样严密，但应用于 QC 方法的原则也可用于过程控制方法。对每个方法进行分级可能是有用的，使用下面的标准来确定要求的转移程度：

- **Analytical Complexity**: Including requirements for a specific academic or scientific background, extensive instrument expertise or an extensive set of method particularities impacting the results of the analysis (pH is classified as a simple method, whereas an HPLC assay is classified as complex) 复杂分析：包括要求特定的学术或科学背景、广泛的仪器专业知识或影响分析结果的广泛的方法特性组合（pH 被分类为简单方法，而 HPLC 含量方法被分类为复杂的）
- **Product Specific or Product Independent**: For example, pH monitoring is a product-independent method whose result is not affected by the chemical, whereas the extent of reaction assays is product specific 产品专用或独立于产品：例如，pH 的监控是独立于产品的方法，该结果不被化学物影响，而反应程度的含量检 测是产品专用的

● **RU Experience**: The RU's history of using the analytical methods required /RU 的经验：RU 使用所要求的分析方法的历史

The necessity to monitor the manufacturing process can be also faced with a process analytical technology approach that is based on accurate risk analysis and process knowledge. 监控生产工艺的必要性也会面对基于准确风险分析和工艺知识的工艺分析技术方法。

According to the current guidance, process analysis technology is "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" (13). Process analytical technology, when proven, can provide a comparable and valid alternative to traditional in-process analyses. 根据现行的指南，工艺分析技术指"通过及时测量（如，过程中控）原料和过程物料和工艺关键质量和性能属 性，从而确保最终产品质量的一个设计、分析和控制生产的系统"（13）。工艺分析技术，如提供，则相对传统 的过程分析能提供一个比较和有效的不同方式。

4.3.4 Cleaning Validation 清洁验证

An important part of TTP implementation is the cleaning of the equipment train and facility used for the manufacturing process. The objective of cleaning is to confirm the reliability of the cleaning procedure so that routine analytical monitoring may be reduced. During the manufacturing process, pharmaceutical products and APIs can be contaminated by other pharmaceutical products or APIs if the facility processes multiple products. Virus segregation should also be considered in relevant cases for API manufacture (e.g., mammalian cell). Adequate cleaning procedures are essential to minimize the risk of contamination and cross-contamination, operator exposure, and environmental effects. Once the cleaning has been validated, a risk assessment may be performed to determine whether the level of routine monitoring has been reduced. This risk assessment must include the risk of cross-contamination.
TTP 执行的一个重要部分是生产工艺使用的设备链和设施的清洁。清洁的目的是确保清洁程序的可靠性，这样可以减少日常分析监控。在生产过程中，如果是多品种共线生产，则 API 和制剂可能被其他 API 或制剂污染。在相关的 API 生产（如，哺乳动物细胞）中还应该考虑病毒的隔离。充分的清洁程序是减少污染和交叉污染，暴露操作和环境影响带来的风险的基本要素。一旦清洁得到验证，可以执行风险评估来确定日常监控的水平是否得到减少。该评估必须考虑交叉污染的风险。

Analytical methods should be challenged in combination with the sampling methods to demonstrate both the levels of recovery from the equipment surface and the reproducibility of the results. Analytical testing of swab or rinse samples should be validated before the cleaning validation study is carried out. 分析方法应结合取样方法进行挑战，以证明设备表面的回收率水平和结果的可重复性。擦拭或淋洗样品的分析 测试应当在清洁验证研究开展前得到验证。

The unit transferring a process should provide information on cleaning procedures that have minimized cross-contamination, including: 转移工艺的单位应当提供已经最小化交叉污染的清洁程序的信息，包括：

● Solubility information on active ingredients, excipients, and vehicles 活性成分、辅料和载体的溶解性信息
● Minimum therapeutic doses of active ingredients 活性成分的最小给药剂量
● Therapeutic category and toxicological assessment 治疗分类和毒性评估
● Existing validated cleaning procedures 现有的验证过的清洁程序
● Cleaning validation reports (chemical and microbiological) 清洁验证报告（化学和微生物）
● Cleaning agents used (efficacy and evidence that they do not interfere with analytical testing for residual active ingredients) 使用的清洁剂（效力和不干扰检测活性成分残留的证据）
● Recovery studies to validate the sampling methodology 验证取样方法的回收率研究

Limits should be established for product residues, including a rationale that takes into account relevant characteristics of the starting material (e.g., potency, toxicity, solubility, corrosiveness, and temperature sensitivity), manufacturing equipment design and configuration, cleaning agent used and its residue, and rinsing processes. A risk assessment may be performed of these limits as well, and its results should be shared with the RU. 应当建立产品残留限度，包括考虑起始物料的相关特性（如，效能、毒性、溶解度、腐蚀性以及温度敏感性）， 生产设备的设计和构造，清洁剂的使用及其残留以及淋洗程序等的基本依据。也可以对这些限度开展风险评 估，其结果应当和 RU 分享。

The quality unit at the RU should have validated cleaning and maintenance procedures for buildings, equipment, services, and support systems that affect the product, process, or method being transferred.
RU 的质量部门对影响被转移的产品、工艺或方法的建筑、设备、公共设施和支持性系统应当有经过验证的清洁程序及维护保养程序

Based on information on product residue limits identified by the SU, the RU should determine its own practical, achievable, and verifiable cleaning validation limits based on the materials involved, their properties, and their therapeutic dose. A risk assessment can be performed to help establish these limits.
根据 SU 识别的产品残留信息，RU 应当根据涉及的物料及其属性和给药剂量，决定自己的可操作的、可行的以及可确认的清洁验证限度。

4.3.5 Process Validation 工艺验证

Process validation is the collection and evaluation of data from the process design stage through commercial production. These data provide science evidence that a process is capable of consistently delivering high-quality product. Process validation is part of the technology transfer to a new building, a new company, a new partner, etc. successful process validation depends on the development of a reproducible and reliable process during process development. Process validation is a major objective of a TTP (4.14). Successful process validation allows for regulatory approval submission and subsequent commercial manufacturing. 工艺验证是从工艺设计阶段到商业生产的数据收集和评价。这些数据对一个工艺持续提供高质量产品的能力提　供了科学证据。当技术转移至新建筑、新公司、新合作方等等时，工艺验证是技术转移的一部分。成功的工艺　验证取决于工艺开发阶段开发的可靠而可重复的工艺。工艺验证是一个 TTP（4.14）的主要目标。成功的工艺　验证使得法规批准注册和随后的商业生产得以进行。

Process validation should be performed under a pre-approved protocol detailing acceptance criteria, and the results should be summarized in a final report. 工艺验证应当在事先批准的有详细可接受标准的方案下执行，并总结结果形成最终报告。

Strategic planning for process validation begins during step 2, and the team is formally launched after this process is successfully completed. Successfully completing deliverables for step 2 allows the initiation of actual process validation campaign runs, and the results of these runs are summarized for submission readiness. The deliverables in step 4 include elements needed for process performance qualification and continued process verification. A full explanation of details regarding process validation can be found in PDA Technical Report No. 60-Process Validation: A Lifecycle Approach (4).
工艺验证的战略计划始于第 2 步，并且在这个过程成功完成后，这个小组得以正式启动。成功的完成第 2 步的可交付成果，可以启动实际的工艺验证项目，并总结得到的结果准备递交。第 4 步的可交付成果包括工艺性能确认和持续工艺确认需要的元素。有关工艺验证的详细完整的阐述可参见 PDA 技术报告第 60 号-工艺验证：一个生命周期的方法（4）。

4.3.5.1 Components of Process Validation 工艺验证的组成

It is crucial that TTPs take into account all aspects of the process validation lifecycle. Key items that need to be identified during process validation are:
TTP 考虑到工艺验证生命周期的所有方面是关键性的。在工艺验证时需要识别的关键项目有：

- Process parameters 工艺参数
- Critical process parameters 关键工艺参数
- In-process controls 过程控制
- Critical in-process controls 关键过程控制
- Process ranges/boundaries 工艺范围/限度

Further prerequisites for a successful process validation include:
成功的工艺验证的更多前提条件包括：

- Risk assessments at stages 1, 2, and 3 在阶段 1、2 和 3 的风险评估
- Process parameter reports summarizing the rationale for parameter categorization and ranges
总结参数分类依据和范围的工艺参数报告

● Qualification and validation of manufacturing equipment and automation, including associated utilities/facilities 生产设备及其自动化的确认和验证，包括相关的公用工程/设施
● Effective manufacturing procedures 有效的生产程序
● Qualification and validation of analytical methods and instruments 分析方法和仪器的验证和确认

For legacy products, revises of historical data can be used along with control charts, process capability, and the six-sigma methodologies. For more complex operations, a design of experiments may be used. 对于老产品，历史数据的修订可以使用控制图、工艺能力和 6-西格玛方法。对于复杂的操作，可能要使用实验 设计。

4.3.5.2 Process Validation Studies 工艺验证研究

Full-scale manufacturing consistency studies should be performed for each step in the process or each unit operation. The studies should demonstrate that process parameters can be maintained within pre-established set-points and limits and that outputs from each process step are consistent with expectations. These studies should be performed prospectively, and the number of lots to be validated should be documented. 应当在工艺的每步、每个单元操作进行完全规模的持续生产研究。研究应证明工艺参数能保持在预定的设置点 和限度以内，并且每步的产出是和预期一致的。这些研究应事先做，并且记录要验证的批次数量。

Validation of the equipment should be carried out by the RU with the cooperation of the SU, with special attention to the review of qualification protocols. Installation qualification (IQ) requirements should be determined by a mechanical completion analysis for confirmation and verification of all of the required equipment parts. This is especially important for newly built departments/plants. Verification of the correct assemblage of the system (commissioning) should be followed by IQ, operational qualification (OQ), and performance qualification (PQ).
设备的验证应当通过 RU 在 SU 的合作下开展，特别注意审核确认方案。安装确认（IQ）的要求应当通过对所有要求的设备部件的确认和完整的机械分析来确定。这对新建的工厂/部门尤其重要。在做 IQ、OQ 和 PQ 前，应进行系统正确组装的确认（试车）。

4.3.5.3 Required Documents 要求的文件

The minimum required information and/or documents required for process validation are:
工艺验证要求的最小信息和/或文件有：

● Definition of the critical product attributes based on known or expected clinical effects of the measured product attributes (determined in risk assessment 根据测量的产品属性（根据风险评估 1 确定）已知的或期望的临床结果而制定的关键产品属性。
● Classification of controlled parameters (process “inputs”) as minor, major, or critical. Process development and process characterization studies based on risk assessment 2 and 3 provide the rationale for the categorization of parameters. These also set parameter ranges for the process validation studies. 控制参数（工艺“输入”）的分级，如一般、重大或关键。工艺开发和根据风险评估 2 和 3 的工艺特性研究提供了参数分类的依据。这些也给工艺验证研究设置了参数范围。
  - Critical control points: steps at which control can be applied and that can reduce or eliminate a risk to an acceptable level 关键控制点：可以应用控制的点，并且可以减少或排除风险至一个可接受水平
  - In-process control: checks during production that monitor the process and allow adjustment within normal operating parameters that result in maximum yield or business
  efficiency 过程控制：生产过程的检查，可以监控工艺并允许在正常操作参数内调整以取得最大收率或商业效率
  - Critical in-process control: checks during production that monitor the process and allow adjustments within specified limits. This could include environmental controls as well. 关键过程控制：生产过程的检查，可以监控工艺并允许在特定限度内调节。这也可以包括环境控制。
● A process flow diagram that describes the details of process steps for each unit operation. 详细描述每个单元操作的工艺步骤的工艺流程图。
● Process parameter reports that summarize the rationale for the categorization and ranges for the process parameters, including critical process parameters, in-process controls, and critical in-process controls. 总结了工艺参数分类和范围依据的工艺参数报告，包括关键工艺参数、过程控制和关键过程控制。
● Review of potential process hazards regarding chemical, biological, physical, and environmental impacts. The environment, health, and safety groups should work with the manufacturing group to remove or minimize the risks

identified. 有关化学、生物、物理和环境影响的潜在工艺危害的审核。环境、健康和安全团队应当和生产团队一起工作来去除或最小化识别的风险。

Both parties should jointly write the process validation report and the process validation master plan. The process validation report should be approved by the quality unit, summarize specific tests performed and their results along with pre-defined acceptance criteria, and address deviations encountered during the study. A process validation master plan report should summarize the results and draw conclusions as to whether the overall process is validated (4.14). 双方应联合编写工艺验证报告和工艺验证主计划。工艺验证报告应该被质量部门批准，总结开展的特定检测及 其结果和预定的可接受标准，并描述在研究期间发现的偏差。工艺验证主计划报告应当总结结果并给出整体上 一个工艺是否得到验证（4.14）的结论。

4.3.6 Campaign Summary Reports 阶段性总结报告

The campaign summary reports capture lessons learned from manufacturing batches and are useful baseline reports for reference during subsequent analysis for regulatory filling or process history. 阶段性总结报告可以吸取生产批得到的教训，并且在后续的法规注册或工艺历史分析要参考时是有用的基础报 告。

4.3.7 Continued Monitoring 持续监控

Once the strategy is developed, regular meetings should be scheduled to manage the project timeline. Identify all activities and responsible parties, and maintain process visibility. Agendas and meeting minutes should be maintained for all meetings. These meetings ensure that documents are reviewed and approved within agreed timelines and provide routine updates to involved parties, including QA, manufacturing, and development units. 一旦确定策略，应当安排定期会议来管理项目的时间限制。识别所有的活性和负责方，并保持过程的可见性。 所有会议的议程和会议纪要应该被保存。这些会议确保文件在同意的时间限内得到审核和批准，并且向相关方 包括 QA、生产和研发部门提供例行更新。

4.3.8 Application of cGMPs 现行 GMP 的应用

The ease with which a TTP progresses depends on the stage of development and the level of application of cGMPs. Process transfer aiming at the production of batches with increasing cGMP expectations must meet the requirement of improving some steps of the process itself.
TTP 的轻松进展取决于开发的阶段和现行 GMP 的应用水平。着眼于生产批的工艺转移有更高现行 GMP 期望，有些步骤一定要提高工艺自身。

In the European Union, cGMPs dedicate a specific annex to investigational medicinal products manufacturing (15).
在欧盟现行 GMP，临床实验药品生产有专门的附录（15）。

In this instance, change control procedures should take into account this potential need for increased GMP expectations. Products manufactured at later stages of development (Phase 2 or 3 of clinical studies) should have a nearly complete level of cGMP application.
在这种情况下，变更控制程序应考虑这方面潜在的更高 GMP 期望的需求。在开发后期（临床研究第 2 或 3 期）生产的产品应当有几乎完整的现行 GMP 应用。

As such, the transfer from clinical manufacturing stage to full commercial scale should be managed as a transfer between commercial sites. The organization of TTP activities and macro-activities are still valid for this process and will need to be considered.
这样，从临床生产阶段向完全商业规模转移时应当按商业场所间转移来管理。TTP 活动和宏观活动的组织在这个过程仍然是有效的，仍需被考虑。

4.4 Stage 4: Licensing and Manufacturing 阶段 4：批文和生产

The license document is completed and submitted to regulatory agencies, and routine commercial manufacturing is initiated. An after-action review is an important activity during this sage as a means to drive continuous improvement of the technology transfer business process. The risk ranking in the previous stage can be revised based on the results of the risk mitigation actions implemented. A final gateway review occurs to decommission the technology transfer team.

注册文件完成并递交至法规机构，日常商业生产启动。这个阶段的事后评估是一个重要活动，是驱动技术转移业务过程的持续改进的方法。在前期阶段的风险顺序可根据风险控制的实施结果来修改。最终的节点审核完成后可以解散技术转移小组。

4.4.1 Process Scale Up 工艺放大

Technology transfer between development and commercial production generally involves a scale-up activity and requires attention to the process and product requirements. For this reason, the preliminary assessment and gap analysis step needs to take into consideration this critical difference between the SU and the RU. Involvement of the R&D department is usually greater than in the transfer of an established commercial process. Strong regulatory and quality compliance assessments are done immediately after the TTP generation, to evaluate the impact on the regulatory submission. 开发至商业生产之间的技术转移通常包括放大活动，并且要求注意工艺和产品要求。出于这个原因，初步评估 和差距分析步骤需要考虑 SU 和 RU 之间在这方面的关键不同处。即使转移一个成熟的商业工艺，研发部门的 参与通常是很好的。TTP 生成后立即完成强有力的监管和质量符合性评估，以便评价对法规注册的影响。

Change management is considered even more critical due to the nature of the project for the unavoidable changes that the process required during scale-up. Appropriate procedures for tracking these changes should be in place, and the report issued at the end of the project has to summarize reasons for changes, and the scientific rationale for decisions taken during the project. After a scale-up process is finalized and validated, the monitoring step assumes a key role to properly evaluate the reproducibility and the consistency of the changes adopted during the project. Annual or biannual verification steps are suggested to measure trends in results and highlight any activities that need to be implemented. 变更管理甚至被视为更关键，因为项目本身在工艺放大时有不可避免的变更。恰当的跟踪这些变更的程序要建立，并且在项目结束时颁发的报告应当总结这些变更的原因和项目过程中作出的决定的科学依据。

4.4.2 Monitoring of Production Batches 监控生产批

Follow-up involved the strict monitoring of the production batches by the SU and the RU for an established period of time or number of batches. This occurs during the licensure and manufacturing stage in the business process.
SU 和 RU 在一段时间或一定批次内要进行严格的生产批监控的跟踪。这发生在批文和商业化生产阶段。

After the follow-up period, the technology transfer personnel should prepare the technology transfer report that describes whether the RU is able to reproduce the technology according to the expected quality specifications. Approval of the report should state officially the acceptance of full responsibility for the transferred technology by the RU. A pre-determined number of batches produced at the RU should also undergo a stability study. 跟踪期之后，技术转移人员应当起草技术转移报告，描述 RU 是否有能力重现达到预期质量标准的技术。报告 的批准应当正式声明 RU 完全接收了被转移技术的责任。在 RU 生产的一些预定数量的批要进行稳定性研究。

Statistical comparison between historical data at the SU and start-up/following-up data at the RU is recommended to highlight any differing data trends or distributions.
建议开展 SU 的历史数据和 RU 的初期/跟踪数据的统计比较，突出显示任何不同数据的趋势或分布。

4.5 Stage 5: Project Closure 阶段 5：项目结束

After licensure, the technology transfer closure is formalized in a dedicated document (i.e., a technology transfer report). Main tasks, milestones and changes to the original plan along the project are summarized. Lessons learnt are described and deeply analyzed to provide strong background for further improvements. Moreover a verification plan needs to be set up in this phase of the project for the continuous monitoring of the technology transferred. 取得批文后，技术转移用专门的文件正式结束（如，技术转移报告）。应当总结项目进行的主要任务、里程碑和 对原计划变更。描述得到的教训并深入分析以便将来改进提供有力的背景。并且在这个项目阶段需要建立一个 确认计划，用于持续监控转移的技术。

This stage begins when the goals and objectives of the TTP are finished. Benefits, whether tangible or intangible must be identified and communicated during this stage, allowing the organization to improve future projects by preventing problems and creating contingency plans. This closing stage involves a confirmation of the appropriateness and risk tolerance of the organization’s risk management policies.

这个阶段以 TTP 的目标和目的结束而开始。这个阶段应当识别和交流有形的或无形的利益，使得组织能防止问题并建立防止意外的计划来提高将来的项目。此结束阶段包括对组织风险管理决策的适宜性和风险承受能力的确认。

In fact, based on the assessment done in the planning phase of the project, potential risks are identified and a mitigation plan is set up and implemented afterwards. As a part of the project closure step, effectiveness of actions is verified. The same approach used in risk definition (such as QRM tools; see Section 5.0) Can be used to recalculate the risk priority number (RPN) at the end of the mitigation action. 事实上，根据项目计划阶段作的评估，潜在的风险得到识别，建立消除计划并随后执行。作为项目结束步骤的 一部分，措施的有效性要进行评估。用于风险的界定的同样方法（如 QRM 工具，参见第 5.0 节）可在消除措施 结束时用于重新计算风险指数（RPN）。

The technology transfer is considered officially completed and closed if the corrective actions are successful.
如果整改措施是成功的，那么技术转移可以认为正式完成并结束。

A summary report should be generated containing information related to the non-GMP (such as development and laboratory trials) and GMP manufacturing activities, including:
应生成总结报告，包括有关非 GMP（如开发和实验室小试）和 GMP 生成活动的信息，如下：

- Process overview 整体工艺概况
- In-process and drug substance release and characterization data 过程控制和原料药放行和特性数据
- Equipment list 设备列表
- Critical/major deviations 关键/重大偏差
- Lessons learned 得到的教训
- Technology transfer metrics 技术转移指标
- Results of all the deliverables in the technology strategy document 技术策略文件中的所有可交付成果的结果
- Verification schedule for the process 过程时间表的核实

The operations groups should sign both the technology transfer protocol and report. Signing of the report by the RU establishes the acceptance of responsibility for execution of the transferred technology and the conclusion of the follow-up period. Implementation of agreed-upon corrective actions should be considered part of the follow-up period and overseen by both the SU and RU.
操作团队应签署技术转移方案和报告。RU 签署报告意味着接受执行被转移技术的责任以及跟踪期的结论。商定的整改措施的执行可以被视为跟踪期的一部分，并得到 SU 和 RU 的监管。
蒲公英论坛翻译作品

5.0 Application of Quality Risk Management to Technology Transfer
5.0 质量风险管理在技术转移中的应用

5.1 Overview 概述

During the TTP, internal (mainly related to the RU) and external (mainly related to the SU and external suppliers) variables place it at risk. The TTP team must identify and mitigate the impact of these variables. ICH Q8, Q9, Q10, and Q11 provide examples of tools and principles to achieve this objective. The approach used to design space in pharmaceutical development, in which the relationship between the process inputs (material attributes and process parameters) and the CQAs are assessed and described, can be applied during TTP management **(2, 6, 16, 17)**. 在技术转移项目（TTP）过程中，内部（主要是接收方）和外部（主要是转移方和外部供应商）的变化使其具 有风险。技术转移团队必须识别和减小这些变化的影响。ICH Q8, Q9, Q10 和 Q11 提供了工具的例子和原则以 达成这个目标。药物研发的设计空间使用的方法，其中对工艺输入（物料属性和工艺参数）与关键质量属性（CQAs）之间的关系进行了评估和描述，可以用于 TTP 管理**(2, 6, 16, 17)**。

As applied to technology transfer, QRM should cover the risks involved in the process being transferred from the SU to the RU as they relate to the maintenance of product quality (meeting the defined specifications or quality attributes) or the performance quality of an analytical method (depending on the stage of qualification or validation). 应用在技术转移时，QRM 应当涵盖从 **SU** 转移到 **RU** 的工艺相关风险，因它们与保持产品质量有关（符合制定的 质量标准或质量属性）或者与分析方法的性能质量（取决于确认或验证的阶段）有关。

This technical report only addresses aspects of QRM that are specific to technology transfer activities. PDA has published several reports on QRM to which readers should refer for further discussion, analysis, and practical applications of QRM. The main tenets are detailed in PDA Technical Report No.54-Implementation of Quality Risk Management for Pharmaceutical and Biotechnology Manufacturing Operation (7). 这篇技术报告只提出了技术转移活动有关的 QRM。PDA 发表过几篇关于 QRM 的报告，里面能给读者提供关于 QRM 更多的讨论、分析和实际应用。主要的原则详见 PDA 技术报告第 54 号-制药和生物技术生产操作的质量 风险管理的执行（7）。

5.2 QRM in Technology Transfer 技术转移中的 QRM

QRM principles are broadly accepted in industry and are enablers of the pharmaceutical quality system. The primary purpose of QRM in biopharmaceutical manufacturing is so identify and evaluate modes of product or process failures for the purpose of ensuring product quality and patient safety. The benefits of QRM in TTPs include leveraging information from the design and qualification stages to provide information back to process validation activities as part of continuous process verification.
QRM 原则在工业领域中被广泛接受并且促进了药品质量体系。QRM 在生物制药生产中的主要目的是识别和评估产品或工艺的失败模式，以确保产品的质量和病人的安全。TTPs 中 QRM 的好处包括利用设计和确认阶段的信息反过来为连续工艺确认一部分的工艺验证活动提供信息。

Applied to technology transfer, QRM may be used to evaluate risk associated with each step of the project as well as the impact of the new product/process and related raw materials on existing products and/or facility and process controls. 应用在技术转移中，QRM 可以被用于评价每步项目相关的风险，也可以评价新产品/工艺的影响和已知产品和/ 或设施和工艺控制相关的原料。

The purpose of QRM applied to a TTP is to review the proposed transfer of manufacturing process to ensure that potential risk to the patient regarding the quality, safety, and efficacy of the drug product have been identified and are adequately controlled.
QRM 应用于 TTP 的目的是审核拟转移的制造工艺，以确保药品质量、安全和有效性相关的对病人的潜在风险能够被识别和充分控制。

Specifically, this QRM should ensure that:
具体地，QRM 应当确保：

- The sources of variability that have the potential to impact CQAs have been identified
- 能够识别对 CQAs 有潜在影响的变化根源

- The appropriate risk mitigation strategies and controls have been integrated into the process to minimize and control potential change-related hazards that could result in the production of batches that do not meet predetermined specification/CQAs
- 将合适的风险降低策略和控制整合到工艺中以降低和控制潜在的变更相关的危害，而这些危害会导致生产批不符合预定的质量标准/CQAs

- All critical unit operations and associated quality and critical parameters that must be controlled to ensure final drug product quality are identified
- 所有关键单元操作和相关的质量和关键参数必须加以控制，以确保最终药品的质量得到支持

The expectations of such a multidisciplinary QRM review of the proposed commercial/development process are:
对提出的商业/研发工艺的多学科 QRM 审核的期望是：

- Ensuring that sources of variability that could impact final drug product CQAs have been identified
- 确保识别会影响最终药品 CQAs 的可变性来源

- Ensuring that appropriate risk mitigation strategies and controls have been integrated into the process to minimize and control potential quality hazards to the patient
- 确保合适的风险降低策略和控制已经被整合至工艺中以减小和控制对病人的潜在质量危害

- Identifying critical unit operations and associated critical parameters that have a high risk of affecting CQAs
- 识别有高度风险影响 CQAs 的关键单元操作和相关的关键参数

QRM should address at least:
QRM 至少应当写明：

- Processing operations and parameters (including batch record instructions)
- 工艺操作和参数（包括批生产指令）

- Impact of new equipment, facilities, and supporting utilities (e.g., clean air, WFI, cleanrooms)
- 新的设备、设施和辅助性设施（比如洁净空气，WFI 和洁净室）的影响

- Potential for contamination from internal sources
- 来源于内部的潜在污染

- Potential for contamination from external sources

- 来源于外部的潜在污染

- Training of management, engineering staff, operators, and QA/QC personnel on the transferred process
- 对转移工艺相关的管理者、工程人员、操作人员和 QA/QC 人员进行培训

QRM must be focused on key areas such as:
QRM 必须集中在关键领域，比如:

- Identifying critical unit operations and CPPs that could be impacted by the transfer
- 识别可能会被转移影响的关键单元操作和 CPPs

- Identifying potential for contamination from internal and external sources
- 识别源自外部和内部的潜在污染

- Ensuring that batch record instructions are adequate to document operations and control human variables
1. 确保批生产指令对于记录操作和控制人的可变性是足够的

5.3 Stages of QRM in Technology Transfer 技术转移中 QRM 的阶段

The stages of QRM in technology transfer are as follows.
技术转移中 QRM 的阶段如下：

5.3.1 QRM planning QRM 计划

The technology transfer team must establish the context for the TTP. This will include the identification of internal and external factors as well as which QRM tools to use. External context may involve competitive, financial, regulatory, legal, environmental and cultural aspects. Internal context may involve company policies and procedure, system, operational objectives, personnel training and knowledge, available resources, and culture. A governance model, including responsibility and accountability assignments, must be developed in this step and include the matters that are subject to risk-based decisions. The risk determination of the subjects will provide the group with the necessary awareness of risk. A policy for enterprise risk management should be in place at this stage. Requirements and constrains, goals and objectives, and key performance indicators (including the success criteria) must be determined and agreed upon. The technology transfer team should be skilled in basic project management to design a plan that takes into account cost (including material and personnel resources); scheduled (including supply of the product being transferred; scope; technology associated with the project; and the quality, safety, and efficacy of the product.
技术转移团队必须建立 TTP 的环境。这包括确定内外部因素以及使用哪种 QRM 工具。外部环境可能涉及竞争、财务、法规、法律、环境和文化方面。内部环境可能涉及公司政策和程序、系统、经营目标、人员培训和知识、可利用资源和文化。一个包括职责和责任分配的管理模型必须在这个阶段提出且要包括必须根据风险进行决策的事务。根据风险确定的事务会给团队提供必要的风险意识。应当在此阶段建立公司级风险管理政策。需求和限制、目标和宗旨以及关键成绩指标(包括成功标准)必须在此阶段确定和批准。技术转移团队应当基本项目管理技能，设计一个包括费用（包括物料和人力资源）、时间表（包括转移产品的供应）、范围、项目相关的技术和药品的质量、安全和有效性的计划。

5.3.2 QRM Implementation (execution and control stage) QRM 实施（执行和控制阶段）

It is not expected that many risk management activities will be performed during the execution stage. A rigorous planning stage reduces the need for decision-making during the execution process. Processes where contingency plans (e.g., use of alternate suppliers or contract manufacturers) have been developed from the beginning may help to manage new unforeseen risks. The same risk assessment tools and control mechanisms must be used to manage those new risks. It is important to monitor risks and factors affecting risks to ensure that the initial context determination is still valid. 不期望在执行阶段实施很多的风险管理行为。一个严格的计划阶段减少了在执行过程中做决定的需求。在转移初期提出了应急计划（比如使用备用供应商或合同制造商）的工艺能够帮助管理新的未知风险。必须使用相同的风险评估工具和控制机制管理这些新的风险。降低风险和风险影响因素对于保证最初的决策环境依然有效是非常重要的。

5.3.3 Project Closure QRM 项目关闭 QRM

This stage begins when the goals and objectives are fulfilled. Benefits, whether tangible or intangible, must be identified and communicated by the project leader to the project committee during this stage to allow the organization to improve future projects and avoid recurrence of problems or create contingency plans. This closing stage is a confirmation of the appropriateness and risk tolerance of the organization's risk management policies. 这个阶段在目标和宗旨达到时开始。无论有形或无形的效益都必须在此阶段确定且由项目管理者与项目委员会 沟通，从而允许组织改善未来的项目和避免再次发生问题或建立应急计划。项目关闭阶段是确定组织的风险管 理政策的适合性和风险承受力的阶段。

QRM performed correctly during the development phase may mitigate inherent hazards and reduce the criticality of this step. This is true provided that the risk assessments are thorough and define the impact and uncertainty of each step of the development phase, process, and specifications.
在研发阶段正确开展 QRM 能降低内在风险并减小这一步的关键性。当风险评估是彻底的而且能明确每步开发阶段、工艺和质量标准的影响和不确定性时，这种说法是对的。

5.4 Risks of Technology Transfer 技术转移的风险

Often, poor attention to its objectives (e.g., process specifications that are too tight or too broad) destines a TTP to failure. Technology transfer can affect drugs and patients. Consequently, in all technology transfer activities that a project team designs and executes, the team needs to keep in mind the scope of the technology being managed and the potential

impact of technology transfer failure.
通常，对目标（比如太紧或太宽的工艺标准）缺少关注会注定 TTP 的失败。技术转移会影响到药品和病人。因此，在所有由项目团队设计和执行的技术转移中，团队需要谨记技术的管理范围和技术转移失败的潜在影响。

Some common risks that are often overlooked and can negatively affect the TTP are:
以下是一些经常被忽略但会对 TTP 造成不良影响的一般风险：

- Objective that is not clear (or clearly defined)
  目标不清晰（不明确）
- Objective that is not properly communicated and/or shared
  没有进行合适交流和/或分享的目标
- Objective that cannot be operationally translated
  操作上无法转化的目标
- No assessment of the effects of changes to the objective
  没有对目标变化结果的评估
- Lack of change control
  缺乏变更控制

Among the risks to be considered prior to embarking on a TTP, regardless of its scope, are the cost of the project and potential return on investment to determine an acceptable cost/benefit ratio based on internal RU and SU targets or criteria.
不管范围如何，在 TTP 开始之前需要考虑的风险是项目的花费和潜在的投资回报，根据 RU 和 SU 的内部目标或标准来决定可接受的效益成本比。

5.5 QRM Concepts and Approaches Used in Technology Transfer
在技术转移中使用的 QRM 概念和方法

QRM tools used in accordance with ICH Q9 can facilitate the deliverables for each step in the TTP outlined in this section. The ICH Q9 briefing book also provides general templates to use for QRM. **Table 5.4-1** outlines the application of QRM concepts and approaches at each step.

依据 ICH Q9 使用 QRM 工具可以促进这章中列出的 TTP 的每一步的可交付成果。ICH Q9 要点手册也提供了使用 QRM 的例子。表 5.4-1 列出了每步中使用的 QRM 概念和方法。

Table 5.4-1 QRM Approaches at Each Stage Gate of TTP

表 5.4-1 TTP 每个阶段使用的 QRM 方法

Stage Gate 阶段	Strategy 策略	Analytical &QC Testing 分析和 QC 测试	Regulatory 法规	Process 工艺	Facilities/Engineering 设施/工程	Risk Management and Components 风险管理和要素
1 **Planning** **计划**	Perform preliminary risk assessment prior to beginning late-phase development using risk ranking and/or preliminary hazards analysis approach. 在后期研发开始前使用风险排序和/或初步危害分析方法来进行初步的风险评估。					
2 **Process Readiness** **工艺准备就绪**	Update preliminary risk assessment (transition to preliminary hazard analysis [PHA] 更新初始风险评估（转换至初步危害分析[PHA]）	Update risk assessment (transition to PHA) for SU and RU readiness for analytical method transfer (AMT) 更新风险评估（向 PHA 转换），为 SU 和 RU 完成准备分析方法转移（AMT）	Risk mitigation through service level agreement (SLA) and quality agreement between SU and RU 通过服务水平协议（SLA）和 SU 和 RU 间的质量协议降低风险	Update risk assessment (transition to PHA) for manufacturability of late-phase development process 为后期开发工艺的可生产性更新风险评估（向 PHA 转换）	Update risk assessment (transition to hazard operability analysis [HAZOP] for operating process at manufacturing site 为生产场所的操作工艺更新风险评估（转为危害与可操作性分析[HAZOP]	Update risk assessment (transition to PHA) for RMs/components, including assessment of the impact of any changes in the suppliers or manufacturing sites of the RMs 为原料/组分更新风险评估（向 PHA 转换），包括评估供应商或原料生产地变更带来的影响
3 **TTP Implementation & Qualification** **TTP 实施和确认**	Review and update risk assessment/PHA from stage gate 2 if necessary. Mitigate identified high risk. 审核和更新风险评估/PHA，如果有需要从阶段 2 开始。 降低已识别的高风险。					
4/5 **Licensure / Manufacturing/Project Closure** **许可/制造/项目关闭**	Convert PHA risk assessment from stage gate 3 to FMEA/failure mode, effects, and criticality analysis (FMECA) risk assessment, including reevaluation of risk ranking after risk mitigation plan implementation. 转换阶段 3 的 PHA 风险评估为 FMEA/失败模型，有效性和关键性分析（FMECA）风险评估，包括风险降低计划实施后对风险排序的重新评估。					
	Update risk assessment from stage gate 4 for commercial process 为阶段 4 商业化工艺更新风险评估	Complete risk assessment for SU and RU readiness for AMT 完成 SU 和 RU 的 AMT 的风险评估	Risk mitigation through SLA and quality agreement between SU and RU 通过 SLA 和 SU 与 RU 的质量协议降低风险	Update risk assessment for manufacturability of commercial process 为商业工艺的可生产性更新风险评估	Update risk assessment (HAZOP) for operation process at commercial site 更新商业化生产地操作工艺的风险评估（HAZOP）	Update risk assessment for RMs/components, including assessment of the impact of any changes in the suppliers of manufacturing sites of the RMs 为原料/组分更新风险评估，包括评估供应商或原料生产地变更带来的影响

5.6 QRM Planning QRM 计划

As a company begins to apply a QRM approach, the first step will consist of providing training to personnel involved in GMP operations to familiarize them with ICH Q9 and the principles laid out in the document. As a result of the above approach, technology transfer team members, trained in the QRM approach, will act according QRM principles and tools throughout the life of TTP.
作为刚开始应用 QRM 方法的公司来说，第一步包括培训 GMP 相关操作的员工，使他们熟悉 ICH Q9 和这篇文件中提出的相关原则。作为上述方法的结果，培训了 QRM 方法的技术转移团队成员能够将 QRM 原则和方法贯彻在整改 TTP 生命周期中。

It is highly recommended, as a second step, to set policies and procedures determining the use of various qualitative and quantitative tools and their application. To select where first to apply QRM, companies may consider implementation of QRM for a particular product or family of products. If this method is chosen, special attention must be paid to avoid the creation of different layers of compliance. 第二步高度推荐制定方针和程序来确定需要使用的各种定性定量工具以及其应用。选择从哪儿开始使用 QRM 时，公司可能需要考虑在一个特定产品或者熟悉产品上应用 QRM。一旦这个方法被选定，就需要特别注意确保 风险级别的一致性。

Finally, companies must include their decision for using QRM in the technology transfer strategy document at the project start.
最后，在项目开始时公司就必须在技术转移方案文件中写明决定使用 QRM。

5.6.1 Selection of a QRM Approach 选择一个 QRM 方法

The selection of a risk management approach should be applied along the TTP. This approach will facilitate decision-making at different points throughout the TTP while ensuring that all activities are performed in a manner that protects patient safety.
风险管理方法的选择应该应用在整个 TTP 过程中。此方法将有利于在 TTP 周期中不同点做出的决策都能保证所有行为都在保护病人安全的前提下进行。

To realize the utmost benefit from QRM, companies must adapt their culture, system, and procedure. They must shift from a risk-averse to a risk-aware culture by creating procedures and tools that enable individuals to apply benefits from QRM to the TTP.
要实现到 QRM 的最大利益，公司必须采用自己的文化、系统和程序。公司必须通过建立能够使人员将 QRM 的优势应用到 TTP 中的程序和工具，从风险规避文化转变为风险意识文化。

It may be helpful to refer, for project management purposes, to the elements of the risk management process as defined in PDA Technical Report 54, ISO 31000 (project considerations), and ICH Q9 (process/product considerations) **(2, 16, 18-20)**.
为了项目管理的目的，参考 PDA 技术报告第 54 号，ISO 31000（项目注意事项）和 ICH Q9（工艺/产品注意事项）中的风险管理过程的元素是很有帮助的**(2, 16, 18-20)**。

5.6.2 Creation of a QRM plan 制定 QRM 计划

Firms should develop a plan to implement and maximize the use of QRM throughout all operational systems and company areas. This plan should be documented in the site master file and/or the master validation plan. 公司应当建立一个计划来实施和最大限度地在所有操作系统和公司范围内使用 QRM。这个计划应当被记录在工 厂主文件和/或验证主计划中。

A roadmap must be designed from the very beginning of the project to ensure comprehensive project management, including the risk assessment steps below. The roadmap for QRM implementation should be established as a holistic approach rather than a project-specific approach. It may be helpful for the technology transfer team to refer, from a project management perspective, to the elements of the QRM process as defined in the literature **(2, 16, 18-20)**. 在项目之初必须设计一个蓝图以确保涵盖下面提到的风险评估步骤的综合项目管理。QRM 实施蓝图应当作为整 体方法而不是特殊项目的方法而建立。从一个项目管理角度来说，技术转移小组参考文献中**(2, 16, 18-20)**的 QRM 程序元素是非常有帮助的。

Successful application of QRM in technology transfer requires establishment of a QRM plan early in the TTP and

formalization of the plan (where applicable) in the technology transfer protocol. The QRM plan should describe the TQM tools to be used, the rationale for their selection, the risk ranking/filtering criteria to be used, and any underlying assumptions. This document serves the following purposes:
在技术转移中成功应用 QRM 要求在 TTP 早期建立一个 QRM 计划，并且在技术转移方案中将计划正式化（适用时）。QRM 计划应当描述要使用的 TQM 工具，选择的理由，要使用的风险排序/筛选的标准和任何基本的假设。这份文件有以下目的：

- Aligns cross-functional participants regarding the basis of the transfer team's decision-making
  基于转移小组的决策，将跨职能的参与者结合起来

- Informs senior management on project analysis, risk identified, and mitigation plan
  告知高级管理人员关于项目分析、识别的风险和消除计划

- Ensures consistency over time as ongoing development or validation information supporting the transfer is used to update risk assessments and influence future decision and/or activities 当后续支持转移的开发或验证信息用于更新风险评估和影响未来的决定和/或行为时，确保其随着时间 的一致性。

- Identifies participants and their responsibilities in risk assessment
  确定风险评估的参与者及其职责

- Defines the responsibilities of the applicable management teams or functional leaders that approve risk reduction activities and authorize acceptance of unmitigated related risks. The technology transfer team must define the criteria for selection of management teams with oversight of the transfer as well as key stakeholders accountable for the overall success of the project. These teams and individuals provide appropriate sponsorship of the project and secure resources for QRM activities (in addition to other transfer related activities), and they must be informed of or approve critical risk acceptance decisions across the entire project. These teams and stakeholders should be identified on a master transfer plan. 定义合适的管理团队或职能领导的职责，他们批准降低风险的行为并授权接受未经消除的有关风险。 技术转移团队必须对整体监管转移并作为项目整体成功的关键受益人的管理团队的选择明确标准。这 个团队和个人为项目提供了合适的支持，并确保 QRM 活动的资源（包括其他转移相关活动），而且他们 必须被通知或批准整个项目过程中的关键的风险接受决定。这些团队和受益人应当在转移主计划中被 明确。

The QRM plan should define criteria for identifying critical risk factors and hazards so that senior management is informed of critical issues and their status and remains informed.
QRM 计划应当为识别关键风险因素和危害定义标准，这样高级管理者就能了解关键事件以及其状态，并能持续了解。

Risk assessment teams, as part of the technology transfer teams, should refer to the master technology transfer plan to ensure that the proper stakeholders are used for the risk assessment. The QRM plan should also define criteria for identifying critical risk factors and hazards so that senior management is informed of critical issues and their status. 作为技术转移团队的一份子，风险评估团队应当参考技术转移主计划来确保将合适的受益人用在风险评估中。
QRM 计划也应当确定识别关键风险因素和危害的标准，这样高级管理者就能了解关键事件以及其状态。

It is recommended to define project triggers and milestones for the TTP based on general QRM concepts. It is also advisable to evaluate the transfer environment using the volatility, uncertainty, complexity, and ambiguity (VUCA) model. The VUCA elements present the context in which organizations view their current and future state. The VUCA tool can be used in strategic leadership environment to present boundaries for planning and policy management. QRM tools will be preferentially used from a project perspective. The roadmap defined at the project level must include triggers for all stages: planning, process readiness, qualification, and licensure and manufacturing.
根据常规 QRM 概念建议为 TTP 定义项目触发器和里程碑。将易变性、不确定性、复杂性和模糊性（VUCA）模型用于评价转移环境也是明智的。VUCA 元素体现了组织考察目前和未来状态所处的环境。VUCA 工具可以被用于战略引导环境来呈现规划和政策管理的界限。QRM 工具从一个项目的角度应该被优先使用。在项目层面定义的蓝图必须包括所有阶段的触发点：计划、程序准备、确认、许可和制造。

5.6.3 Identification of QRM Personnel 确定 QRM 人员

Stemming from the previous concepts, it is reasonable to include the determination of the risks and risk tolerance for the project in the goal of the TTP team that is composed of the transferring and receiving operations, quality, and enabling functional groups (e.g., finance, engineering, and logistics). Risk tolerance is defined by two considerations: the project and the process/product.
源于之前的概念，在 TTP 团队的目标中确定项目的风险和风险承受能力是合理的，由转移和接收操作、质量和功能团队（比如财务，工程师和后勤）组成。风险承受能力的确定从两方面考虑：项目和工艺/产品。

At a minimum, the team should include representative from the process development, manufacturing, analytical development, QA, and QC units. Special emphasis must be placed on including information that could indicate an impact on product safety, identity, stability, purity, and quality. By using a cross-functional team, issues impaction stability, specifications, and the use of analytical methods can more easily be identified and addressed. Failure to take these issues into account can lead to transfer delays or even failure as there may be unknown factors related to the change that could impact stability or drive a process closer to specification limits compared to its performance at the originating site.
团队至少应当包括工艺研发、制造、分析方法开发、QA 和 QC 部门的代表。可能显示对产品安全、均一性、稳定性、纯度和质量有影响的信息应当重点强调包括进来。通过使用一个多功能团队，影响稳定性、质量标准和使用的分析方法的问题可以更容易被发现和解决。没有考虑这些因素可能会导致转移延迟甚至是失败，因为可能存在与变更相关的未知因素影响稳定性或使工艺相对来源地的表现而接近质量标准的限度。

A variety of stakeholders outside the project team include local, regional, and international regulatory authorities. Patient safety, through managing the risk to quality, should be of prime importance (2). Risk is evaluated by the diverse risk assessment by the stakeholders involved because each stakeholder may perceive different potential risks, assign each a different probability of occurrence, and attribute different severities to each other. 项目团队以外的各利益相关方包括当地、地区和全球的法规主管机构。通过质量风险管理，病人的安全是最重 要的(2)。风险通过相关利益方通过不同的风险评估方法来评估，因为每个利益相关方可能会察觉不同的潜在风 险，给出不同的发生概率和判断不同严重性。

5.7 Risk Assessment 风险评估

Based on the overall project knowledge and the initial tasks agreed on and completed, the same systematic process for the assessment, control, communication, and review of risk described in ICH Q9 to identify and rank project variables and inputs with a potential impact on the project goals can be used by the technology transfer team. Moreover, due to quantitative output of the risk assessment, in which the risk is not only described but also ranked, a well-defined decisional critical path can be properly identified. The financial and time requirements for each task can be assessed on the basis of a scientifically sound approach, allowing for project management that is in compliance with regulatory authority expectation.
根据整体项目知识和最初同意和完成的任务，技术转移小组可以使用 ICH Q9 描述中评估、控制、交流和审核风险相同的系统流程对项目变量和对项目目标有潜在影响的输入项进行识别和排序。此外，由于风险评估的输出是定量的，也就是风险不仅被描述还可以排序，一个明确定义的决策关键路径可以被适当确定。每个任务的财务和时间需求可以在科学的方法基础上进行评估，使项目管理符合法规主管机构的期望。

The deliverer of the TTP should provide criteria and information regarding hazards and critical steps associated with the product, process, or method to be transferred, which will serve as a basis for a QRM exercise.
TTP 的交付者应当提供有关被转移的产品、工艺或方法的危害和关键步骤的信息和标准，这是实践 QRM 的基础。

Risk assessment is completed by comparing each step against the CQAs to determine which ones require further characterization or assessment of historical data (if available). The application of a risk process considering process development allows for scientific understanding to identify potential parameters that may affect the process CQAs. This can reduce the number of process steps to be further characterized and provide a baseline for establishing independent parameters during scale-up or transfer.
风险评估的完成通过将每步与 CQAs 比较来决定哪一步需要进一步鉴定或评估历史数据（如有）。风险评估过程中考虑到工艺开发，对识别可能对工艺 CQAs 有潜在影响的参数能有科学的理解。这样能减少需要进一步鉴定的工艺步骤，并能为在放大或转移期间建立独立参数提供基准。

Identification and scoring of risk factors and their associated hazards based on predetermined severity and occurrence criteria should result in a comprehensive list of activities to be completed to facilitate the successful completion of the

transfer. The product of these two criteria provides a risk-based means of prioritizing hazards and risk-reduction activities. These activities could include additional characterization or validation studies, facility modifications, or acquisition of new equipment or expertise. Input from the technical subteams and other SMEs should establish a detailed understanding of the effort and time required to complete the identified items. 风险因子的识别和打分以及基于预先决定的严重性和发生率标准的相关危害性，应该得出一个需要完成的活动 的综合列表，以促进转移的顺利完成。这两个标准的产品提供了基于风险的优先考虑危害和风险降低行为的方 法。这些活性应当包括额外的鉴定或验证研究、设施改进或获取新设备或专家。技术子团队和其他 SME 的输入 应当能建立一个对已确定项目所需的时间和努力的详细理解。

5.7.1 Types of Risk Assessment 风险评估的种类

The RU and SU can decide on the particular parameters for choosing the type of risk assessment. Indeed, the team could decide to use all of them to assess risks. The following are three possible types of risk assessments:
RU 和 SU 可以决定具体参数以选择风险评估类型。的确，团队可以决定使用所有方法来评估风险。以下是三种可能的风险评估方法：

5.7.1.1 Risk Assessment 1 风险评估 1

A risk assessment can be performed to include the identification, documentation, and risk assessment of the product attributes and of the CQAs and their target ranges. Individual quality attributes are assessed to determine their impact on product safety and efficacy as well as performance characteristics that affect safety and efficacy (e.g., stability, pharmacokinetics and clearance along with immunogenicity). This assessment helps determine the ranges, the basis for these rangers, and the potential impact. This assessment also provides reference to the data for each product attribute (if available). This risk assessment is a living document that needs to be revised throughout the lifecycle of the product to take into consideration and properly evaluate all of the changes that are happening. 进行风险评估可以包括对产品属性和 CQA 及其目标范围进行识别、记录和风险评估。对单一质量属性进行评估 以确定它们对产品安全性和有效性以及影响安全性和有效性的性能特征（比如稳定性，药物动力学和免疫原性 清除）。这类评估帮助确定范围，这些范围的基础以及潜在的影响。这类评估也可以为每种产品属性提供参考数 据（如有）。这类评估是一个动态的文件，需要在产品整个生命周期中不断被修改，并考虑和评估发生的所有变 更。

5.7.1.2 Risk Assessment 2 风险评估 2

A second type of assessment uses a system of risk ranking and filtering in which the individual process parameters and noncompendial raw materials are evaluated for their potential impact on product quality and process consistency. Results from these risk assessments can be a guide to the level of process characterization needed to understand the impact of each process parameter on quality attributes and process consistency. The intent of this assessment is to provide a risk rating from a product quality and/or process performance perspective. 第二种风险评估采用一个风险排序和筛选的系统，在该系统中各个工艺参数和非药典原料对产品质量和工艺一
致性的影响都会被评估。这些风险评估的结果可以为工艺特性水平提供指导，该工艺特性水平需要理解每个工艺参数对质量属性和工艺持续性的影响。这个评估的目的是从产品质量和/或工艺性能方面提供一个风险评级。

5.7.1.3 Risk Assessment 3 风险评估 3

A third type of risk assessment is an inductive risk analysis designed to identify potential modes of process failure associated with operations parameters that may affect product quality and/or process consistency. This assessment should include risk identification and prioritization and a mitigation plan. It may also reduce the amount of additional data needed to complete the TTP. 第三种风险评估是一个归纳风险分析，旨在确定可能影响产品质量和/或工艺持续性的操作参数相关的潜在的工 艺失败模式。这种评估应当包括风险识别和优先排序以及风险降低计划。这种评估也可以减少完成 TTP 所需的 额外数据量。

5.7.2 Risk Assessment Tools 风险评估工具

Some risk management tools mentioned in ICH Q9 are (16):
ICH Q9 中提到的风险管理工具有：

- Basic risk management facilitation methods (flowcharts, check sheets, etc.) 基本风险管理方法 （流程图，检查

表等）

- FMEA 失败模式和影响分析（FMEA）
- FMECA 失败模式、影响和关键性分析（FMECA）
- Fault tree analysis 失败树分析（FTA）
- Hazard analysis and critical control points (HACCP) 危害分析和关键控制点（HACCP）
- HAZOP 危害与可操作性分析（HAZOP）
- PHA 初步危害分析（PHA）
- Risk ranking and filtering 风险排序和筛选
- Supporting statistical tools 支持性统计工具

QRM tools are useful in prioritizing transfer team activities in two ways: 1) they provide the means to quantitatively rank (prioritize) and filter risk factors and risk-reduction activities across the entire project, and 2) they provide a means for documenting risk-ranking criteria and rationales for prioritization Application of QRM tools can assist in identifying, quantifying, and prioritizing risk associated with the TTP. However, the output from using these tools is only as good as the information entered, so it is crucial to ensure that the risk assessment is performed by a broad cross-functional group.
QRM 工具在两个方面对优先选择转移项目行为是有用的：1）它们为整个项目的风险因子和降低风险的行为提供了定量排序（优先排序）和筛选。2）他们提供了风险排序的标准和依据的文件记录，因为 QRM 工具的优先应用可以帮助 TTP 相关风险的识别、定量和优先选择。然而，这些工具的结果只能与输入信息一样好，所以确保一个广泛的跨功能团队执行风险评估是非常重要的。

PDA Technical Report No. 44: Quality Risk Management for Aseptic Processes and Technical Report 54: Implementation of Quality Risk Management for Pharmaceutical and Biotechnology Manufacturing Operations provide guidance on how to apply risk assessment tool to pharmaceutical processes (7, 21). The ISPE Baseline Engineering Guide Volumes 1 (Active Pharmaceutical Ingredients) and 7 (Risk-Based Manufacture of Pharmaceutical Products) are other potential resources (22, 23).
PDA 技术文件第 44 号：无菌工艺质量风险管理和技术文件第 54 号：制药和生物技术生产操作的质量风险管理的实施，为如何将风险评估运用于制药工艺中提供了指导(7, 21)。ISPE 基础工程指南卷 1（原料药）和卷 7（基于风险的药品生产）是其他可用的资源(22, 23)。

5.7.2.1 Risk Ranking and Prioritization 风险排序和优先排序

Following completion of the site selection process, the product to be transferred and the recipient facility may be evaluated using a risk ranking and filtering (RRF) tool. The RRF tool is used to determine potential risk factors and hazards across all aspects of the transfer, such as adequacy of the recipient facility quality system, introduction of new raw materials, or process changes impacting product stability. This method provides a highly selective list of risk factors and associated corrective or preventive measures that reflect the priorities, constraints, and available resources of the transfer team.
选址过程完成后，可以使用风险排序和筛选（RRF）工具对待转移产品和接收方设施进行评估。RRF 工具是用于确定转移各方面潜在的风险因子和危害的，如接收方质量体系的完善性、新原料的引入或影响产品稳定性的工艺变更。该方法为风险因子和相关的预防或纠正措施提供了高选择性的列表，能反映转移小组的优先性、限制和可用资源。

RRF typically includes application of risk-based scoring criteria. Using resource, financial, or time-based scoring criteria will enable the transfer team to prioritize risk factors using multiple filters. This method provides a highly selective list of risk factors and associated corrective or preventive measures that reflect the priorities, constraints, and available resources of the transfer team.
RRF 通常包括应用基于风险的打分。使用基于资源、资金或时间的打分标准让转移小组能使用多种“过滤器”给风险因子优先排序。该方法为风险因子和相关的预防或纠正措施提供了高选择性的列表，能反映转移小组的优先性、限制和可用资源。

Scoring transfer-related risk in aggregate can be helpful given the broad range of hazards evaluated across multiple disciplines and the difficulty of evaluating multiple risk assessment (conducted for each individual problem or event) separately. In addition, performing this risk ranking exercise using a high-level, cross-functional transfer team (as opposed to technical subteams) ensures that prioritization decisions are made at appropriate levels in the organization and with representation from multiple impacted stakeholder groups. The risk ranking can be revised based on the results of the risk mitigation actions implemented. An illustration of this process is outlined in **Table 6.3.1-6: Risk Analysis**. 对转移相关风险进行总体打分是有帮助的，可以给出广泛的多学科的危害评估以及对多个风险评估综合评价的

难度（为每个单独的问题或事件进行）。此外，使用一个高水平、跨职能的转移小组（相对于技术子小组）来执行风险排序能够确保适当级别的组织和多个受影响利益团体的代表来决定优先级别。风险排序可以根据风险降低行为的执行结果进行调整。这一过程的说明详见**表 6.3.1-6: 风险分析**.

For example, the transfer team may identify several unacceptable hazards and many less critical hazards but lacks the resources to sufficiently address all risk factors within a given time frame. By applying both risk-based and resource-based filters, the team can quickly narrow down the list of risk-reduction activities and focus on only those high-priority risks that the team has available resources to address. 比如，转移小组可能发现了数个不可接受的危害和很多次关键的危害，但是缺乏足够的资源在限定时间内界定 所有的风险因子。转移小组同时使用基于风险和资源的“过滤器”，就能迅速减少风险降低行为的列表并集中可 用资源解决高优先级的风险。

Performance of this ranking exercise by the transfer team is critical to ensure that resource-based prioritization decisions are made with full consideration of transfer team priorities, resource availability, and budgetary constraints. Generally, the transfer team is better suited to make these decisions than technical teams with less cross-functional representation and a potentially narrow view of general organizational concerns. 转移小组进行这种排序是非常关键的，可以保证基于资源的优先级排序是在考虑了转移小组优先级、可用资源 和预算限制的基础上做出的。通常情况下，转移小组比技术小组更适合做出这些决定，因为技术小组拥有的跨 职能代表更少且对总体组织考虑的视野比较窄。

The complexity of the RRF activity should reflect the complexity of the process being transferred. For example, TTPs typically require participation from multiple units or require long-team dedication of specific resources. Filtering criteria may be set up to reflect resource availability so that high-priority, cross-functional projects are preferentially selected based on the availability of limited personnel or other resources.
RRF 行为的复杂性应当反映待转移工艺的复杂性。比如，TTP 通常需要多个部门的参与或需要特定资源的长期投入。设定的筛选标准需要反映可用资源，这样可以在有限的人员或其它资源的可用性基础上优先选择高优先级、跨部门的项目。

5.7.2.2 Assessment of Regulatory Gaps 法规差距的评估

An analysis should be performed to identify gaps between applicable SU environmental, health, and safety regulations and those that govern the RU. It may be useful to create a list of all of the chemical/material inputs, outputs, by-products, and wastes used and/or generated by the process to aid in the analysis. Risk assessment should be performed on differences to determine their potential impacts on the TTP. The differences in regulations between regional governments could potentially impact how materials are handled, stored, and disposed. Areas that could have an overall impact on how the materials are handled or processed due to varying regulatory requirements and to QA, technical, and environmental, health, and safety considerations are:
应开展分析来识别 SU 适用的环境、健康和安全法规与管理 RU 的法规之间的差异。对工艺使用和/或产生的化学/物料投入、产出、副产物和废物建立一个列表来帮助分析可能是有用的。风险评估应当针对差异开展以确定其对 TTP 的潜在影响。地方政府之间的法规差异可能会对如何管理、储存和处理物料有潜在影响。因为不同的法规要求和 QA、技术和环境、健康以及安全考虑，对如何管理或处理物料有总体影响的方面包括：

- Occupational exposure limits 职业暴露限值
- Compound hazard categories 有害化合物种类
- Fire/explosion regulations 防火防爆条例
- Personal protective equipment requirements 个人防护设施的要求
- Regional bands or limitations on compound classes 化合物类别的地区性禁止或限制
- Waste disposal requirements 废物处理需求
    - Environmental assessment requirements 环境评估需求

5.7.2.3 Assessment of RU Readiness RU 准备状态评估

The SU and RU need to evaluate the RU’s readiness to perform the chemistry as part of the risk assessment. This may involve evaluation of the RU’s experience in performing the types of processes described by the SU. It may be useful to rank each of the reaction steps from easy to complex.
作为风险评估的一部分，SU 和 RU 需要评估 RU 对执行化学工艺的准备状态。这可能会涉及评估 RU 在执行 SU 描述的这类工艺的经验。将每步反应从简单到复杂进行排序可能是有用的。

5.8 Risk Mitigation 风险降低

To accomplish a successful technology transfer, QRM must be both efficient and effective. Efficiencies in prioritizing transfer team activities, identifying resource requirements, and establishing meaningful timelines can be realized through the tools used for risk analysis.
要成功完成技术转移，QRM 必须同时是高效的和有效的。技术团队活动的优先排序、确定资源需求和建立有意义的时间限的效率可以通过使用风险分析工具来实现。

5.8.1 Experiments to Confirm Key Process Parameter Ranges 确认关键工艺参数范围的实验

The purposes of the experiments during the TTP are to confirm key process parameters and fill in the gaps identified in the risk assessment. The experiments are not designed to redevelop or optimize the process.
TTP 期间的实验的目的是确认关键工艺参数和弥补风险评估发现的差距。这些实验不是设计来重新开发或优化工艺的。

Qualified laboratory-scale or pilot-scale models should be established, preferably at the RU. Depending on the agreement between the SU and the RU, the qualified models may be maintained at the SU if they are not established at the RU.
合格的实验室规模或中试规模模型需要被建立，最好在 RU 建立。根据 SU 和 RU 之间的协议，合格的模型如果没有在 RU 建立的话，可以在 SU 保存。

Experimental design and protocol are based on the established scale-down models and the ranges of the key process parameters provided by the SU. Design-of-experiment methods need to be used in the experimental design. These methods call for the use of raw materials from approved vendors that will supply the commercial operations in the scale-down model experiments. The acceptance criteria should be clearly defined in the protocol. The experimental results are documented in the summary report, and conclusions should be drawn as to whether the key process parameter ranges are confirmed.
实验设计和方案基于 SU 提供的已建立的小规模模型和关键工艺参数。基于实验的设计方法需要用于实验设计。这些方法需要使用已批准的支持商业操作的供应商提供的原料，这些供应商将会为小规模模式实验供应物料。方案应明确定义可接受标准。实验结果需要在总结报告中记录，对于是否确认了关键工艺参数的范围应该有结论。

5.8.1.1 Demonstration Runs 证明性运行

After the key process parameter ranges are confirmed at the laboratory or pilot scale, additional experiments maybe run at the commercial scale (depending on the complexity of the process) prior to process validation, such as demonstration or engineering runs. Products generates from the demonstration runs must not be used commercially. 在实验室或中试规模确认关键工艺参数范围后，工艺验证前可能进行额外的商业化规模（根据工艺的复杂性） 实验，比如证明性运行或工程运行。证明性运行得到的产品不得用于商业。

For well-defined platform or relatively simple processes, demonstration runs may not be necessary. For complicated processes, demonstration runs are suitable to demonstrate the scalability of the process at the RU. Demonstration runs also help discover potential gaps in equipment, instrumentation, automation, utility, CIP, etc. 对于明确的平台或相对简单的工艺，证明性运行不是必需的。对于复杂的工艺，证明性运行对于证明工艺在 RU 的可放大性是合适的。证明性运行另一方面能够帮助发现设备、仪器、自动化、公用设施、CIP 等方面的潜 在差距。

A PFD based on the develop history report should be ready prior to the demonstration runs. The PFD should capture the process and equipment flow, general process chemistry, CPPs, raw material specifications, forward processing criteria (or intermediate specifications), sampling plan, etc. A protocol for the demonstration runs should be prepared to document, at a minimum, the purpose, scope, roles and responsibilities, test plan, and acceptance criteria. Batch production records must be available to document the appropriate operating conditions and any special instruments for the demonstration runs.
基于开发历史报告的 PFD 应当在证明性运行前准备好。PFD 应当包括工艺和设备流程、通用化学过程、CPP、原料质量标准、工艺推进标准（或中间体质量标准）、取样计划等。应当准备证明性运行的方案，至少记录目的、范围、角色和职责、测试计划和接受标准。应当有批生产记录来记录合适的操作条件和任何证明性运行的使用的特殊仪器。

Intentional deviations in operating parameters from the target set point may be used to test process robustness during the demonstration runs.
在证明性运行中可以对操作参数目标设定值进行有意偏离，用于测试工艺的耐受性。

Depending on how well controlled the CPPs are at the commercial scale, the CPP ranges may need to be adjusted after the demonstration runs. The demonstration run results and gaps found, corrections made during the runs, and recommendations are documented in a summary report.
取决于商业规模 CPP 的控制良好程度，证明性运行后可能需要调整 CPP 范围。证明性运行的结果和发现的差距、运行中进行的修正、以及建议都在总结报告中记录。

Additional demonstration runs may be required if the recommended actions must be taken prior to process validation. Demonstration runs can be costly. Cost and benefits need to be considered carefully in conjunction with the risk assessment. 如果建议的措施必须在工艺验证前执行，可能需要额外的证明性运行。证明性运行可能花费很高。花费和收益 需要与风险评估一起被仔细考虑。

5.8.2 Cycles of Risk Assessment, Data Collection, Risk Mitigation, and Closure
5.8.2 风险评估、数据收集、风险降低和关闭的周期

To bridge the gaps identified during the initial risk assessment and mitigate the risks, data can be collected through experimentation at different scales and/or data mining of the SU's database. 为了跨越最初风险评估和风险降低之间的差距，数据可以通过在不同规模的实验和/或对 SU 的数据进行数据挖 掘而得到。

Data calibration is a process to assess whether the risk-mitigation results are acceptable and whether the technology transfer is successful. Data evaluation is not one-time exercise and should be incorporates into milestone (or stage gate) reviews. Examples of stage gates are the laboratory-scale data review prior to the pilot plant testing; the pilot scale data review prior the production scale testing; the data review of the demonstration runs prior to the process validation; and post-process validation data review. 数据校准是一种评价风险降低结果是否可以接受和技术转移是否成功的方法。数据评估并不是一次的行为，应 当整合到里程碑审核（或阶段审核）中。阶段节点的例子有在中试实验前进行实验室规模的数据审核；生产规 模实验前进行中试数据审核；工艺验证前进行证明性运行的数据审核；工艺验证后数据审核。

Two questions need to be answered at each data review:
每次数据审核时需要回答两个问题

- Are the data sufficient to support the mitigation plans developed based on the risk-assessment results?
- Have the critical success factors been produced as demonstrated by the data?
- 已有数据是否足够支持基于风险评估结果提出的风险降低计划？
- 关键成功因素是否被数据证明？

The personnel involved in the data evaluation should include the technology transfer project leader (or project manager); experienced scientists and engineers from SU and RU; and representatives of QA, QC laboratories, operators, and senior management. The data review results should be documented, and conclusions need to be drawn regarding whether each milestone has been successfully achieved. Any action items from the data review team should be addressed by the project leader/manager.
数据评价涉及的人员应当包括技术转移项目领导（或项目经理）；来自 SU 和 RU 的有经验的科学家和工程师；以及 QA、QC 实验室，操作人员和高层管理的代表。数据审核的结果应被记录，此外需要得到关于每个里程碑的目标是否达到的结论。任何从数据回顾小组得出的行动项目应得到项目领导/经理的注意。

Additional risk assessment may be needed after more knowledge is acquired through data reviews. When new high risks are identified, whether these risks are acceptable must be determined. If they are not acceptable, new risk mitigation measures must be developed and additional data should be collected. This risk assessment/data collection/data review circle continues until all risks are reduced to an acceptable level. 通过数据审核得到更多信息后，可能需要额外的风险评估。当新的高风险被确定后，必须确定这些风险是否可 以被接受。如果它们不可被接受，需要提出新的风险降低措施和收集额外的数据。这个风险评估/数据收集/数据 审核的循环需要一直进行指导所有的风险都被降低到可接受水平。

6.0 Case Studies 案例分析

In the following pages, three cases are provided to show the application of the principles, concepts, and tools of QRM to the TTP.
接下来，我们提供了3个案例展示如何将质量风险管理的原理、概念和工具应用于技术转移过程中。
The first case study focuses on the analytical transfer of a method, whereas the second and the third case studies focus on manufacturing activities.
第一个案例聚焦于分析方法的转移，而第二和第三个案例重点讲述了生产活动的转移。

6.1 Case Study 1: Analytical Method Transfer 案例1：分析方法的转移

Although an AMT may occur at any point in the method and product lifecycle, analytical methods are often co-transferred with the manufacturing process during product development and /or after commercial licensure.
尽管在方法和产品生命周期中任何阶段都可能出现分析方法转移，通常都是在产品开发和/或获得生产许可后，将分析方法和生产工艺一起进行转移。

The stages of an AMT include a preliminary evaluation and preparation of the new laboratory to receive the test method, development of an approved method transfer protocol, and application of suitable statistical tools to analyze the results. the outcome is documented in a method transfer report.
一个分析方法转移包括接收该分析方法的新实验室进行初步评估和接收准备，建立方法转移方案并得到批准，运用适当统计工具对结果进行分析。将结果记录在方法转移报告中。

For all AMTs, the responsibilities of the SU's and RU's laboratories should be established. The quality and / or service agreement(s) should clarify all conditions and responsibilities. In addition to the preparation and sharing of samples, critical reagents, and standards to be used during the AMT studies, some continuous post-AMT testing (monitoring) should be considered (4,12). Table 6.1-1 lists the suggested responsibilities for each laboratory and provides some examples of how tasks and responsibilities could be shared by both laboratories during AMT.
对于所有的分析方法转移，均应建立转让方和受让方实验室的职责。质量和/或服务协议应明确所有条件和职责。除了方法转移研究中所用样品、关键试剂和标准品的制备和共享，还需考虑进行一些方法转移后的连续测试（监控）（4.12）。表6.1-1列举了各实验室的职责，并举例说明了在方法转移期间两个实验室如何共享任务和职责。

Table 6.1-1 Suggested AMT Responsibility Matrix 方法转移中的职责矩阵

Laboratory 实验室	Suggested Responsibilities 建议的职责
SU laboratory 转让方实验室	• Assess feasibility/readiness 评估可行性/准备情况 • Compile QC/process data 编写QC/工艺数据 • Organize training, if required 需要时，组织培训 • Establish the transfer package 建立转移包 • Write transfer protocol based on requirements of both laboratories and

	knowledge of methods prior to transfer 依据双方实验室的要求和对方法的认识，在转移前起草方法转移方案 • Establish protocol acceptance criteria 建立可接受标准 • Allocate resources for training and transfer study 分配培训和转移研究的资源 • Provide critical reagents and samples 提供关键试剂和样品 • Provide troubleshooting support 提供技术支持 • Approve the transfer report 批准转移报告
R U laboratory 受让方实验室	• Review the transfer package 审核转移包 • Define the transfer process, including training requirements 确定转移程序，包括培训需求。 • Inform the donor laboratory of potential issues identified (such as different suppliers of critical equipment) 将发现的潜在问题（如关键设备制造商不同）告诉转让方实验室 • Allocate resources for training and transfer study 分配培训和转移研究的资源 • Analyze transfer data 对转移数据进行分析 • Write the transfer report 起草转移报告 • Inform the donor laboratory of the outcome of the transfer 将转移结果告诉转让方实验室 • Approve the transfer report 批准方法转移报告

6.1.1 General AMT Strategy 分析方法转移策略

The strategy used for an individual method to be transferred and / or to support a product transfer can vary depending on the exact circumstances. Options for strategies are illustrated in USP < 1224> Transfer of Analytical Procedures *(10).* A comparative study model is further described below.

用于方法转移和/或支持产品转移的策略应随具体环境不同而变化。策略选项见USP<1224>分析方法的转移（10）。下文进一步描述了比对研究模型。

6.1.2 Design of Comparative AMT Test Studies 分析方法转移比对研究实验的设计

The AMT protocol should include a study design specifying method parameters to compare, samples to test, justified acceptance criteria, and the statistical methodology to evaluate the results (see Table 6. 1.2-1).

分析方法转移方案应包括：明确待比对方法参数的实验设计、待测试样品、适当的可接受标准以及评价结果的统计学方法（见表6.1.2-1）。

Table 6.1.2-1 General AMT Design Parameters and Considerations

分析方法转移的实验设计参数和设计要点

AMT Design Parameter	Considerations

分析方法转移的实验设计参数	设计要点
How many representative batches? - Matrix approach (number of different sample types and/or batches to be evaluated) 多少个代表性批次-矩阵法（待评价的不同样品类型和/或批次数量）	Two or three batches bracketing the expected active protein concentration ranges could be used. The selected materials should be representative of routine samples. 可采用预定蛋白浓度的2或3个批次交叉设计。所选物料应为具有代表性的常规样品。 Retain samples, reference standards, samples at the extremes of acceptance limits, stability samples, and/or spiked samples should be used, depending on the situation. 根据具体情况，可采用留样、参照品、接近可接受限度的样品、稳定性样品和/或加标样品。 For impurity tests, samples may be spiked or degraded so that the level of the impurity is below and/or above the acceptable quality limit (AQL) (and/or specification limit). If samples with a measurable impurity level are not available, it might be necessary to prepare spiked samples to evaluate the accuracy and precision of measurable amounts of impurity/degradation levels during the AMT studies. 对于杂质检测，可在样品中添加标准样品或将其降解，使杂质水平低于和/或高于可接受质量限（和/或标准限度）。如果在分析方法转移研究中，没有达到可检测杂质水平的样品，必须制备加标样品，以评价杂质的可检测量/降解水平的准确度和精密度。 If there are differences in the formulation, the range of formulation differences should be tested. The rationale for the selection of representative AMT samples should be documented in the AMT protocol. 如果处方存在差异，应对处方差异的范围进行测试。方法转移中代表性样品的选择理由应记录在转移方案中。
How many replicates per sample and laboratory? (Number of independent runs) 每个样品和实验室的复样有多少？（独立测试的数量）	The number of replicates depends on the repeatability and intermediate precision performance of the method to be transferred and the desired confidence level(s) for meeting product specifications. The AMV report and other related data sources (for example, routine test results) should be reviewed. 样品的份数取决于待转移方法的重复性和中间精密度，以及为了符合产品标准所需的置信区间。应审核分析方法验证报告和其他相关数据（如日常测试结果）。
How many Intermediate precision variability factors are used? 采用了多少个变异因子？	At least two critical factors should be selected based on prior knowledge of which factor(s) may have the greatest expected impact on variations in test results. 根据以往知识，应选择至少两个关键因子，这些因子可能对检验结果变动有最大影响。

6.1.3 Selecting AMT Performance Characteristics 选择方法转移的性能特性

The intended purpose of the method should be used to justify the rationale of the study design and acceptance criteria for each method transfer. Table 6. 1.3-1 provides an example of

performance characteristics to be compared between laboratories for different types of methods. Other performance characteristics covered during the validation studies may also be considered.
分析方法应被用来证明每一方法转移的试验设计和可接受标准的合理性。表6.1.3-1列举了不同方法在实验室间转移需比较的性能特性。也可考虑验证研究中涵盖的其他性能特性。

Table 6.1.3-1 Examples of Method Types and AMT Performance Characteristics 方法类别和方法转移的性能特性示例

Type of Method 方法类别	Sample AMT Performance Characteristics 方法转移性能特性举例
Identity tests 鉴别	System suitability, specificity, and qualitative comparison (if applicable) 系统适用性、选择性和定性比较（适当时）
Process and/or product related impurities (quantitative) 工艺和/或产品相关杂质（定量）	System suitability, precision, and accuracy 系统适用性、精密度和准确度 Consider several concentration levels: minimum reportable quantity and/or quantitation limit(s) and 120% of the product specification 设计几个不同浓度水平：最低可报告量和/或定量限，产品限度的120%。 Stability samples may need to be included to assess stability-indicating capabilities when relevant 适当时，需包含稳定性样品，以评估方法指示稳定性的能力
Impurities(qualitative, limit) 杂质（定性、限度）	System suitability, and detection limit(s) 系统适用性、检测限
Assay - content and potency 检查-含量和效价	System suitability, precision, accuracy, range, and stability samples may need to be included to assess stability-indicating capabilities, as relevant 系统适用性、精密度、准确度、范围，必要时也可用稳定性样品评估方法指示稳定性的能力。

6.1.4 AMT Documents 分析方法转移文件

AMT processes are documented through AMT protocols and AMT reports. The AMT protocol typically consists of the sections listed in Table 6. 1.4-1.
分析方法转移过程记录于转移方案和报告中。分析方法转移报告通常包括表6.1.4-1所列内容。
Table 6.1.4-1 Typical AMT Protocol Sections
表6.1.4-1典型的方法转移方案

Section No. 章节编号	Section Title 标题	Subsections 分段
NA	Protocol approval 方案批准	Protocol title and signatures with job titles and responsibilities 方案标题、签名以及职位和职责
NA	List of protocol sections 方案章节列表	Table of contents, list of figures (if applicable) and list of tables 目录表、图表清单（适当时）

1	Introduction 介绍	Intended use and sample(s) description 目的和样品描述
2	Method and product/process 方法和产品/工艺	Brief description and (target) specifications 简介和（目标）质量标准
3	Samples, materials, equipment, and instruments 样品、物料、设备和仪器	Sample preparation and storage, materials, equipment, instruments, and personnel 样品制备和存放、物料、设备、仪器和人员
4	Historical assay performance 检测方法运行历史情况	Summary of historical data for assay control, s ample, process capabilities, design space limits (if available, and prior analytical platform technology method performance (if applicable) 检测过程控制、样品、过程能力、设计空间限度（如有，以及以往分析平台检测方法的运行情况）的历史数据汇总
5	AMT characteristics and design 分析方法转移中方法特性和设计	AMT characteristics, statistics, acceptance criteria, and justification(s) 分析方法转移中方法特性、统计分析、可接受标准，以及理由
6	AMT execution matrix 分析方法转移的实施矩阵	Visualized execution process map(s) and/or execution matrix tables 可视化的实施流程图和/或执行矩阵表
7	Data analysis 数据分析	Calculation samples and proposed statistical tests 计算示例和建议的统计方法
8	Procedures, references, and guidelines 程序、参考和指南	SOP(s), AMV protocol / report(s) and other references SOP、分析方法验证方案/报告和其他参考文件

The AMT report describes the results of implementation of the protocol, compares these results to the acceptance criteria, and draws a conclusion regarding the acceptability of the transfer.
分析方法验证报告描述了方案实施结果，并将这些结果与可接受标准进行比较，并做出是否可以接受转移的结论。

6.2 Case Study 2: Manufacturing Process Transfer

案例2：生产方法转移

6.2.1 Overview of Manufacturing Process Transfer 生产方法转移概述

The installation of the manufacturing process for a recombinant protein-based vaccine occurred through two different TTPs. The initial technology transfer from the R&D unit to the manufacturing unit (development to commercialization TTP) resulted in the manufacturing of lots that were used in Phase 3 clinical trials and for launch supply. After this initial TTP, a second TTP was conducted (intra-company TTP) to a scaled-up purification facility which was required to meet the projected market supply requirements.

一个重组蛋白疫苗生产工艺是通过两种不同的技术转移过程建立的。通过研发机构至生产企业（从开发至商业生产的技术转移）的首次技术转移，所生产批次可用于三期临床和上市销售。之后进行二次技术转移（公司内技术转移），在商业生产厂房进行批量放大，以满足市场供货需求。

The manufacturing process consists of yeast-based fermentation, purification, and reassembly of the recombinant protein virus-like-particles (VLPs); adsorption to an adjuvant; and sterile formulation and filling. Key challenges during process development included protein expression in a defined media fermentation and control of VLP aggregation and stability. These challenges were overcome via the TTP to produce a small scale process suitable for early phase clinical testing.
生产过程包括酵母菌发酵、纯化、重组蛋白类病毒颗粒的繁殖、辅助剂的吸附以及无菌配料和灌装。工艺开发中的关键挑战包括特定培养基发酵时蛋白表达、类病毒颗粒的聚集控制以及稳定性。通过技术转移解决这些挑战，建立小批量生产工艺，用于早期临床测试。

6.2.2 Case Description: Development to Commercialization TTP 案例描述：从开发至商业生产的技术转移

The TTP was initiated with a facility fit analysis to compare the unique aspects of the processing equipment in the existing fermentation facility to the process as defined in R & D. This led to targeted development work to better fit the process into the intended manufacturing facility. For example, the relative scale of the fermentation seed process was modified and tested to fit into the fixed equipment in the existing facility. In addition, some facility changes were required to meet the needs of the process. A new purification facility was required, and close collaboration between the R&D and manufacturing units led to an agile design that met the processing needs. Finally, the formulation and filling process was transferred to an existing facility.
通过进行匹配分析启动技术转移，将现有发酵厂房中使用的加工设备的特殊性与研发中确定的工艺进行比较。这样可进行针对性开发工作，以将工艺和预定生产厂房更好地结合在一起。例如，调整发酵种子工艺的相对批量，以适应现有厂房中设备的需要。另外，需进行一些厂房变更以满足工艺的要求。需要建立一个新的纯化厂房，通过研发和生产部门的紧密合作，进行灵活设计以满足工艺需要。最后，将配料和灌装工艺转移至现有厂房中。

A risk assessment was performed to characterize the process parameters and attributes. The product's CQAs were identified, and the process experts determined the associated CPPs that were responsible for controlling the CQAs.
进行风险评估，以确定工艺参数和工艺特性。识别产品关键质量特性，工艺专家确定相关关键工艺指标对关键质量特性进行控制。

Other attributes that were important for process consistency (key product attributes and operating parameters) were also identified to further define the manufacturing process. The ranges associated with these attributes and parameters were determined experimentally. However, in most cases, the limits were known "success" values rather than those at the boundary of failure due to the complexity of the process and product. The ranges were

approved by the R&D unit and the manufacturing organization (operations, quality, and technical operations) and were the basis for process validation.
The ranges for CQAs and CPPs were maintained for all components, except that some were changed due to process scale and planned process changes.
也要识别其他对于工艺稳定的特性（关键产品特性和操作参数），以进一步确定生产工艺。通过试验确定这些特性和参数的范围。然而，多数情况下，由于工艺和产品的复杂性，这些限度只是已知的“允许”值而不是“不合格”的边界值。研发和生产部门（操作、质量和技术部门）批准这些范围，并作为工艺验证的基础。所有关键质量特性和关键工艺参数范围应稳定，除了一部分因批量调整和计划的工艺变更而更改。

A well-defined business process existed in the enterprise and was used to organize and manage the TTP for the product. The features of the business process included:

Formation of a technology transfer team that was responsible for executing the technology transfer plan. Members of this team included representatives of R&D, operations, quality, technical operations, and regulatory units.
企业应建立明确的产品技术转移组织和管理的流程。该流程应包括：建立技术转移计划实施小组。组员应包括研发、生产、质量、技术和法规部门代表。

Appointment of a technology transfer leader who was responsible for organizing and managing the team and reporting progress to a governing authority.
任命一个技术转移负责人，负责小组的组织和管理，并向监管部门报告进度。

A governance team of cross-functional leaders that oversaw the technology transfer plan and served as a decision-making body when issues were encountered. The team chartered the project and team and oversaw the project using a "stages and gates” approach. Stages are logical groups of associated activities and tasks that are part of a TTP. Stage gates are review points that are defined in advance by the governance team and focus on project status, key milestones for the next stage, and, importantly, the risks and risk mitigation plans for the project. For example, production of process validation lots was considered a distinct stage, and a stage gate review was conducted by senior leadership to ensure readiness for the process validation series and communication of the potential risks to the process validation lots.
建立由多部门负责人组成的领导小组，监督技术转移计划的执行，并在出现问题时作为决策机构。该领导小组掌管整个项目，采用“阶段和关卡”法管理技术转移项目。阶段是技术转移过程中各组相关活动和任务。关卡是领导小组提前确定审核点，关注项目进展、下一阶段的关键节点，更重要的是该项目的风险和风险降低计划。例如，工艺验证批的生产被认为是个独特阶段，应由管理层进行关卡审核，以保证工艺验证准备充分，并对工艺验证批潜在风险进行讨论。

A project management system used to ensure sound project definition and execution control. During the initiation and planning stage, a project plan was produced and was reviewed by the governance team. The plan resulted in approved schedule milestones that the technology transfer team was expected to meet. This stage also included definition of key assumptions and project risks that governed the project plan.
采用项目管理系统来保证项目界定清晰，并进行合理的执行控制。在启动和设计阶段，应建立

项目计划，并由领导小组审核。按照该计划，批准技术转移小组期望达到的预定重要节点。该阶段也包括确定关键的预期以及项目风险，并据此对项目计划进行管理。

An execution stage consisting of process readiness in the manufacturing facilities (for example, IQ /OQ and engineering lots), completion of process validation lots, and licensure of the facilities.
执行阶段包括生产厂房的工艺准备（例如，安装确认/运行确认和工程测试批次）、完成工艺验证批次，以及生产许可。

The process validation lots were used in Phase 3 clinical trials, which conclusively demonstrated the successful transfer of the process technology form the R&D to the manufacturing unit. Approval of the manufacturing facilities occurred concomitantly with product regulatory approval.
工艺验证批次用于三期临床试验，以证明研发到生产技术转移的成功。生产厂房的批准与产品的批准一同进行。

6.2.3 Intracompany TTP 公司内部的技术转移

To limit the capital expenditures before obtaining critical clinical performance data, a small-scale purification facility was used as the initial manufacturing facility to produce process validation lots used in the Phase 3 clinical studies and to manufacture drug substance for product launch. However, the expected market demand exceeded the capacity of the launch facility. Consequently a scaled-up purification facility was constructed.
为了在获得关键临床数据前对资金投入进行控制，采用小规模纯化厂房进行三期临床研究中工艺验证批次的生产，并生产原料药用于制剂的上市销售。然而，由于市场需求预期超过了该厂房的生产能力，又建造了更大的纯化厂房。

The process for the new facility was scaled up, which required targeted process changes to manage the larger production scale. For example, filter configurations were changed to reflect limitations in mechanical equipment design. In addition, a planned material manufacturing change by the vendor was evaluated in R&D to ensure success in the new factory.
对新厂房的生产工艺进行放大，因生产批量扩大需要进行工艺变更。例如，由于机械设备设计限制，对过滤装置进行变更。另外，供应商提供物料的生产工艺变更应由研发部门进行评估，确保在新厂房中顺利生产。

A project team was assembled in the manufacturing organization for the startup of the new facility and technology transfer from the initial purification facility. This team had a similar structure to that described above, although it was based at the manufacturing site. A governance team oversaw project execution and was responsible for rapid decision-making and resolution of issues escalated by the project leader. A communication plan was defined and implemented to ensure alignment in the organization concerning project implementation.
生产部门建立项目小组负责新厂房的建设和从小规模纯化厂房进行的技术转移。该小组与上文所述组织架构类似，尽管它属于生产部门。一个领导小组管控整个项目的执行，负责快速决策，以及项目负责人提出问题的解决。应确定实施计划，并得到执行，确保整个组织内项目协调实施。

Because the drug substance was a recombinant protein that was considered a well-characterized biologic, a comparability approach was taken for licensure of the new purification facility. This approach was aligned with the guidance in ICH Q5E Comparability *of* Biotechnological/Biological *Products subject to Changes* in their Manufacturing Process and provide a framework for evaluating the impact of the process changes and scale-up on product safety and quality (22).
因为原料药是个重组蛋白，是个清晰表征的生物制品，通过一致性研究获得新纯化厂房的生产许可。该研究应按照ICH Q5E指南“生物技术/生物制品生产工艺变更的一致性研究”进行，为评估工艺变更和批量放大对产品安全和质量的影响（22）提供框架。

A summary of the business process deployed for comparability is shown in Figure 6.2.3.1. Comparability consisted of demonstration of both process performance measures (e.g., key process attributes) and product quality attributes (e.g., product specifications). The expected results for these measures were defined by statistical analysis from production lots made in the launch facility. A weighing approach was used for the analytical measures to account for the relative importance of test results; for example, due to its impact on product quality the potency test was considered a more important measure than the characterization test.
一致性研究流程见图6.2.3.1。一致性研究包括证明工艺性能量值（如关键工艺特性）和产品质量特性（如产品质量指标）的一致性。这些量值的预期结果通过上市生产厂房制造批次的统计数据来确定。考虑检验结果重要性不同，对分析量值采用了加权法，例如，由于效价测试对产品质量的影响，通常认为它是个表表征测试更重要的量值。

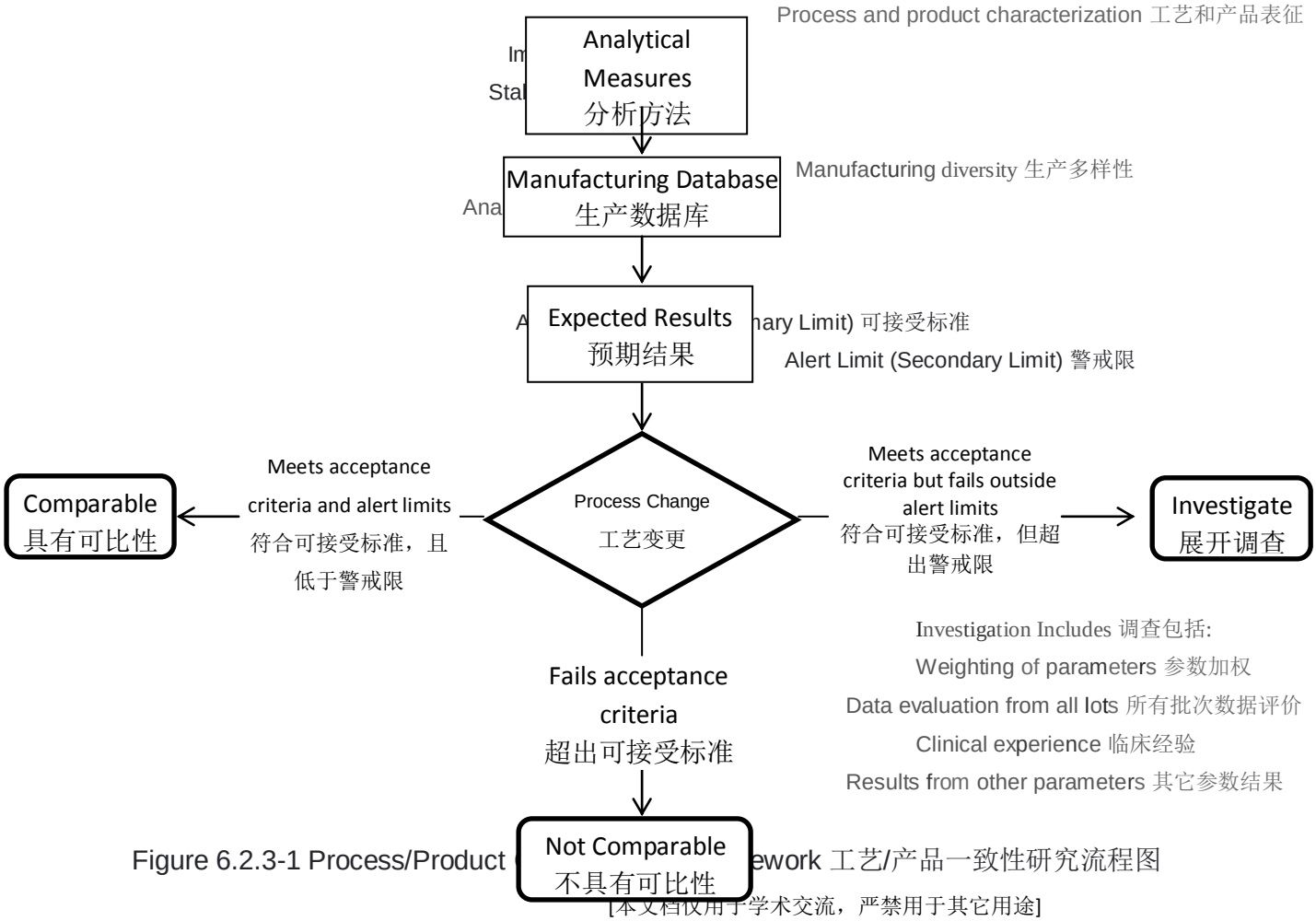


Figure 6.2.3-1 Process/Product [illegible]ework 工艺/产品一致性研究流程图

The process validation lots made in the new purification facility were tested according to the requirements in the comparability protocol. All lots made were deemed to be comparable to the small-scale launch facility, which led to the successful licensure of the facility without clinical studies.
对新纯化厂房生产的验证批按照一致性研究方案的要求进行检验。所有生产的批次与小规模上市销售厂房生产的批次具有可比性，则无需进行临床研究即可获得新厂房的生产许可。

6.2.4 Conclusion 结论

A successful production history lasting more than five years after licensure demonstrates the success of the technology transfer process used for this product.
批准生产后，五年以上可靠的生产数据表明该产品的技术转移是成功的。

6.3 Case Study 3: Manufacturing Process Transfer: QRM Application to Start-Up Evaluation

案例分析3：生产工艺转移：质量风险管理在启动评价中的应用

6.3.1 Use of Quality-by-Design Principles 采用质量源于设计的原则

The example in this section shows how quality-by-design principles can help the technology transfer team plan appropriate activities to mitigate risks along the project path (23).
本节的示例展示了质量源于设计原则如何帮助技术转移小组采取适当措施降低项目进程中的风险。

The objective of this example is the technology transfer of an injectable, small-volume parenteral solution from the manufacturing site of the originator firm (SU) to the manufacturing site of a CMO (RU). Supporting information and concepts can be found in PDA Technical Report No. 44: Quality Risk Management for Aseptic processes and PDA Technical Report 54: Implementation of Quality Risk Management for Pharmaceutical and Biotechnology Manufacturing Operations (7,21).
该示例介绍了将一个小容量注射剂从发起人公司（转让方）技术转移至合同加工单位（受让方）。支持信息和概念见PDA技术报告44：无菌加工工艺的质量风险管理，PDA技术报告54：制药和生物技术生产运营中质量风险管理的实施（7，21）。

As described in Figure 6.3.1-1, by processing the deliverables received by the SU, including information on the process and product to be transferred to the new site, the RU can conduct a risk analysis followed by a mitigation plan using a risk priority numbering approach.
如图6.3.1-1所述，通过对转让方交付物（包括待转移至受让方的工艺、产品信息）的处理，受让方可采用风险优先级法进行风险分析，并采取风险降低措施。

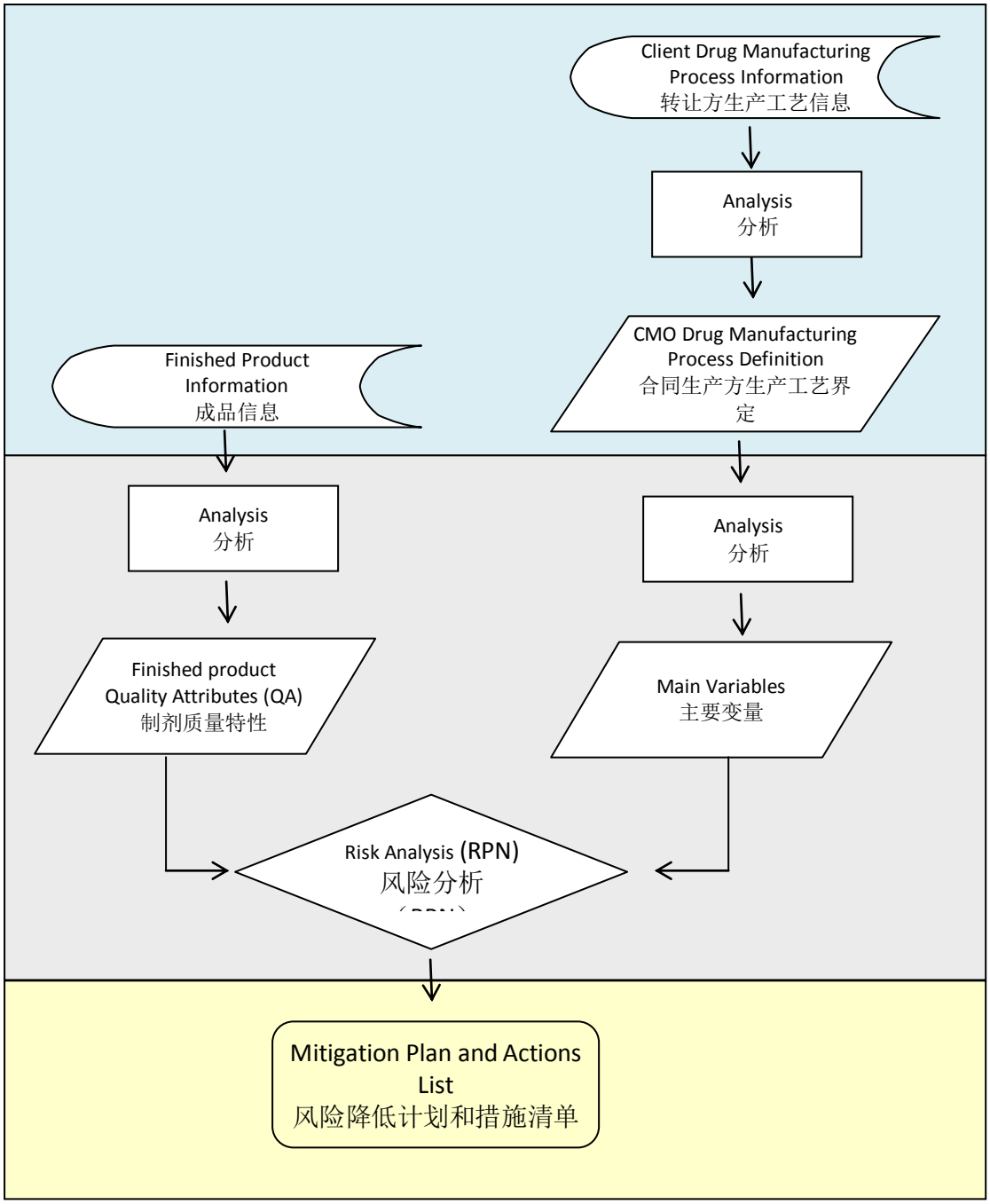


Figure 6.3.1-1 Overall Process Mapping 流程图

As a first activity based on site knowledge, the RU develops a new manufacturing process scheme that accounts for the modifications needed to implement the original manufacturing process at the new site.
根据现有知识，受让方首先建立一个新的生产流程图，并应考虑到在新厂房中生产时原生产工艺需要进行的调整。

The RU defines the main variables that could affect product quality attributes based on the new process scheme (Table 6.3.1-1). The main variable categories include:
受让方确定主要变量，根据新的工艺流程图这些变量可能影响产品质量特性（表6.3.1-1）。主要变量包括以下几类：

- Process/facility 工艺/厂房
- Primary packaging components 内包材组件
- APIs and excipients 原料药和辅料

Table 6.3.1-1 Examples of variables definitions 变量示例

List of Main Items Considered for the Evaluation 用于评价的主要项目	Relative Variables 相关变量		
Process 工艺	Mixing 混合	Filling 灌装	Identification 贴签
	Holding 暂存	Stoppering 压塞	Wrapping 包裹
	Compounding 配料	Crimping 轧盖	Visual Inspection 灯检
	Grade C filtration C级区过滤	Solution transfer 溶液转移	Secondary packaging 外包装
	Grade A filtration A级区过滤	Steam terminal sterilization 最终蒸汽灭菌	Line cleaning 清场
Primary packaging and GMP materials 内包材和GMP物料	Stoppers 胶塞	Filters 过滤器	Fixed tube 固定管道
	Vials 西林瓶	Disposable tubes 一次性管道	Gasket 垫片
	Seals 密封件	Disposable bag 一次性物料袋	
API and excipient attributes 原料药和辅料特性	API pH 原料药pH	API density 原料药密度	Excipients attributes 辅料特性
	API appearance 原料药外观	API osmolality 原料药摩尔渗透压	

The SU transfers the quality attributes of the products to the RU (Table 6.3.1-2).
转让方将产品的质量特性转移给受让方（表6.3.1-2）。

Table 6.3.1-2 Examples of Quality Attributes Definition 质量特性举例

Quality Attributes 质量特性		
Appearance 外观	pH	Volume in container 装量
Identity 鉴别	Density at 20℃ 密度（20℃）	Cosmetic appearance 外观微小缺陷
Assay 含量	Osmolality 摩尔渗透压	Sterility 无菌
Impurity 杂质	Particle matter 可见异物	Endotoxins 内毒素

The two teams merge the newly developed manufacturing process with the quality attributes of the product received to assess which variables could affect the product and how they can be controlled.
两个小组将收到的产品质量特性与新建立的生产工艺结合起来，评估可能影响产品的变量以及如何对其进行控制。

To take further advantage of the analysis, a risk number can be assigned to each variable based on its severity, occurrence, and detection.
为更好地利用风险分析，可基于严重性、发生概率和可检测性确定一个风险值。

This activity, done at the beginning of the project, can detect the most likely potential causes of technical failures during the TTP and allow planning for mitigating those risks. Following ICH Q9, the risk can be estimated based a combination of three main factors:
这项工作应在项目开始阶段进行，可在技术转移时发现导致转移失败最可能原因，并可采取措施降低这些风险。根据ICHQ9，风险可基于三个主要因素的组合预估：
Severity (S) 严重性
Occurrence (O) 可能性
Detection (D) 可检测性

Severity considers the potential impact on the quality attributes of the product and, hence, on patient health. It can be rated based on the table below:
评估严重性时应考虑风险对产品质量特性以及患者健康的潜在影响。可根据下表进行分级：

Table 6.3.1-3 Severity Definition and Rating 严重性的界定和分级

SEVERITY 严重性	RISK CLASSIFICATION 风险级别	VALUE 风险值
No impact on product's quality attributes or on patient health 对产品质量特性或患者健康没有影响	Low 低	1
Moderate impact on product's quality attributes and on patient health 对产品质量特性或患者健康有一定影响	Medium 中	2
Severe impact on product's quality attributes and on patient health 对产品质量特性或患者健康有严重影响	High 高	3

The occurrence factor is defined as the frequency of occurrence of the event. It can be rated as shown in Table 6.3.1-4.
可能性则定义为事件发生的频次。可根据表6.3.1-4进行分级。

Table 6.3.1-4 Occurrence Definition and Rating 可能性的界定和分级

OCCURRENCE 可能性	RISK CLASSIFICATION 风险级别	VALUE 风险值
Highly improbable or impossible that the negative event will occur 不良事件不可能或极不可能发生	Low 低	1
Some possibility that the negative event will occur 不良事件有可能发生	Medium 中	2
Highly probable or certain that the negative event will occur 不良事件极可能或确定发生	High 高	3

The detection factor is defined as the probability of detecting the events if they occur, based on the control system in place. It can be rated as shown in Table 6.3.1-5.
可检测性是指如果不良事件发生，基于现有控制系统可以检测出来的可能性。可根据表6.3.1-5进行分级。

Table 6.3.1-5 Detection Definition and Rating 可检测性的界定和分级

PROBABILITY 可检测性	RISK CLASSIFICATION 风险分级	VALUE 风险值
Highly probable or certain that the negative event will be detected by the control system in place 现有控制系统极可能或确定能够检测出不良事件	Low 低	1
Some possibility that the negative event will be not detected by the control system in place 现有控制系统可能无法检测出不良事件	Medium 中	2
Highly improbable or impossible that the negative event will be detected by the control system in place 现有控制系统极不可能或不可能检测出不良事件	High 高	3

Based on the definitions and ratings of severity, occurrence, and detection, risk rank can be calculated using the formula R= S x O x D.
根据严重性、可能性和可检测性的定义和分级，可用公式风险=严重性x可能性x可检测性计算而得。

A team evaluation is needed to identify acceptance criteria. For example, in Table 6.3.1-6 a risk (R) < 9 is deemed acceptable and no actions are needed to mitigate this risk.
应进行小组评价，确定可接受标准。例如，在表6.3.1-6中，小于9的风险是可接受的，因此无需采取措施降低该风险。

Based on the risk criteria and ranking, a mitigation plan is established by the team. After the plan is implemented, the risks are evaluated again to confirm that they have been mitigated.
根据风险可接受标准和风险评级，转移小组确定风险降低计划。在实施后，再次对风险进行评估，以确认风险已经降低。

Table 6.3.1-6 Risk Analysis 风险分析

Analysis 分析				Risk Priority Number Evaluation 风险优先级评价				Mitigation Plan 风险降低措施
Item 项目	Variable 变量	QA Impacted 受影响的质量特性	Potential criticality/cause of lack of quality attribute description 质量特性关键程度/造成质量特性缺失的原因	Severity 严重性	Occurrence 可能性	Detection 可检测性	RPN 风险优先级	Consideration / Action 解决思路/措施
Process 工艺	Mixing and compounding 混合和配料	pH	Dissolution speed is insufficient for complete dissolution and a homogenous system. 溶解速度不足以完全溶解，并获得均匀体系	3	3	1	9	During the performance qualification, the mixing device of the tank used in the RU will be challenged. 在性能确认中，对受让方使用的罐混合装置进行挑战
		Osmolality 渗透压	Dissolution speed is insufficient for complete dissolution and a homogenous system. 溶解速度不足以完全溶解，并获得均匀体系	3	3	1	9	Mixing studies will be agreed on by the SU and performed during the engineering batch. 混合研究应获得转让方同意，并在工程测试批进行。
		Appearance 外观	Mixing system is not appropriate to guarantee uniform batch mixing 混合系统无法确保混合均匀	3	3	3	27	The user requirements of the RU tank have properly defined the mixing needs based on the characteristics of the colloidal system. 基于胶体体系的特性，受让方配料罐的用户需求已明确混合要求 The initial evaluation and information sharing between SU, RU, and the disposable technology Supplier have identified the appropriate mixing device. 通过转让方、受让方和技术服务商的初步评价和信息分享，已确定适当的混合装置。 The PQ challenge of the mixing system will include appropriate tests suggested by the supplier/owner of the technology 混合系统的PQ挑战试验应包括相关供方/技术所有人建议的测试。
		Density 密度	Temperature of the system is outside the range specified by the SU 系统的温度超出转让方指定的范围	2	1	1	2	No further action needed. The colloidal system is not sensitive to temperature. The RU WFI loop cooling and temperature control system will guarantee a 15-25℃ range. 无需采取进一步措施。胶体体系对温度不敏感。受让方注射用水的回路冷却和温度控制系统将保证温度处于15-25℃的范围
			Sampling mode device can affect the analysis 取样装置可能影响分析结果	3	2	2	12	The sampling system will be made of pharmaceutical-grade glass. The SU has collected data on compatibility, and the solution is declared compatible with glass devices. 取样系统由医药级玻璃制成。转让方已收集相容性资料，证明溶液与玻璃取样装置是相容的。
		Sterility	Preparation time can affect the	3	2	2	12	Validation activities will include hold time challenges according to a

		无菌	bioburden level of the final compounded solution 制备时间可影响配置溶液的生物负载水平					dedicated protocol. 验证活动包括按照制订的方案进行暂存时间的挑战试验 Chemical characteristics and microbiological attributes of the solution will be analyzed. 对溶液的化学和微生物特性进行分析
	Grade C and grade A filtration C级区和A级区过滤	Particulate matter 颗粒性物质	Particles release from disposable hoses may impact the particulate matter profile 一次性管路释放的颗粒可能影响溶液中可见异物组成	3	2	3	18	Use Silicon, platinum-cured, disposable hose certified for pharmaceutical use for solution transfer. 采用铂金固化的一次性硅胶软管进行溶液转移，应有适用制药使用的证明。 To address particle release from the hoses used in grade C, filter the solution three times before filling (0.45µm +0.22/0.2µm in grade C area and 0.22/0.2µm in grade A area). 针对C级区使用软管的颗粒物质脱落，在灌装前将溶液过滤三次（C级区：0.45µm +0.22/0.2µm；A级区：0.22/0.2µm） Regarding the particle release from the hoses used on the filling machine, a final 100% visual inspection will be done. Vials with a particle matter defect will be rejected. 对于灌装机上软管脱落的颗粒，可对产品进行100%的目检。有可见异物缺陷的瓶子将被剔除。
			Mixing system shedding may impact the particulate matter profile 混合系统剥落物可能影响溶液中可见异物组成	3	3	3	18	Supplier has provided leachable/extractable documentation and certifications. 供应商提供溶出试验文件和证明 Compatibility studies to be conducted with specified analytical methods with the supplier. 应和供应商一起按照规定的分析方法进行相容性研究
		Particle matter 可见异物	Release from the filter membrane may impact the particle matter profile of the solution. 过滤膜脱落的颗粒可能影响溶液中可见异物的组成	3	2	3	18	Regarding the release from the filters used in grade C, the solution is sterile filtered before filling. A final 100% visual inspection will be done. Vials with a particle matter defect will be rejected. 对于C级区过滤器的颗粒脱落问题，可在灌装前进行无菌过滤。进行100%的目检。剔除有可见异物缺陷的瓶子。
		Sterility 无菌	A filter with an integrity issue can compromise the sterility of the solution 完整性有问题的过滤器将影响溶液的无菌性	3	1	1	3	The filter arrives in the RU with the integrity certification of the supplier. 受让方购买过滤器时应要求供应商提供完整性证明。 According to the RU's procedure, each 0.22/0.2µm filter is tested after and before use. 按照受让方的程序，每一0.22/0.2µm过滤器在使用前后进行完整性测试。 Leachable/extractable documentation and certifications will be provided by the supplier. 供应商提供溶出试验文件和证明 If needed, specific analysis can be done by the supplier to identify possible leachables and extractables. 需要时，供应商可进行特殊的分析，以找出可能的溶出物 Adsorption and compatibility studies will be performed as a part of the filter validation. 吸附和相容性验证应作为过滤器验证的一部分

			A filter can become clogged 滤器可能被堵塞	3	1	1	3	Clogging of the filter with potential impact on the sterility of the overall process is evaluated in a preliminary phase of the transfer, including supplier trial scale up of their size. Analysis of the exact filtration system and critical process parameters that will be used during drug manufacturing are necessary. Both velocity max or pressure max trials are reliable and can anticipate potential failures. Media fill challenge of the filter change procedure is a valid practice to downgrade the associated risk and estimate the impact on sterility as a result of the filter change. 在转移的前期应对过滤器的堵塞以及其对整个工艺无菌性的潜在影响进行评价，这包括供应商的批量放大试验。需要对药品生产中使用的具体过滤系统和关键工艺参数进行分析。最大流速或最大压力试验都是可靠的，并能预估可能的故障。过滤器更换程序的培养基灌装挑战试验是降低相关风险，以及估计过滤器更换对无菌影响的一种好方法。
		pH	Adsorption on the membrane filter can impact density, osmolality, and pH of the solution 过滤膜的吸附可能影响溶液的密度、渗透压、pH	3	3	3	27	Adsorption studies will be done as a part of the filter validation. 吸附研究应作为过滤器验证的一部分进行 High impact has to be considered in the case of biological compounds due to the potential impact of changes in preservative concentrations. 因为防腐剂浓度变化的潜在影响，对于生物制品尤其应考虑吸附的重大影响
		Density 密度	Incompatibility between filter and solution can modify the system's chemical profile. 过滤器和溶液不相容，可能改变系统的化学成分	3	3	3	27	Compatibility studies will be done as a part of the filter validation. 相容性试验应作为过滤器验证的一部分进行
		Sterility 无菌	Clogging issue can have an impact on the microbiological growth attributes and chemical characteristics of the solution. 堵塞可能对微生物生长、溶液的化学特性有影响	3	3	2	18	The appropriate size of the filter will be defined in the RU with a specific laboratory trial with the filter supplier. The solution will be filtered through the filter until clogging occurs. Volume filtered, time of filtration, surface area, and flow rate will be analyzed and correlated. 过滤器尺寸应由受让方和过滤器供应商一起通过试验确定。将溶液通过过滤器直到发生堵塞。对过滤的溶液体积、过滤时间、表面积和流速进行分析和关联。 The RU's minimum filter size will be defined. A dedicated protocol and report will be issued with the results of the trial. 确定受让方的最小过滤器尺寸。应建立单独的方案、报告，并应包括试验结果。
			Holding time before filtration can increase the bioburden of the compounded solution. 过滤前暂存时间可能会增加配制溶液的生物负载	3	2	2	12	During the validation activities, the holding times will be challenged according to a dedicated protocol. 在验证时，应根据单独的方案进行暂存时间的挑战试验 The chemical characteristics and microbiological growth attributes of the solution will be analyzed. 对溶液的化学特性和微生物生长特性进行分析
	Filling 过滤	Volume in container	Incorrect filling weight can result in out-of-range container volume. 灌装重量不正确会导致装量超标	3	1	1	3	No further actions are needed because the RU's procedures are already in place to periodically check the weight of the solution dosed into the vials during filling activities. 无需采取进一步措施，因为受让方有程序要求在灌装过程中定期检查瓶中溶液

		装量						重量。
		Particle matter 颗粒性物质可见异物	Particle released from the tube can impact the particle matter profile of the solution. 管路释放的颗粒会影响溶液中可见异物的组成	3	2	3	18	Certified silicon, platinum cured, disposable hose for pharmaceutical uses will be chosen for the solution transfer. 采用医药级的一次性铂金固化硅胶管进行溶液转移 A final 100% visual inspection will be done. Vials with a particle matter defect will be rejected. 对产品进行100%的目检。剔除有可见异物缺陷的瓶子
	Stoppering 压塞	Sterility 无菌	Incorrect positioning of the stopper on the vials can result in incorrectly closed containers. 加塞位置不正确导致容器密封不正确	3	1	1	3	An appropriate sensor device is in place in the RU to check the correctness of the position of the stopper on the vials before the crimping step. 受让方有适当感应装置在轧盖前检查胶塞位置是否正确
	Crimping 轧盖	Cosmetic appearance 微小外观缺陷	Incorrect sealing of the vials can result in cosmetic defects 轧盖不当导致的微小缺陷	2	1	1	2	No further actions are needed because according to the Receiving Unit standard approach, a validation of crimping will be done. 无需采取进一步措施，接收方有相应标准程序，并进行轧盖的验证 The validation will take into consideration the cosmetic appearance of the vials. 验证中需考虑瓶子的微小外观缺陷 Moreover, according to the RU's standard approach, the cosmetic appearance of the crimped vials is periodically checked during the batch. 而且，根据受让方标准程序，该批生产过程中将定期对轧盖后瓶子的外观进行检查。
		Sterility 无菌	Incorrect sealing of the vials can result in non-closure of the vials 轧盖不当导致瓶子密封不严	3	3	3	27	Validation of the crimping step will be done. During validation, the correctness of the crimping will be challenged from a cosmetic point of view and from a container closure point of view by a dye intrusion test. Vials will be analyzed by ultraviolet-visible light spectroscopy after immersion in a solution of methylene blue. 对轧盖进行验证。验证中通过染料浸入试验对轧盖中微小外观缺陷和容器密封性进行挑战。将瓶子浸入亚甲蓝溶液中，然后采用紫外-可见分光光度法进行分析
	Steam terminal sterilization 终端蒸汽灭菌	Sterility 无菌	Assurance of an appropriate sterility cycle has to be guaranteed to provide the required lethality. 应有适当的灭菌行程，提供所需的致死率。	3	3	2	18	The terminal steam sterilization cycle will be validated to guarantee sterility assurance. 对终端的蒸汽灭菌行程进行验证，确保无菌
		pH	pH shift due to thermal stress can modify the chemical characteristics and, consequently, the stability of the solution after the terminal sterilization. 因热应力导致的pH漂移，可能改变灭菌后溶液化学特性、稳定性。	3	3	1	9	A technical report on the previous lots manufactured will be shared between RU and SU. The pH shift will be calculated. 受让方和转让方应共享以前生产批次的技术报告。计算pH的漂移大小。 Based on the report, an appropriate pH range prior to terminal sterilization will be set. 根据该报告，确定终端灭菌前适当的pH范围 An in-process control and an appropriate pH adjustment step prior to terminal sterilization will be introduced in the batch record to guarantee the correct pH of the final sterilization solution.

		Appearance 外观	Flocculation and coagulation events due to thermal exposure may impact the use and stability of the solution. 曝热导致的絮凝和凝固事件可能影响溶液的使用和稳定性	3	3	1	9	在批记录中增加终端灭菌前的中控和pH调整步骤，保证灭菌后溶液pH的正确 The validation batches manufactured in the RU will undergo a stability study to confirm that no changes of the system profile have occurred. 受让方生产的验证批应进行稳定性研究，确保效期内产品质量稳定 Appearance is one of the tests performed on the solution at the end of the process after the terminal sterilization. 外观是终端灭菌后溶液测试项目之一
	Identification 标识	Cosmetic appearance 微小外观缺陷	An incorrect setting of the laser printer used for the identification of the vials could impact vial identification. 标识物的激光打印机设置错误，影响产品的正确标识	3	1	1	3	No further actions are needed. The RU's procedure that is already in place guarantees the correctness of the setting of the laser printer. Moreover, during the production activities, the accuracy of the vial identification label is checked periodically. 无需采取进一步措施。受让方有程序保证激光打印机设置正确。而且，生产中还定期检查标识物的准确性
	Wrapping (bulk package) 包裹（散装）							
	Visual inspection 目检	Cosmetic appearance 微小外观缺陷	A defects checklist that has not been properly reviewed can lead to vials sent to the SU not matching the SU's expectation. 缺陷清单未被适当审核，导致发给转让方的瓶子不符合转让方的要求。	3	1	1	3	A checklist dedicated to the products will be generated based on the RU's experience and the SU's requirements. The checklist will be reviewed and approved by the SU as well. Appropriate training will be conducted for the visual inspection department operators. 根据受让方的经验和转让方要求建立产品专用清单。该清单也应得到转让方审核和批准。对目检人员应进行适当培训。
	Secondary packaging 外包装							
	Line cleaning 清场	Density, osmolality, and impurity 密度、渗透压和杂质	Possible residual material from the previous batch may be transferred to the next batch and could modify the chemical profile of the solution. 上一批次可能的残留物转移至下一批次，并改变溶液的化学特性	2	3	2	12	Specific cleaning validation activities will be done to validate the cleaning procedure to be applied after each batch is manufactured. 进行特定的清洁验证，对每批生产后采用的清洁程序进行验证
			An incorrect average run length (ARL) can lead to a false evaluation of the cleanliness status of the line. 错误的平均运行长度（ARL）会导致对生产线清洁状态的错误评价	3	1	2	6	As a part of the cleaning validation, appropriate calculation will be done to define the ARL based on current guidelines. 作为清洁验证的一部分，按照现有指南通过适当计算确定ARL All cleaning validation activities will be detailed in dedicated protocols and reports reviewed and approved by the SU. 所有清洁验证活动应在验证方案、报告中详细描述，并由转让方审核和批准
			Use of an inappropriate analytical method can lead to false results.	3	1	2	6	A specific method to analyze the WFI at the end of the cleaning procedure will be developed and validated to guarantee the accuracy and

			不正确的分析方法将导致错误的结果					reproducibility of the results obtained. 应建立对清洁结束时WFI进行分析的方法，并进行验证。保证获得结果的准确性和重现性。
Primary Packaging & GMP materials 内包材和GMP物料	Stoppers 胶塞	Impurity 杂质	Cross-contamination with other products can compromise the quality of the solution. 与其他产品的交叉污染将降低溶液质量	3	2	3	18	All lines and machine parts in contact with the product will be dedicated to avoid cross contamination. 与产品接触的所有生产线和机器部件应专用，以避免交叉污染。
			An impurity from the stopper can modify the solution's chemical profile. 胶塞引入的杂质会改变溶液的化学组成	3	2	3	18	
			The coating material can modify the solution's chemical profile. 涂布物质可能改变溶液的化学组成	3	2	3	18	The stopper components have been chosen by the SU during the development studies. 在开发研究时转让方已对胶塞组分进行研究
		Appearance 外观	Substances released from the stopper or from the coating can include flocculation or coagulation events in the solution. 胶塞或涂布物质释放物质可导致溶液絮凝或凝结。	3	2	1	6	The same stoppers will be used to guarantee the lack of anomalous interactions with the stopper coating and rubber. 采用相同的胶塞，确保不会与胶塞涂布物和橡胶发生异常作用。 Stability data were collected by the SU, no interaction issues were reported to RU. 转让方已收集稳定性数据，没有向受让方报告相互作用问题。
			Substances released from the stopper or from the coating can modify the appearance of the solution. 胶塞或涂布物质释放物质可改变溶液外观	3	2	1	6	
		Sterility 无菌	The bioburden of the stopper can impact the effectiveness of currently used and validated sterility cycles. 胶塞的生物负载可影响所采用的经验证灭菌方法的有效性	3	1	3	9	A risk assessment will be done to compare the stoppers currently used in RU with the SU stoppers to evaluate the possibility for using a sterilization cycle already validated by the SU. In cases which no comparable stoppers are found, a new stopper sterilization cycle will be validated. 进行风险评估，对受让方和转让方使用的胶塞进行比较，以评价采用转让方已验证的灭菌方法的可行性。
		Particle matter 可见异物	Release from the stopper may impact the particle matter profile of the solution 胶塞释放的颗粒性物质可影响溶液的可见异物组成	3	2	3	18	A final 100% visual inspection will be done, vials with a particle matter defect will be rejected. 进行100%目检。剔除有可见异物缺陷的瓶子
	Vials 瓶	Impurity 杂质	Impurities released from the glass can impact the solution profile. 玻璃释放的杂质可影响溶液化学组成	3	2	3	18	
			Leachables and extractables from the glass can modify the chemical profile of the solution. 玻璃溶出物可改变溶液的化学组成	3	2	3	18	Type I glass of USP / EP grade will be used. The validation batches produced will be analyzed via a stability study. All release tests will be repeated regularly during the stability program to confirm that no anomalous changes to the system profile have occurred. 采用USP/EP级Ⅰ类玻璃。验证批应进行稳定性考察。在考察期间定期重复所有放行测试项目，以确认产品质量的稳定性。
		Appearance 外观	Leachables, extractables, and ions can induce flocculation or coagulation of the system. 溶出物和离子可导致溶液系统的絮凝或凝	3	2	1	6	

			结				
		Cosmetic appearance 微小外观缺陷	Vials of finished product can be rejected for cosmetic defects. 成品可能因为微小缺陷而剔除	2	2	1	4	No further actions are needed. Incoming statistical checks will be done on each lot of vials prior to use. An agreement with the supplier is in place that defines appropriate AQLs for each defect. These AQLs are in line with the cosmetic requirements received by the SU. 无需采取进一步措施。在进厂使用前对每批瓶子进行取样检查。同供应商一起建立各缺陷项适当的可接受质量水平。这些可接收质量水平应与转让方收到的对微小缺陷要求相一致
		Endotoxins 内毒素	An incorrect depyrogenation cycle can impact the endotoxin level of the final product. 不当的除热原工艺可影响成品的内毒素水平	3	1	3	9	Validation activities will be done on the funnel to determine an appropriate depyrogenation cycle. 进行隧道烘箱验证，确定合适除热原方法 A maintenance program is in place for all of the equipment used in production. 生产中所有设备均应建立维护计划 The raw data of each vial depyrogenation cycle must be attached to the executed BR. 每一除热原疗程的原始数据必须附在已执行批记录后
		Particle matter 可见异物	Material released from the glass can modify the particle matter profile of the final product. 玻璃释放的物质可改变制剂中可见异物的组成	3	1	1	3	Type I glass of USP/EP grade will be used. A validated cycle will be applied to wash the vials before the depyrogenation step. 采用USP/EP级Ⅰ类玻璃。应对除热原前洗瓶步骤进行验证 A final 100% visual inspection will be done. Vials with a particle matter defect will be rejected. 进行100%目检。剔除有可见异物缺陷的瓶子
	Seals 密封件	Cosmetic appearance 微小外观缺陷	Damaged seals can impact the crimping step and / or lead to rejected vials. 密封件损坏可影响轧盖和/或导致产品报废	2	2	1	4	No further actions are needed. Incoming statistical checks will be done on each lot of seals prior to use. 无需采取进一步措施。在进厂使用前对每批密封件进行取样检查
	Filters 过滤器	See filtration step of the process section. 见工艺部分过滤步骤						
	Plastic Disposable Bag for solution preparation 配液用一次性塑料袋	Density, osmolality, and pH 密度、渗透压和pH	Impurities from the product contact layer can modify solution chemical characteristics. 与产品接触表面的杂质可改变溶液化学特性	3	3	3	27	Leachables / extractables documentation and certifications will be provided by the supplier. 供应商应提供溶出试验文件和证明 In case of further necessity, specific analyses can be done by the supplier to identify possible leachables and extractables. 必要时，供应商应特定分析，以识别可能的溶出物
		Appearance 外观	Release from the product contact layer of the bag can generate flocculation or coagulation events. 产品接触面释放物可导致絮凝或凝结问题	3	3	1	9	Compatibility studies will be done together with the supplier using specific analytical methods. 和供应商仪器采用特定分析方法进行相容性研究
		Impurity	Leachables and extractables from the	3	3	3	27	Appropriate in-process controls of pH, density, osmolality, and appearance, are established to check the correctness of the prepared solution’s attributes.

		杂质	product contact layer can modify the chemical profile of the solution. 产品接触面溶出物可改变溶液化学组成					进行适当的中间控制，包括pH、密度、渗透压和外观，检查配制的溶液特性是否正确
		Particle matter 可见异物	Release from the product contact layer of the bag can modify the particulate matter profile of the final product. 产品接触面释放物可改变产品的可见异物组成	3	1	1	3	A final 100% visual inspection will be done. Vials with a particle matter defect will be rejected. 进行最终的100%目检，剔除有可见异物缺陷的瓶子
	Filters 过滤器	See filtration step of the process section. 见工艺部分过滤步骤						
	Fixed transfer line and contact parts of the filling machine 灌装机上固定转移管路和接触部件	Density, osmolality, and pH 密度、渗透压和pH	Adsorption to the lines or product contact parts can impact the chemical profile of the solution. 管路或产品接触面的吸附可影响溶液的化学组成	3	2	2	12	The chemical and microbiological characteristics of the solution prepared will be analyzed prior to filling, and a complete set of analyses will be done at the end of the manufacturing for release of the lots. 在灌装前进行配制溶液的化学和微生物特性检查，在产品放行时进行全面检验
			Incompatibility issues can modify the chemical profile of the solution. 不相容问题可改变溶液的化学组成	3	2	2	12	The compatibility of the system with all the materials used throughout the process will be confirmed with the SU. If there are no data available or in case of doubt, appropriate compatibility studies can be agreed with the SU and performed in RU. 系统与工艺中使用所有物质的相容性应由转让方确认。如果没有相关数据或存在疑问，应同转让方协商适当的相容性试验，并在受让方进行
		Sterility 无菌	Inappropriate sterilization procedures can negatively impact the sterility assurance of the process. 不当的灭菌程序会降低工艺的无菌保证水平	3	1	3	9	A validation of the SIP cycle will be done. Dedicated procedures will be issued to manage the sterilization of the line. 进行在线灭菌行程的验证。采用特定的程序进行管理的灭菌 All the raw data of the temperature profile during sterilization will be attached to the executed BR for each batch. 灭菌过程所有温度原始数据应附在每批已执行批记录后 A bioburden analysis of the solution at the end of the preparation and prior to terminal sterilization will be established as in-process controls. 作为中控步骤，在配制后和最终灭菌前进行溶液的生物负载检查
	Gasket (PTFE and silicon) 垫圈（PTFE和硅胶）	Density, osmolality and impurity 密度、渗透压和杂质	Adsorption to the lines can impact the chemical profile of the solution. 管路的吸附可影响溶液的化学组成	3	2	2	12	The chemical and microbiological characteristics of the solution prepared will be analyzed prior to filling and a complete set of analyses will be done at the end of the manufacturing for release of the lots. 在灌装前对配制溶液的化学和微生物特性进行分析，产品放行前进行全项检验。
			Incompatibility issues can modify the chemical profile of the solution. 不相容问题可改变溶液的化学组成	3	2	2	12	The compatibility of the system with all the materials used along the process will be performed with the SU. If there are no data available or in case of doubt, appropriate compatibility studies can be agreed on with the SU. 和转让方一起进行工艺使用的所有物料与系统的相容性研究。如果没有相关数据或存在疑问，应同转让方商定适当的相容性研究
		Particle matter 可见异物	Material released from the gasket material can modify the particle matter profile of the solution 垫圈释放的物质可改变溶液可见异物组成	3	1	1	3	No further actions are needed. Regarding the release from the gaskets used in the solution preparation grade C area, the solution is filtered 0.22/0.2 µm before the acquasant (or surge tank) of the filling machine. Moreover a final 100% visual inspection will be done. Vials with a particle matter defect will be rejected.

								无需进一步措施。针对C级区配液使用的垫圈的物质释放问题，可在灌装机缓冲罐前将溶液通过0.22/0.2 μm过滤。而且还进行最终产品的100%目检。剔除有可见异物缺陷的瓶子
API attributes API特性	API appearance API外观	Appearance 外观	Anomalous appearance of the API can modify solution appearance. API外观异常可改变溶液外观	3	1	1	3	
	API particle matter API颗粒性物质	Particle matter 可见异物	Insoluble matter in the API can impact the solution's particle matter level. API中不溶性物质可影响溶液中可见异物的水平	3	1	2	6	
	API density, pH, and osmolality API的密度、pH和渗透压	pH, density, and osmolality pH、密度和渗透压	Anomalous pH, density, or osmolality can impact the chemical characteristics of the solution pH、密度或渗透压异常可影响溶液的化学特性	3	1	1	3	An internal API specification will be issued with well-defined range for each test. 建立API内控标准，确定每一测试项目的适当接受范围 Each lot will be analyzed and released prior to its use in production. 在放行用于生产前，对每批API进行检验。
	API bioburden API生物负载	Sterility 无菌	High bioburden of the API can impact the overall bioburden prefiltration of the compounded solution API生物负载偏高可影响配制溶液过滤前生物负载水平	3	1	2	6	
	Excipient's attributes 辅料特性	pH, density, osmolality, appearance, and particle matter,sterility pH、密度、渗透压、外观、颗粒性物质、无菌	Each excipient characteristics can impact the final product quality. 每一辅料特性均可影响最终产品质量	1	2	2	4	Internal specifications will be issued with well-defined ranges for each excipient test. 建立辅料内控标准，确定每一测试项目的适当接受范围 Each lot of each excipient will be analyzed and released prior to its use in production. 在放行投入生产前对每批辅料进行检验