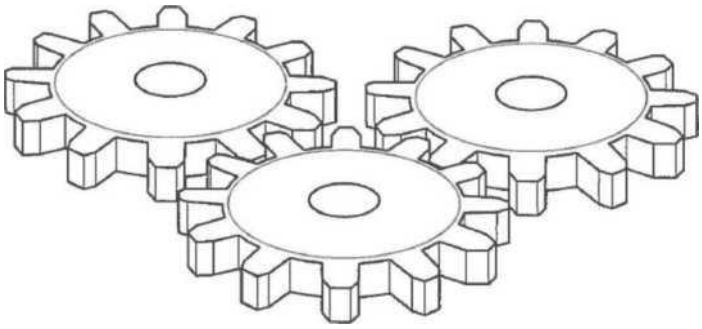
PDA 技术报告 No.54
质量风险管理在制药和生物制品生产中的实施

Technical Report No. 54

Implementation of Quality Risk Management For Pharmaceutical and Biotechnology Manufacturing Operations



Paradigm Change in Manufacturing Operations℠

PDA

Parenteral Drug Association

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1.0Introduction

1.0 引言

This technical report provides detailed guidance for the application and implementation of quality risk management (QRM) principles throughout the product lifecycle. The report emphasizes QRM application during commercial manufacturing and integrating QRM into the Pharmaceutical Quality System (PQS). Companion documents provide detailed examples of characteristic operations and how QRM principles and tools can be applied for biotechnology and sterile manufacturing of APIs, drug product (liquids and solids) manufacturing, packaging and labeling (e.g., *PDA Technical* Report No.44).

这份技术报告提供了产品整个生命周期运用和贯彻质量风险管理的详细指导。 报告强调在药品商业生产的过程中使用质量风险管理，并使质量风险管理与制药 质量体系融为一体。类似的文件(例如 PDA 技术报告 44 等)提供了详细的操作指导，说明质量风险管理 的原则和工具在生物技术、无菌原料药的生产、药物制剂（液体和固体）的生产， 包装和贴标。

QRM is integral to an effective Pharmaceutical Quality System. Per ICH QlO, *Pharmaceutical Quality System,* QRM is an "enabler" (along with knowledge management) that can provide a proactive (while also supporting a reactive) approach to identifying，scientifically evaluating, and controlling potential risks to product quality and patient safety. QRM facilitates continual improvement of process performance and product quality throughout the product lifecycle (1).

质量风险管理对于一个有效的制药质量体系是必须的。根据 ICH Q10 阶段性报告，制药质量体系：质量风险管理（和知识管理一起）能够提供积极有效的去鉴别、科学评价，以及控制产品质量的潜在风险和保障患者安全。在产品的生命周期内，质量风险 管理能够促进连续地改进工艺性能和产品质量（1）。

Per ICH Q9, *Quality Risk Management,* "Risk management is the systematic application of quality management policies， procedures， and practices to the tasks of assessing, controlling, communicating, and reviewing risk."(2) *It is important to understand that risk assessment is not synonymous with risk management.* To be effective，risk management should holistically encompass the entire product lifecycle. QRM is a living process and should be managed based on knowledge gained throughout the product lifecycle. ICH Q9 specifically provides guidance on the principles and tools of QRM(2).

ICH Q9 阶段性报告，质量风险管理：“风险管理是系统地应用质量管理政策、程序、以及评估方案去控制，描述，以及回顾风险”。对于理解风险评估不是风险管理的同义词是至关重要的。为了达到效果，风险管理应贯穿于产品的整个生命周期。质量风险管理是一个动态的过程，应依据产品整个生命周期的知识进行管理。ICH Q9 明确地为质量风险管理提供了实施原则和工具。

Implementation of QRM offers many benefits to industry and regulators. When applied effectively,these tools and principles enable more effective and consistent risk-based decision-making (by regulators and industry') regarding the quality of drug substances and drug (medicinal) products across a product's lifecycle. When successfully integrated into a company’s PQS ， QRM may reduce the level of regulatory oversight that is applied to a company. This idea is further developed in ICH Q10, which discusses the potential opportunities to be gained from the use of

QRM in terms of risk-based approaches. Effective risk management ensures better understanding of the product and process by identifying gaps in knowledge and can enable a company to prioritize and focus resources appropriately.

贯彻质量风险管理能够给业界和监管者带来许多益处。在产品的生命周期内应用风险管理的工具和原则做出以风险为基础的决策（法规和监管），将对药用物质和药品的质量产生积极的作用。对公司而言，当质量风险管理能与公司的质量管理体系有机地融合在一起的时候，能够降低质量监管机构对公司的监督水平。在 ICH Q10 中进一步讨论了使 用基于风险评估的方法带来潜在的益处。通过有效的风险管理使公司认识到产品和工艺的优先顺序，以及更合理地调整资源。

QRM has been well established in the device and other non-pharmaceutical industry sectors. Over the last few years, the pharmaceutical and biotechnology industries have begun to implement the principles and tools laid out in ICH Q9 in order to ensure that safe and efficacious drug products are consistently delivered to every patient.

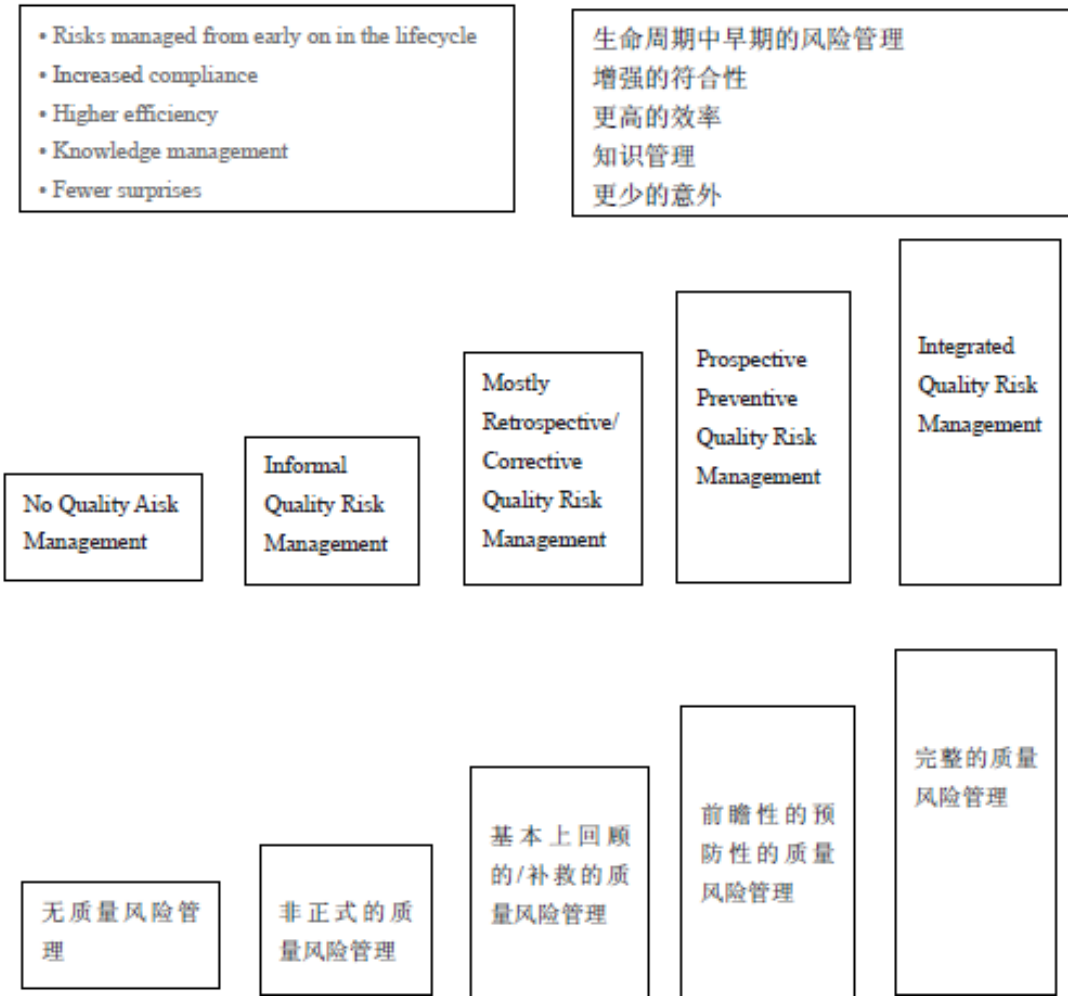
在机械工业和其他非制药工业部门已经使用质量风险管理。过去几年来，制药和生物技术工业已经使用 ICH Q9 的原则和工具确保每位患者能够使用到安全有效的药品。

Realization of QRM is an evolutionary process. It requires a paradigm shift in mindset， behaviors and in the way people work. Figure 1-1 depicts an example of a maturity model for QRM.

质量风险管理是不断完善发展的。在人们的工作中需要转变观念和行为。图 1-1 描述了质量风险管理模型的发展成熟过程。

图 1-1 一个完整的质量风险管理模型的例子

Figure 1-1 Example of a Maturity Model for QRM



Process Maturation
过程改善

1.1Purpose and Scope
1.1 目的和范围

The task force that developed this report was comprised of experienced professionals from risk management， manufacturing, technology, quality, and regulatory authorities. The broad diversity in experience and expertise in the task force enabled rich, balanced discussions from industry and regulatory perspectives; therefore, the content in this report does not represent the QRM practices of any one particular organization.

这本报告的作者由来自具有专业经验的风险管理、制造、技术、质量以及法规的 权威人士组成。作者广泛的经验和意见能够有见解平衡地在业界和法规观点进行 讨论：因此，本报告的内容不代表任何特定组织的质量风险管理实践。

The task force recognizes that there are many approaches that can be used for implementation of the ICH Q9 guideline. This report is intended to align with ICH Q9 and presents information that can be helpful to the reader on how to implement QRM. .The objective is not to represent or replace regulatory requirements and guidance; nor does it establish legally enforceable requirements.

工作组认识到有许多种途径能够用来贯彻执行 ICH Q9 的指导方针。报告的目的 是与 ICH Q9 保持一致以及介绍信息帮助读者如何去贯彻质量风险管理。

This technical report was distributed for public review and comment prior to publication to ensure its suitability as a valuable guide for QRM implementation.

这本技术报告在出版之前分发给公众以便检查和解释，确保他能够成为贯彻质量 风险管理有价值的指南。

2.0 Glossary of Terms
2.0 术语表

The glossary of terms is based on definitions provided in current ICH, FDA, EU, ISO, and other regulatory guidelines, standards, or industry publications. In some instances, two definitions are provided where both are applicable. Where definitions are not available in such sources, the best available definition has been adopted or developed by the task force. Refer to ICH Q9 for a summary of the common risk management tools. The following terms and definitions have been used in this technical report:

术语表的定义基于现行的 ICH, FDA, EU, ISO,以及其他的法规指导原则，标准， 或业界出版物。一些情况下，会提供两种适用的定义。有些定义在一些源头不适 用，工作组会采纳或发展最合适的定义。适用于 ICH Q9 的普通风险管理工具的 总结。下面的条款和定义在本技术报告中使用：

As Low As Reasonably Practicable (ALARP)
合理可行（ALARP）

The ability to reduce risk. ALARP has two facets: technical and economic. *Technical practicability* refers to the ability to reduce risk regardless of cost. *Economic* practicability refers to the ability to reduce risk without making the product too

costly to produce. (ISO 14971)
降低风险的能力。合理可行（ALARP)有两个方面：技术和经济。技术的可行性 是不考虑成本指降低风险的能力。经济的可行性是指降低产品制造环节的费用而 降低风险的能力(ISO 14971)。

Commissioning
调试
A well planned, documented, and managed engineering approach to the start-up and turnover of facilities, systems, and equipment to the end user that results in a safe and functional environment that meets established design requirements and stakeholder expectations. (ISPE Active Pharmaceutical Ingredients Baseline Guide Second Edition [June 2007])
以一种计划有序、存档合理、管理严谨的方法，用于设施、系统、设备的启动及 运作，以使终端使用者在一个安全的、功能的环境中操作。这种环境满足既定的 设计要求和系统责任人的预期（ISPE 原料药指南第二版 2007 年 6 月）

Continual Improvement
持续改进
Recurring activity to increase the ability to fulfill requirements. (ICH Q10, ISO 9000:2005)
提高满足需求的能力的反复性活动(ICH Q10, ISO 9000:2005)。

Control Strategy
控制策略
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.(ICH Q10)
源自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的相关参数与属性(ICH Q10)。

Corrective Action 纠正措施
Action to eliminate the cause of a detected non-conformity or other undesirable situation.
NOTE: Corrective action is taken to prevent recurrence whereas preventive action is taken to prevent occurrence. (ISO 9000:2005)
为减少导致已发现不合格或其他不理想情形的起因而采取的措施。
注意：纠正措施是用来预防重复发生而不是预防措施用来预防发生(ISO 9000:2005)。

Criticality
临界
A classification of an item (e.g., process, equipment,parameter) that expresses the significance given to the impact of that item, and should therefore be controlled or monitored to ensure product quality, safety or efficacy.
项目的分类（例如过程，设备，参数）用来表达他的影响的重要性，为了确保产 品质量，安全或效率应该被控制或监控。

Critical Process Parameter (CPP)

关键工艺参数(CPP)

A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality.(ICH Q8[R2])

一个可变的工艺参数对质量关键属性有影响，为确保工艺会产生期望的质量应该 被监控或控制(ICH Q8[R2])。

Critical Quality Attribute (CQA)

关键质量属性（CQA)

A physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality. (ICH Q8[R2])

一种物理的，化学的，生物的或微生物的在合适限度，范围，或分布的属性或特 性来确保期望的产品质量(ICH Q8[R2])。

Current Good Manufacturing Practices(cGMPs):

现行药品生产质量管理规范(cGMPs)

Practices and systems that are required to be followed for pharmaceutical manufacturing to ensure that the products produced meet specific requirements for identity, strength, quality, and purity.

为确保产品的生产符合鉴别、浓度、质量和纯度的具体要求制药业所需遵守的规 范和体系。

Decision Maker(s)

决策者

Person(s) with the competence and authority to make appropriate and timely quality risk management decisions. (ICH Q9)

有能力和权力做出恰当并及时的质量风险决策的人。

Detectability

可检测性

The ability to discover or determine the existence, presence, or fact of a hazard. (ICH Q9)

发现或确定危险存在，出现或事实的能力。

Enabler

支持者

A tool or process which provides the means to achieve an objective. (ICH Q10)

为实现目标提供方法的工具或程序。

Event Tree Analysis (ETA)

事件树分析(ETA)

A systematic technique that employs forward logic to construct a graphical representation of consequences resulting from an initiating event.

由开始的事件引起的逻辑关系图示的一种系统化的技术。

Failure Mode and Effects Analysis (FMEA)

失效模式与影响分析

A systematic method for identifying, analyzing, prioritizing and documenting potential failure modes, their effects on system, product and process performance, and the possible causes of failure in order to prevent defects from occurring.

一种系统化的方法用来鉴别、分析、划分顺序以及记录潜在的失效影响，失效影 响对系统、产品和工艺性能产生影响，用来预防发生失效发生原因的可能性。

Fault Tree Analysis (FTA)
故障树分析
A deductive technique used to analyze the causes of faults (defects). The technique visually models how logical relationships between failures,human errors, and external events can combine to cause specific faults.
一种用来分析故障（缺陷）原因的推论性的方法。此种技术模型形象地展示了造 成故障原因的不足、人为差错外部事件之间的逻辑关系。
Harm
伤害
Damage to health, including the damage that can occur from loss of product quality or avai1ability. (ICH Q9)
对健康的损害，包括产品质量或有效性降低所造成的损害。
Hazard
危险
The potential source of harm. (ISO/ IEC Guide51, ICH Q9)
伤害的潜在来源(ISO/ IEC 指南 51, ICH Q9)。
Hazard Analysis and Critical Control Points(HACCP)
危害分析与关键控制点(HACCP)
A systematic, proactive, and preventive tool for assuring product quality, reliability， and safety.(WHO Technical Report Series No 908, 2003Annex 7)
一种确保产品质量，可靠性，安全性的系统化、前瞻的以及预防性的工具。
Hazard and Operability Analysis (HAZOP)
工艺危害分析
A structured, systematic and qualitative technique for examination of a planned or existing process or operation in order to identify and evaluate problems that may represent risks to personnel or equipment,or prevent efficient operation.
为了鉴别和评估对人员或设备的风险，或更有效率地工作，检查计划、已有过程 或操作的一种结构的、系统化的、定量的技术。
Intended Use/Intended Purpose
预期的用途/预期的目的
Use for which a product, process or service is intended according to the specifications， instructions and information provided by the manufacturer. (ISO14971:2007)
根据说明书，操作指南以及制造商提供的信息来使产品，工艺或服务来符合预期 的用途(ISO14971:2007)。
Knowledge Management
知识管理
Systematic approach to acquiring, analyzing,storing, and disseminating information related to products, manufacturing processes and components.(ICH Q10)
系统化地获取，分析，储存和传播与产品、制造过程和组分相关的信息(ICH Q10)。
Lifecycle
生命周期
All phases in the life of a product from the initial development through marketing until the product's discontinuation (ICH Q8).

从产品的最初设计到上市，直到产品退市的生命中的所有阶段 Occurrence
可能性
Probability that an event potentially leading to harm will occur.
一个潜在的事件导致伤害发生的可能性。
Pharmaceutical Quality System (PQS)
制药质量管理体系
Management system to direct and control a pharmaceutical company with regard to quality.(ICH Q10 based upon ISO 9000:2005)
指导和控制质量的药厂的管理体系。
Preliminary Hazard Analysis (PHA)
预防危害分析
A tool of analysis based on applying prior experience or knowledge of a hazard or failure to identify future hazards, hazardous situations and events that might cause harm, as well as to estimate their probability of occurrence for a given activity, facility,product or system. (ICH Q9)
根据先前危害和故障方面相关的经验、知识，用 PHA 分析工具，确定未来的可能 导致伤害的危险，危险情形、事件，估计它们在给定活动、设备、产品或系统中 发生的可能性。 (ICH Q9)
Preventive Action
预防措施
Action to eliminate the cause of a potential non-conformity or other undesirable potential situation.
NOTE: Preventive action is taken to prevent occurrence whereas corrective action is taken to prevent recurrence. (ISO 9000:2005)
为消除潜在不合格的原因或其他不期望的情形而采取的行动。
注意:预防措施被用来预防发生，而纠正措施被用来预防重复发生(ISO 9000:2005)。
Process Qualification
工艺确认
Confirming that the manufacturing process as designed is capable of reproducible commercial manufacturing. (FDA Guidance on Process Validation,January 2011)
确认所设计的商业生产工艺在商业化生产阶段是能够再现的(FDA 工艺验证指 南,2011 年 1 月）。
Process Validation
工艺验证
Collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality products.
(FDA Guidance on Process Validation, January 2007)
从工艺设计阶段到商业化生产阶段收集并评价数据，建立科学的证据证明此工艺 能够连续生产质量稳定的产品(FDA 工艺验证指南,2007 年 1 月)。
Product Lifecycle
产品生命周期
All phases in the life of a product from the initial development through marketing until the product's discontinuation. (ICH Q8[R2])
从最初的产品开发到上市，直到产品退市各个生命阶段。

Qualification
确认
Action of proving and documenting that equipment or ancillary systems are properly installed,work correctly and actually lead to the expected results. Qualification is part of validation, but the individua1 qualification steps alone do not constitute process validation. (ICH Q7)
为证明设备或辅助系统适合安装，正常工作且能实现预期的结果所进行的活动。确认是验证的一部分，但是单独的确认步骤不能构成工艺验证（ICH Q7）。 Quality
质量
The degree to which a set of inherent properties of a product, system or process fulfills requirements. (ICH Q9)
对于一个产品，系统或过程所具有的一系列内在属性满足需求的程度。
The suitability of either a drug substance or a drug product for its intended use. This term includes such attributes as the identity, strength,and purity. (ICH Q6A)
药用物质或药品符合预期用途适用性。这些项目包括例如鉴别，浓度，纯度等属 性(ICH Q6A)。
Quality Risk Management (ORM):
质量风险管理
A systematic process for the assessment, control,communication and review of risks to the quality of the drug (medicinal) product across the product lifecycle. (ICH Q9)
在产品的生命周期内，评估、控制、沟通和回顾药品质量风险的系统化过程。 Quality Target Profile (OTP)
质量目标属性
A target product profile is a prospective and dynamic summary of the quality characteristics of a drug product that ideally will be achieved to ensure that the desired quality, and hence the safety and efficacy, of a drug product is realized. The target product profile forms the basis of design for the development of the product. (ICH Q8[R2])
预期和动态的汇总药品的质量特性，从理论上确保达到期望的质量、安全、有效。产品目标质量属性基于产品的开发设计(ICH Q8[R2])。
Residual Risk
风险残留
Risk remaining after risk control measures have been implemented. (derived from ISO14971:2007)
在采取风险控制措施后残留的风险（来自 ISO14971:2007）
Risk
风险
The combination of the probability of occurrence of harm and the severity of that harm.(ISO/EC Guide 51)
伤害发生的概率和严重性的组合（ISO/EC 指南 51）
Risk Analysis
风险分析
The estimation of the risk associated with the identified hazards. (ICH Q9)
评价风险与已经识别危害的联系。
Risk Assessment

风险评估

A systematic process of organizing information to support a risk decision to be made within a risk management process. It consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards. (ICH Q9)

系统化地应用信息做出风险决策的风险管理过程。其包括危害因素的识别，以及 分析和评价风险与危害因素的联系。

Risk Acceptance

风险接受

The decision to accept risk. (ISO Guide 73)

决定接受风险(ISO 指南 73)

Risk Communication

风险沟通

The sharing of information about risk and risk management between the decision maker and other stakeholders. (ICH Q9)

在决策者和相关利益者之间分享有关风险和风险管理的信息。

Risk Control

风险控制

Actions implementing risk management decisions.(ISO Guide 73)

实施风险管理决策的行动(ISO 指南 73)

Risk Decision

风险决策

A determination of acceptance or rejection of risk.

一个接受或拒绝风险的决定。

Risk Evaluation

风险评估

The comparison of the estimated risk to given risk criteria using a quantitative or qualitative scale to determine the significance of the risk.(ICH Q9)

运用一个定量的或定性的尺度将风险与给定的风险标准进行对比评估，以确定风 险的重要性。

Risk Identification

风险鉴别

The systematic use of information to identify potentia1 sources of harm (hazards) referring to the risk question or problem description. (ICH Q9)

系统地运用信息来辨识风险问题或风险描述的伤害（危害因素）的潜在来源。

Risk Management

风险管理

The systematic application of quality management policies, procedures, and practices to the tasks of assessing, controlling, communicating and reviewing risk. (ICH Q9)

系统化地应用质量管理方针，程序和对风险评估，控制，沟通以及回顾任务中的 实践。

Risk Management Report

风险管理报告

Report that summarizes the outcomes of the QRM process.

汇总风险管理过程的成果的报告。

Risk Reduction

风险降低

Actions taken to lessen the probability of occurrence of harm and the severity of

that harm.(ICHQ9)
为降低伤害发生的概率以及严重性所采取的行动。
Risk Review
风险回顾
Review or monitoring of output/results of the risk management process considering (if appropriate) new knowledge and experience about the risk. (ICH Q9)
考虑（如果可能）运用关于风险新的知识和经验来回顾或监控风险管理过程的输 出/结果。
Senior Management
高级管理
Person(s) who direct and control a company or site at the highest levels with the authority and responsibility to mobilize resources within the company or site. (ICH Q10 based in part on ISO 9000:2005)
指导和管理公司或厂区的最高级别人员，有权利和职责对公司或厂区内的资源配 置(部分基于 ISO 9000:2005 的 ICHQ10)
Severity
严重性
A measure of the possible consequences of a hazard. (ICH Q9)
对于某个危险因素可能结果的度量。
Stakeholder
利益相关者
Any individual, group or organization that can affect， be affected by, or perceive itself to be affected by a risk. Decision makers might also be stakeholders. For the purposes of this guideline, the primary stakeholders are the patient, healthcare professional, regulatory authority. and industry.(ICH Q9)
任何能影响，被影响到或认识到自己会被风险所影响的个人，团体或组织。决策 者也可能是利益相关者。本指南的主要的利益相关者是患者，卫生保健专业人士， 药监部门以及业界。
Trend
趋势
A statistical term referring to the direction or rate of change of a variable(s). (ICH Q9)
一个统计学术语，指一个变量变动的方向或比率。

3.0 General Principles On Quality Risk Management Application 质量风险管理应用的基本原则

A combined application of ICH Q8[R2] (Pharmaceutical Development), Q9 (Quality Risk Management) and QI0 (Pharmaceutical Quality System) results in an enhanced knowledge of product performance over a range of material attributes, manufacturing process options, and process parameters to further support the science and risk-based management of the product lifecycle.
ICH Q8（药物开发），Q9（质量风险管理）和 Q10（制药质量体系）的共同应用 在一定程度上提高了对包括物料属性、生产工艺的选择和工艺参数方面的产品性 能的认识，以进一步支持依据科学和风险管理的产品生命周期的管理。

3.1 When, Where, and How to Apply Quality Risk Management 何时、何地和怎样应用质量风险管理

One of the characteristics of a mature PQS is the effective integration of QRM into relevant processes throughout the product and process lifecycles. At each phase in the lifecycle, QRM should be applied at a level that is commensurate with the knowledge available during that phase, and complexity of the process. QRM should start with product design and progress to process design as the product advances to clinical and commercial production. Risk assessments should be revisited throughout the product lifecycle (Figure 3.1-1) as additional process and product knowledge become available. Additionally, QRM can be useful in identifying and managing similar risks for other products to facilitate continual improvement.
成熟的 PQS 的特征之一是在贯穿整个产品和工艺的生命周期中，将质量风险管 理有效地整合到相关的过程管理中。在生命周期的各个阶段，质量风险管理应用 的程度应该与该阶段的可获得的工艺知识和工艺的复杂程度相适应。质量风险管 理应该开始于药物研发阶段，当产品用于临床研究和商业生产时，应将质量风险 管理并入工艺设计中。当获得额外的工艺和产品知识时，应将风险评估重新应用 到整个生命周期（图表 3.1-1)中。除此之外，质量风险管理在鉴别和管理其他 产品的相似风险时很有用，并可以帮助其获得持续的改进。

Figure 3.1-1 Product Lifecycle
图表 3.1-1 产品的生命周期

3.1.1 Quality Risk Management Application During Pharmaceutical Development

药物开发阶段的质量风险管理应用

Per ICH QI0, the intent of the Pharmaceutical Development phase is to "design a product and its manufacturing process to consistently deliver the intended

performance and meet the needs of patients, healthcare professionals, regulatory authorities, and internal customers."(1) This phase provides the basis for scientific knowledge and understanding of the product.
根据 ICH Q10，药物开发阶段的目的是“设计出一种产品，其生产工艺可以按照 其本身的性质持续地生产出符合病人，卫生保健专业人员，监管机构和国内客户 的药品”。（1)这一阶段提供科学知识的基础和对产品的理解。

During development, the application of QRM can support the development of systematic understanding of products and processes beginning early in the lifecycle. The appropriate use of QRM principles can serve the following objectives:
在开发阶段，质量风险管理的应用可以支持对产品系统的认识和对生产周期早期 工艺的开发。质量风险管理原则的合理应用可以实现以下目标：

•Design the product and process to reduce risk to product quality and to the patient.
根据减少对产品的质量和对病人的风险来设计产品和工艺。

•Prioritize the pharmaceutical development studies needed to collect and enhance product knowledge.
优先进行必要的药物开发以收集并提高产品知识。

•Establish a robust control strategy to adequately manage risks to Critical Quality Attributes (CQA) (per ICH Q8[R2]).
建立稳定的控制策略以实现对关键质量属性（CQA)的充分风险管理。（根据 ICH Q8[R2])

Examples of how to apply QRM principles during the development phase include:
如何在药物开发阶段应用质量风险管理原则的例子如下：

•Developing a process that routinely meets critical quality attributes (CQA).
开发一个通常能实现关键质量属性（CQA)的工艺。

•Developing a suitable drug delivery system.
•开发一种合适的药品给药系统。
•Identifying critical process parameters (CPP) and material attributes.
•鉴别关键工艺参数(CPP)和物料属性

•Identifying appropriate ranges for CPP, material attributes and manufacturing controls.
•鉴别关键工艺参数，物料属性和过程控制的合理范围

•Supporting the selection and subsequent qualification of suppliers.
・支持接下来的合格供应商选择
Risk management tools such as Risk Ranking and Filtering or Ishikawa diagram (also known as a Fishbone diagram) may be used to identify variables that may have an impact on a critical quality attribute. These identified variables can then be further analyzed using a qualitative/ semi-quantitative risk management tool such

as a Preliminary Hazard Analysis (PHA). Failure Mode and Effects Analysis (FMEA) may also be useful, particularly during the later stages of development.
风险管理工具如风险定级和筛选或是石川图（也被称为鱼骨图）可以用于鉴别可 能会影响到关键质量属性的变量。这些鉴别出来的变量可以使用定量或半定量的 风险管理工具如初步危害分析（PHA)来进行进一步的分析。失效模式和影响分 析(FMEA)也可能是有用的，特别是在药物开发的后阶段。

3.1.2 Quality Risk Management Application during Technology Transfer 技术转移阶段的质量风险管理应用

Per ICH QI0，the goal of Technology Transfer is to "trasfer knowledge between development and manufacturing or between manufacturing sites to achieve product realization . "(1) QRM application during thetechnology transfer phase can serve the following objectives:
根据 ICH Q10，技术转移的目的是“在药物开发部门与生产部门或在不同的生产 岗位中进行知识转移，以实现药物的最终生产”。（1)质量风险管理在技术转移 阶段的应用可以达到以下目的：

•Assess and manage risks to process and product quality as a result of the transfer or manufacturing scale-up.
•评估和管理工艺和产品质量的风险以达到技术转移和扩大生产的结果。

•Facilitate knowledge transfer.
•帮助知识的转移。

•Drive decisions for control strategies to reduce risk during commercial manufacturing.
在商业化生产的过程中驱动控制策略的决策以降低风险。

The outcomes of the QRM process can be used to implement corrective and preventive actions to appropriately manage identified risks and provide timely management of process controls during the technology transfer process. QRM can be used to develop a risk based validation master plan to determine the extent of the qualification and validation activities. During the technology transfer phase，detailed risk management tools such as an FMEA or Hazard and Operability Analysis (HAZOP) are Often used.
在技术转移过程中，质量风险管理过程的结果可以用来实施纠正和预防措施，以 妥善管理确定的风险并提供及时的过程控制的管理。质量风险管理可以用于开发 一个基于风险的验证主计划以确定确认和验证活动的程度。在技术转移的阶段， 详细的风险管理工具如FMEA 或危险和可操作性分析(HAZOP)会被经常用到。

Per ICH Q10, the goal during Commercial Manufacturing is to "achieve product realization with suitable processperformance， establish and maintain a state of control, faciliitate continual improvement and expand the body of knowledge."(3) QRM application during the Commercial Manufacturing phase can serve the following objectives:
根据 ICH Q10，商业化生产阶段的目的是“用合适的工艺性能实现产品的生产， 建立和维护控制状态，帮助持续改善和扩大知识容量。”在商业化阶段应用质量风 险管理可以达到以下目标：

•Proactively assess and manage risks to process and product quality during commercial operations.
•在商业化运营的过程中可以主动地评估和管理工艺和产品质量风险。

•Establish robust control strategies and adjust (as needed) through continual improvement， to ensure consistent process performance and product quality as intended.
•通过持续的改善以建立稳定的控制策略和调整（如果需要），以确保达到预期的 持续工艺性能和产品质量。

During commercial manufacturing, QRM can be a useful process for effective decision-making as-sociated with change control, discrepancies, failures, or investigations related to product quality or patient safety events. QRM is also useful in the selection and management of suppliers and vendors, and managing risks related to internal and contract manufacturing operations, to ensure a state of control is maintained at all times.
在商业化生产阶段，质量风险管理在有关产品质量或病人安全事件方面的变更控 制，偏差，失败或调查的有效决策时是很有用的过程。质量风险管理在供应商或 供货商选择与管理方面也很有用，通过管理相关内部或委托生产操作的风险，以 确保整个阶段保持在控制状态。

QRM may also be applied to effectively manage risks in the supply chain. Risks to product availability throughout the product lifecycle relate to product storage, distribution, transportation, chain of custody, counterfeiting, diversion, theft， geopolitical issues, compliance, and disaster recovery activities， amongst others. (See Section 5.4, QRM Application in Materials Management.)
质量风险管理也可以有效地应用在供应链风险管理方面。在整个产品生命周期内 保持产品的有效性的风险包括产品的储存，分发，运输，产销监管链，造假，转 移，偷盗，区域政治问题，合规，灾难恢复活动等等其他方面。（具体见 5.4 部 分，物料管理方面的质量风险管理）
Per ICHQlO, the goal of Product Discontinuation activities is to "manage the terminal stage of the product lifecycleeffectively."(1) QRM application during product discontinuation activities can serve the following objectives:
根据 ICH Q10，产品退市活动的目的是“有效地管理产品生命周期的最后阶段” 。 在产品退市活动阶段应用质量风险管理可以达到以下目标：

• Ensure risks to patients and product quality continue to be managed while

product remains on the market.
•当产品仍然在市场上销售时，确保病人和产品质量的风险持续可控。

• Identify and manage risks related to transitioning patients to alternate therapies.
•转移患者至替代疗法时，识别和管理相关的风险。

3.2 Proactive and Reactive Application of Quality Risk Management 质量风险管 理的主动和被动应用

QRM should ideally be proactive because its greatest value is in early identification and management of risks. Retrospective or reactive application of QRM may also be appropriate and add value.
质量风险管理理想的状态应该是主动的应用，因为早期识别和管理风险是非常有 价值的。质量风险管理的回顾和被动应用也可以适应地增加其价值。

ln general, the earlier risks are identified, the more effective their management can be. For example, if a risk is identified during the development of design specifications for a system, the system can be designed to reduce or even eliminate the risk. However, if the same risk is not identified until routine commercial operation of the system, the redesign of the system can be challenging and likely be more costly than if the system had initially been designed to manage the risk appropriately. This would be in addition to the cost of managing potential harm to product quality that might occur due to that risk during commercial operation.
一般来讲，越早识别风险，风险管理措施越有效。例如，如果一个系统的设计标 准在开发阶段就被识别，那这个系统可以设计成减少或消除风险。然而，如果同 样的风险直到系统的常规商业化生产时才被识别，系统的重新设计可能是具有挑 战性的，而且极大可能比在系统的设计初期适当的管理风险的造价更昂贵。另外， 在商业化运营期间，由于那个风险给产品质量带来潜在危害可能会发生额外的管 理成本。

There are ， however, some instances where not all risks can be identified prospectively and risk assessments may need to be performed retrospectively.Examples would be new potential risks identified through a deviation or introduced due to a change such that it impacts the validated status of an existing manufacturing process. ln these instances，deductive risk management tools like Fault and Event Tree Analysis (FTA/ ETA), FMEA, or Fishbone Analysis may be used to determine the contributing cause(s) of the event， and any risks impacting product quality will consequently need to be managed retrospectively.
然而，某些情况下，并非所有的风险都可以如预期般识别，这样就需要执行回顾性 风险评估。例如，通过偏差识别或由于变更影响现有生产工艺的验证状态引进新 的潜在风险。在这些实例中，演绎的风险管理工具如失效和事件树分析(FTA / ETA)，FMEA,或鱼骨图分析可以用来确定事件的相关因素，接下来任何影响产品 质量的风险将需要进行回顾性风险评估。

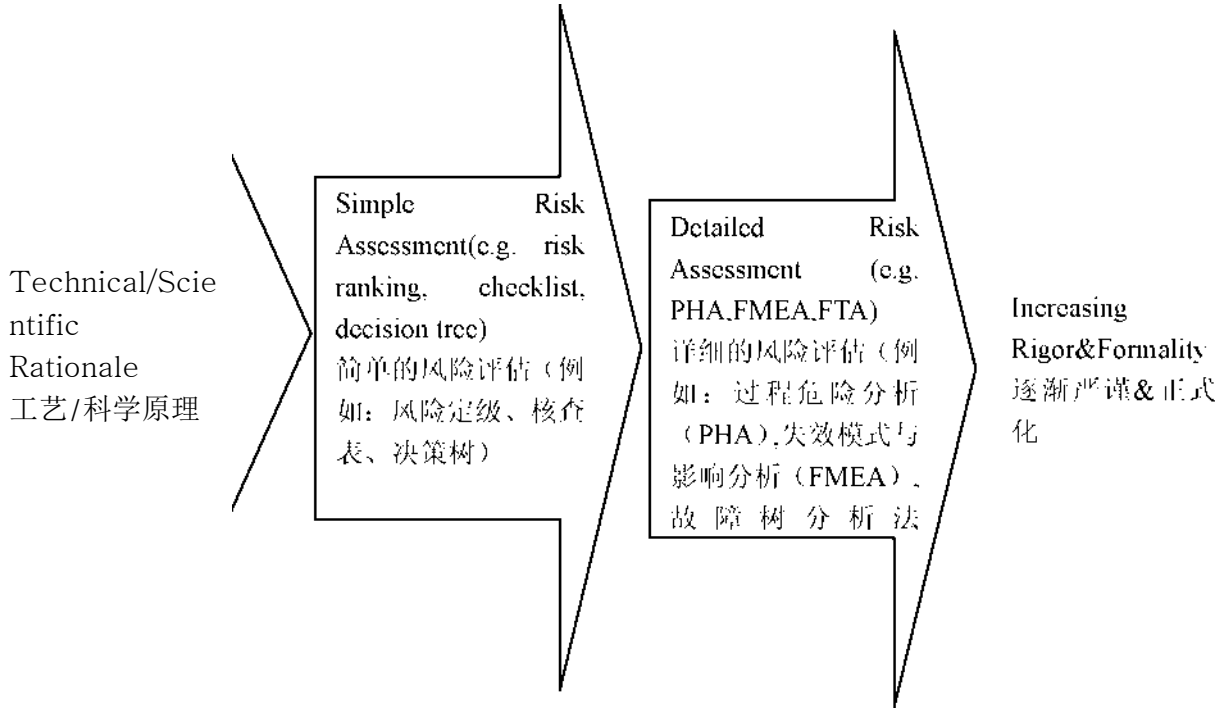
QRM is not an independent Quality System element， but should be integrated into

existing operations and appropriate parts of the PQS. QRM should never be used to deviate from regulations， justify bad practices， defend practices that need to be corrected， or as a substitute for sound science. Compliance with current Good Manufacturing Practices (cGMPs) is a mandate.
质量风险管理不是独立于质量系统的元素，而应该整合到现存的规程中，作为 PQS 适宜的一部分。质量风险管理不应该背离法规，维护不好的操作，应该维护 必需正确的操作、或是科合理学的代名词。符合现行生产质量管理规范(cGMPs) 是强制性的。

3.3Formality of the Quality Risk Management Process
质量风险管理程序的正式流程

One of the principles of QRM as per lCH Q9 is that the level of effort，formality and documentation of the QRM process should be commensurate with the level of risk. lt is neither always appropriate nor always necessaryto use a formal risk management process (2). The use of informal risk management processes (using empirical tools or internal procedures) is also considered acceptable， as long as they meet the intent of lCH Q9. Since QRM provides a suitable knowledge management and documentation framework for previously undocumented or historical knowledge， even simple informal risk management processes can support this objective. Therefore， a risk-based approach can range from a documented scientific rationale to a formal risk assessment methodology (See Figure 3.3-1).
根据 ICH Q9，质量风险管理的原则之一是质量风险管理程序的评估结果，正式 性和文档性应该与其风险级别相适应。合适的或正式的风险管理程序并不是都是 必须的。（2)只要能符合 ICH Q9 的要求，使用非正式的风险管理程序（如使用 经验工具或内部程序）也是被认为是可接受的。因为质量风险管理只是给先前的 非文档化或历史数据提供了一种合适的知识管理和文档框架，所以简单的非正式 的风险管理程序也可以达到此目的。因此，风险管理方法可以从记录科学原理的 文档开始到形成正式的风险评估方法(详见图表3.3-1)。

Figure 3.3-1 Rigor and Formality of QRM Approaches 图表 3.3-1 严谨和正式的质量风险管理方法



The degree of risk management rigor and formality required is influenced by a combination of many factors, including (but not limited to):
风险管理的严谨和正式性要求程度受许多因素的组合影响，包括（但不限于）

• Criticality (e.g., impact on patient safety or product quality) of the risk question
风险问题的危急程度（例如：影响病人安全或产品质量）
Complexity of the issue, process, or system
问题、工艺或系统的复杂性
Availability of relevant historical data and related literature
相关历史数据和相关文献的实用性
Level of available process knowledge and experience
工艺知识和经验的实用性程度

The risk assessment formality spectrum can range in the rigor and formality of facilitation, subject matter experts (SMEs), team structure, tool and documentation as shown in Figure 3.3-2.
风险评估的正式程度包括简易化程度，相关项目专家，组织构架，工具和文件系 统的严谨和正式程度，如图表 3.3-2 所示。

Figure 3.3-2 Rigor and Formality Spectrum for QRM Activities (adapted from ICH Q9 Briefing Pack)
图表 3.3-2 质量风险管理活动的严谨和正式范围（根据 ICH Q9 的会前准备资料改编
QRM Formality Spectrum
质量风险管理正式程度

	More Formal 更正式"	Less Formal ^ 非正式
Facilitation 简易程序	Required 被要求	Helpful but not required 有用但不要求
Team 小组	Customized team of SMEs 组成专门的相关项目专家组	May be existing team,group, committee, etc. 可能存在有小组，团体，委员会等等 会等等
Method 方法	Recongnized Method(s) 被承认的方法	Recongnized method optional or may be customized 随意选取或定制被承认的方法
Documentation 文件系统	Stand-alone report, or Linked to othercontrolled GMP documents 单独的报告，或者跟其他受控的 GMP 文档相关连	May integrate into existingcontrolled GMP documents(ex: change package) 可能整合到现存的受控 GMP 文件中（不包括：变更控制计划）

3.4 Establishing a Quality Risk Management Policy 制定质量风险管理方针

ICH QI0 describes the importance of QRM being integrated into the Quality System as an enabler. The integration process has to begin at the top of the organization. A QRM policy establishes the company's QRM philosophy and guides the incorporation of QRM requirements and principles into the Quality System related to:
ICH Q10 阐述了质量风险管理作为一种有用的工具合并到质量系统中的重要性。 整合的过程必须由企业的上层管理层发起。质量风险管理方针确定企业的质量风 险管理理念，指导企业在以下方面将质量风险管理的要求和原则整合到质量系统中

- Applicability of risk management
- 风险管理的适用范围

- Accountability and responsibility for managing and determining risk acceptability
- 风险管理的问责制和责任制，确定风险的可接受水平

Risk scales
风险的衡量尺度

• Risk control
• 风险的控制

• Risk reviews and communication
• 风险回顾和沟通

• Documentation
• 风险文件的编制

3.5 Management Commitment 管理层的责任

Top-level management support and commitment for the risk management program is essential. Top management endorses the incorporation of QRM into the organization's Quality System and routine operations， including establishing processes for effective implementation of QRM principles and activities，and providing adequate resources. This includes ensuring those involved in QRM activities are qualified and have received the applicable training.
高级管理层的支持和承诺对风险管理的运行是很重要的。高级管理层赞同将质量 风险管理并入到企业的质量系统和常规规程中，包括制定有效执行质量风险管理 原则和活动的程序，提供充足的资源。这里还包括确保参与质量风险管理活动的 人员是有资格的和接受了合适的培训的。

Management has the accountability to create a structure or framework in which the use of QRM is encouraged， its benefits understood， its tools applied appropriately， and users trained adequately on its concepts and application. The organization should identify and train facilitators who take responsibility for coordinating QRM across various functions and departments of their organization.The ultimate goal is to incorporate QRM into everyday practices， similar to how risk management is integrated into the safety， health， environment， and financial processes.
管理层有责任创造一种组织架构或框架，这种组织内，质量风险管理是被鼓励的， 其好处大家都知道，风险管理的工具被合适的应用，使用者在质量风险管理的概 念和应用上得到了充足的培训。负责企业内各个职能部门沟通质量风险管理的促 进者，管理者应该能识别并培训这些促进者。其最终的目的是将质量风险管理整 合到各个日常操作中，就像将风险管理整合到安全，健康，环境和财务等过程中。

To facilitate achieving this goal the organization should identify individuals who:
为使促进者完成这种使命，管理者应该识别有以下特征的个人：

•Have the responsibility to create and maintain the QRM system.
• 具有创造和维持质量风险管理系统的责任。
Can perform risk assessments.
有能力执行风险评估。

• Can review and approve the assessments, and have the authority to make risk reduction and risk acceptance decisions.
•有能力审核和批准评估，有权力做出减少风险至可接受水平的决定。

• Are responsible for communicating the output of the risk assessments.
负责风险评估结果的沟通工作。
3.6 Understanding the Organization and How it Contextualizes Risk 懂得组织机构

并知道如何考虑风险

To develop a shared understanding of the application of QRM among diverse stakeholders, organizations need to develop a full understanding of the requirements and regulatory expectations for QRM.
为了在不同的利益相关方中建立对质量风险管理应用的理解，管理者需要先建立 对质量风险管理的要求和法规标准的全面理解。

An evaluation of the current understanding of QRM in the organization will deliver the baseline from which progress can be measured. The evaluation should include written policies and procedures, practices, and personnel skills and knowledge. Any existing or related QRM activities should be reviewed for evidence of the integration of QRM into the company's Quality System (e.g., auditing processes, change control, deviation management， product development activities).
将当前组织对质量风险管理的理解进行评估，有助于决定风险程序开展的基线。 评估应该包括成文的方针，规程，操作，个人的技能和知识。任何现存的或与质 量风险管理活动相关的（例如：自检过程，变更控制，偏差管理，改善工艺的活 动）都应该审核，作为将质量风险管理整合到公司的质量系统中的证据。

3.7 Integration into Organizational Processes 整合到公司的规程中

Integration of QRM into an organization is a multi-step process that begins with an assessment of existing practices and ends with a fully deployed and realized QRM process. Practical recommendations related to implementation of QRM may include the following:
将质量风险管理整合到组织架构中是一个复杂的过程，其始于对现存的规程进行 评估，终于全面展开和实现质量风险管理程序。关于质量风险管理执行的可行性 推荐可以包括以下内容：

• Performing a gap analysis on current guidelines, procedures, and practices to identify where systems are currently employing QRM. This will allow the measurement of the level of risk maturity in an organization. See Table 3.7-1 ， Risk Management Maturity Level, for a guide to maturity level and expected attitudes and behaviors.
•对当前指导原则、程序和操作规程执行差距分析，可以识别什么系统当前需要 执行质量风险管理。这样可以测量企业风险管理的成熟度。具体见表格 3.7-1， 风险管理成熟级别，是一个成熟级别和预期观点和行为的指导意见。

• Creating QRM policies and procedures based upon the gap analysis findings, including QRM methods and supporting statistical tools.
•根据差距分析的结果建立质量风险管理政策和程序，包括质量风险管理的方法 和相关的统计工具。

• Piloting the policies and procedures to ensure the risk scales, residual risk acceptability process, and reporting mechanisms fit the needs of the organization.
•先对风险方针和程序进行试行，确保建立符合企业需要的风险级别，风险可接 受水平和报告机制。

• Deploying the policies and procedures within the organization by creating a multi-level training strategy。
•通过开展多层次的培训以达到在企业内部推广风险管理方针和程序。

• High-level awareness / QRM overview training for general employee population.
•对普通雇员群体进行高级别风险意识或质量风险管理审核的培训。

• Focused policy, procedure, and risk management tools-based training. This would include hands-ontraining with reallife applications.
•集中对方针，规程和风险管理的基本工具进行培训。其中包括对真实的案例进 行风险评估的培训。

• Creation of internal audit programs to verify that QRM activities and resulting decisions comply with the established standards and procedures.
•建立识别质量风险管理活动的内部审计规程，得到符合已建立标准和规程的决策。

Table 3.7-1 Risk Management Maturity level (adapted from: A Guide to Supply Chain Risk Management for the Pharmaceutical and Medical Device Industries and Their Suppliers 2010)
表 3.7-1 风险管理成熟级别（改编自：药品和医疗器械公司及其供应商的供应链 风险管理指导意见）

Risk Maturity Level 风险成熟级别	Risk Processes 风险规程	Attitude 态度	Behavior 行为	Skills & Knowledge 技能和知识
Skepticism 怀疑阶段	No Formal Processes 没有正式的规 程	Accidents Will Happen 意外会发生	Fear Of Blame Culture 害怕被责备	Unconscious Incompetence 没有意识到不 胜任

Awareness 意识阶段	Ad Hoc Use of Stand Alone Processes 临时使用独立的规程	Suspended Belief 有信仰	Reactive，Fire Fighting 被动的，处理 状况	Conscious Incompetence 意识到不胜任
Understanding & Application 理解并应用阶 段	Tick Box Approach 标记盒子的方法	Passive Acceptance 主动接受	Compliance，Reliance On Registers 依赖法规符合性	Conscious Competence 意识到能胜任
Embedding & Integration 纳入和整合阶 段	Risk Management Embedded In Business 风险管理纳入业务	Active Engagement 积极应对	Risk-Based Decision Making 根据风险决策	Unconscious Competence 无意识的胜任
Robust Risk Management 稳定的风险管 理阶段	Regular Review & Improvement 常规审核并改善	Champion 优胜者	Innovation，Confident & Appropriate Risk Management 创新的，自信 和合适的风险管理	Expert 专家级

3.8 Establishing Communication and Reporting Mechanisms 建立沟通和汇报机制

To fully integrate QRM into the PQS，organizations need to have effective risk communication and reporting processes. Companies will only fully benefit from the implementation of QRM when they are able to quickly respond to residual risks that develop. There needs to be robust information flow through internal and external feedback loops to identify and communicate new risks as they develop. There are many ways to accomplish this， including the use of risk dashboards and internal memoranda. Companies should consider the addition of risk management as an agenda topic for their periodic management meetings at all levels.
为了将质量风险管理（QRM)充分地整合到 PQS 中，组织者必须拥有有效地风 险沟通和报告机制。当企业有能力对产生的残余风险有快速的反应时，其才能从 质量风险管理的执行中充分获利。这样就需要通过内部和外部的反馈机制对强大 的信息流进行识别和沟通新风险的发展变化。有很多方法可以做到这一点，包括 使用风险仪表盘和内部的备忘录。公司应该考虑将风险管理作为他们各个层级的 定期管理会议的常规话题。

Feedback loops are two-way in that as new risks are identified they are communicated internally and that products and processes will be evaluated and modified as needed based upon that information. Policies and procedures should be in place to facilitate external

communications with the public and regulataory agencies, if required.
反馈循环都是双向的，随着新的风险得到识别会引起内部沟通，而产品和工艺会根 据沟通的信息进行评估和修改（如果需要的话）。另外如果需要外部沟通的话， 应该有现成的政策和规程以促进与公共和法规机构的外部沟通。

There should be a method to capture product and process risk throughout the company so that over-all residual risk can be assessed. The vehicle the company chooses to capture the overall residual risk should be based upon the organization's culture, documentation practices and the potential impact of product and process failures.
企业应该有一种捕获所有产品和工艺风险的方法，这样所有的残余风险将得到评 估。汽车公司选择用于捕获所有剩余风险的方法应该基于企业的文件，书面化的 规程和产品和工艺失效的潜在影响。

3.9 Roles and Responsibilities 各自责任

Formal QRM activities are usually undertaken by multi-disciplinary teams and should include SMEs representing relevant functions (e.g.quality unit, business development, engineering, regulatory affairs, production operations, sales and marketing, legal, statistics, clinical safety). A single person may satisfy more than one function or role. Typical QRM roles include:
正式的质量风险管理活动通常由多学科的团队执行，应该包括 SMEs 相关功能的 代表（例如，质量小组，商业开发，工程，法规事务，生产部门，销售和市场， 法规，统计，临床安全）。单一个人可以承担多于一个功能或角色。典型的质量 风险管理角色包括：

• Facilitators who are knowledgeable about, and will facilitate the QRM process.
•促进者是知识渊博的，可以促进质量风险管理进程的人。

•As much as possible, facilitators should be independent from the process being risk assessed in order to maintain objectivity in facilitation (i.e. subject matter or technical experts should not facilitate if possible in order to maintain objectivity). Knowledge of cognitive and other factors, such as human heuristics, mayaffectdecision-makingduringQRMactivities(suchasbrains torming and probability of occurrence estimation);thisunderstandingandabilitytomanageitappropriatelycanbeparticula rlyusefulforfacilitators.
•当进行工艺风险评估时，促进者应尽可能保持独立，以在促进过程中保持客观（例如，为了保持客观，如有可能的话，主题或技术专家不应该做促进者）。认 识的知识和其他因素，例如人类的启发，可能在质量风险管理活动中影响决策者 的决定（例如头脑风暴和评估发生的可能性）；促进者若能理解并能合理的管理 它，它将会特别地有用。

• QRM Lead who may be independent from the facilitator and is responsible for:
•质量风险管理领导应该独立于促进者，他的职责是：

• Leading the development and completion of QRM deliverables such as risk management plans and reports.
•指导质量风险管理具体工作的开展和结题，如风险管理计划和报告。

• Ensuring that the outcomes of the QRM process are approved by the appropriatedecision makers and implemented.
•确保质量风险管理流程的结果被合适的决策者批准并实施。

• Ensuring that riskreview is performed and that QRM documents are updated and maintained current.
•确保执行风险回顾，并保证质量风险管理文件是现行的最新版本。

• Subject matter experts who are responsible for providing technical expertise to support QRM activities， including risk assessment， determination of appropriate risk control measures and their implementation.
•相关科目专家负责为质量风险管理活动提供该科目的专业技术，包括风险评估， 确定和执行合适的质量控制技术。

• Decision Makers who have the competence and authority to make timely QRM decisions (2). Decision makers should be accountable for:
•决策者是具有及时下质量风险管理决定的胜任者和当权者。决策者应负以下责任：

• Ensuring that a QRM process is defined，deployed，and reviewed.
•确保质量风险管理程序被定义好，部署和回顾质量风险。

• Ensuring that adequate resources are available to complete QRM activities， including the implementation of identified risk control measures.
•确保提供足够的资源以完成质量风险管理活动，包括执行被鉴别出的风险控制 措施。

• Reviewing and approving the outcomes of risk management activities，including making risk control (risk reduction and risk acceptance) decisions.
•回顾和批准风险管理活动的结果，包括制定风险控制（降低风险和接受风险） 的决策。

3.10 Heuristics and Biases in Quality Risk Management 质量风险管理的偏离和探索

Heuristics are cognitive behaviors that come into play when people make judgments in the presence of uncertainty.How these behaviors are manifested is still the subject of much research， but there is evidence in literature that heuristics are a source of significant bias and errors in judgment. Human heuristics greatly influence a person's perception of risk (4) and inevitably their opinion of the magnitude of the contributing probabilities and severities. A great deal of research has been performed by experimental psychologists into how risks are perceived. In this respect, three main factors (5) seem to contribute to the operation of this heuristic and influence the output of risk analysis exercises:
探索是当人们需要对不确定过程做判断时出现的一种认知行为。这些行为是如何 表现的仍然是许多研究的科研题目，但有文献证明探索是一种在判断时出现重大偏见和错误的来源。人类探索极大地影响一个人的风险感知（4)和不可避免地 影响他们对风险的概率和严重程度的等级判断。实验性心理学家对风险如何被感知做了大量的研究。在这方面，有三个主要因素（5)似乎有助于这种探索式的运作并影响风险分析练习的输出：

1. Degree of "dreadfulness" associated with the risk.
1. 风险的危害（或可怕程度）。

2. Degree to which the risk was understood.
2. 风险的已知性。

3. Number of people exposed to the risk in question.
3.人类暴露在此种风险下的数量。

Human heuristics also play an important role in both how risks are assessed and perceived. There are various types of heuristics, but three of them are:
人类探索也在风险如何评估和感知上扮演着重要的角色。有很多种类型的探索， 但有三种类型如下：

1. Availability
1. 有效性

2. Representativeness
2.典型性

3. Anchoring andAdjustment
3.固定和调整性
The heuristic of availability relates to the fact that people tend to judge the likelihood of an event in terms of how easily they can recall (or imagine) examples of that event. A person's judgment concerning an event (in terms of its probability of occurrence and its severity) may therefore be influencedby how that person imagines or recalls similar scenarios (6,7).This may lead to a systematic bias andother errors in judgment. Research has shown that people tend to underestimate the frequency of very common hazards and overestimate the frequency of very rare hazards (6 8).
探索过程与以下事实有关，人们倾向于根据其能记得（或想象）该事件的例 子的容易程度来判断事件发生的可能性。一个人关于某个事件的判断（以事件发 生的可能性和严重程度来计）可能会受到该人是如何想象或回忆类似情景的影响 (6,7)。这样可能会导致判断的系统偏见和其他错误。研究表明人类倾向于低估 非常普遍危害的发生频率和高估非常稀少危害的发生频率。

The heuristic of representativeness is related to a person's probability judgment being influenced by their "expecting in the small behavior that which one knows exists in the large." In this instance one can pay more attention to specific details, while ignoring or paying insufficient attention to important probability-related information that is relevant to the problem (8).
探索的典型代表与被影响的人的概率判断有关，如他们 “预计某种小概率行为 被认为大概率行为。”在这种情况，人类就会在特殊的细节上花费过多的精力， 而会忽略或太少关注与问题相关的有重大可能性的信息。

The heuristic of anchoring and adjustment comes into play when people's judgment can be heavily influenced by the first approximation of the value or quantity that they think of or hear (anchor), or is based on "group think." The "anchor" value can then lead to influencing and "adjusting”any subsequent values to be biased towards the "anchor" (6,7).
当人类的判断被他们想到或听到（广播）的最近似的价值或数量严重影响时，或 根据“集体性思维”，启发的固定和调整就会出现。“目标价值”然后会影响或“调整” 随后的价值偏向于“目标价值”

Bias and variability in risk perception are inherently human traits and can be broadly categorized into three recognizable anthropomorphic behavior s. Each of these perceptions should be

recognized, and appropriate bias-mitigation strategies and processes established within the QRM system.
风险认知的偏差和变异本质上是人的特征，可以大致分为三种可认知的拟人化行 为。这三种认知在质量风险管理系统都可以被识别、建立适当的偏见转移策略和 流程。

It is well accepted that we are inherently more comfortable or willing to accept risks that could be considered voluntary(i.e.under our own volition) than involuntary risks (i.e.without our own decision) (9). This seemingly maintains true for voluntary risks, which are calculated to be significantly lower than involuntary risks (10).
普遍认可的是，相对于非自愿性风险（即我们自己不能决定的），我们本质上更 舒适或愿意接受被认为是自愿的风险（例如在我们自己的意志下）（9)。这在自 愿风险上保持是正确的，因其计算出比非自愿风险的关注度偏低（10)。

The phenomenon of human heuristics (unconscious rules of thumb) has profound capacity to bias risk management processes. One human heuristic relates to the fact that people tend to assign likelihood in terms of how easily they can recall (or imagine) that or examples of that event.Generally，people tend to underestimate the frequency of very common hazards and overestimate the frequency ofvery rare hazards (6 8). From a GMP perspective this is important to know， because these humanheuristics may influence how the outputs of QRM exercises performed in GMP environments may be judged and accepted by decision makers，stakeholders and regulatory inspectors.
人类探索式的现象（如拇指无意识的规则）对偏置的风险管理流程有深刻的量程 意义。一个人的探索式思维与涉及到的事实相关，如人们往往根据他们可以回忆（或想象）相关事件例子的容易程度来确定事件的可能性。一般来说，人类你倾 向于低估常见危害发生的频率，而高估了罕见危害发生的频率。从 GMP 的角度 来看，这是很重要的。因为在 GMP 的环境下这些人类的探索可能会影响质量风 险管理操练的结果，而这些结果可能会被决策者，利益相关者和法规监管者所评 判和接受。

An expert's perception of risk can differ markedly from that of a layperson or those personnelless familiar with the specific process，technology or circumstance (11). Generally，laypeople tend to regard as "risky" any technology that is new，imposed on them，unfamiliar，or beyond their control. Suchfindings are probably important to consider when performing GMP-related QRM exercises， given the different groups and stakeholders to whom risk information may be communicated and the highly technical nature of GMP activities in general.
一个专家对风险的感知会与外行人员或对特殊工艺、技术或环境不熟悉的人群明 显不一样(11).一般而言，外行人倾向于把新的、强加给他们的、不熟悉的、他们 控制不了的技术认为是危险的。当执行与 GMP 相关的质量风险管理操作时，这 些发现对决策者来说可能是重要的，风险信息需要与不同的团体和利益相关者沟 通，而一般来说这些信息与高技术性的 GMP 自然属性活动相关。

The human cognitive and behavioral origins， which may bias and adversely affect our judgment in this respect， together with detailed means of addressing QRM， have been previously described (11，12). Effective communication with stakeholders is particularly important because stakeholders form judgmentsabout risks based on their own perceptions，and those perceptions may differ from those who executed risk analysis. In the GMP environment，many existing QRM tools and programs fail to incorporate strategies to address risk perception biases.

如前面章节详细论述了质量风险管理的各个方面而知，人类的认知和行为起源在 这方面可能对我们的判断有偏见并产生不利的影响。与决策者进行有效的沟通特别重要，因为决策者根据他们自己的感知能力对风险进行判断，而这些感知能力 与执行风险分析人员的可能不一样。

While using relevant historical and real-time data such as complaints, investigations, non-conformances and trends contribute greatly in reducing subjectivity and uncertainty in risk assessments, it is also important to counteract the adverse effects that heuristics may exert on QRM activities. To address risk perception bias, a number of features should exist within a company's Quality System. See Table 3.10-1 for a list of several simple, practical strategies that are designed to improve the outcomes of QRM exercises and that should be featured in QRM programs.

当使用历史相关和现时的数据如投诉、调查、不符合项和趋势来有效减少风险评 估的主观性和不确定性时，同时防止启发性思维对质量风险管理活动产生不利影 响也很重要。说到风险认知偏差，一个公司的质量系统可能存在一系列的特征。表 3.10-1 是几种简单的，易操作的策略列表，这些策略被设计来改善质量风险管 理活动的结果，在质量风险管理项目上可以起很重要的作用。

Table3.10-1StrategiestoManageCommonPerceptionBiases 表 3.10-1 管理常见认知偏见的策略

Risk Perception Bias 认知偏见的风险	Management Strategy 控制策略
Voluntary-Involuntary Bias 自觉与不自觉的偏见	•Training and education of stakeholders recognizing this bias; include case studies and examples illustrating how this heuristic operates. •培训和教育可使决策者意识到这种偏见，包括案例学习和 演示该启发性如何运做的实例。 • Multi-disciplinary team with some stakeholders unfamiliar with the risk scenario (e.g. clinical medical, marketing, human factors personnel). •如部分决策者不熟悉风险场景（例如临床药学，销售学，个别 人类特征）可采用多学科团队决策。 • Several decision-makers involved.
Human Heuristics *人类的启发*	• Training and education of stakeholders recognizing the main heuristics that may come into play; include case studies and examples illustrating how those heuristics are manifested. •培训和教育可使决策者意识到主要启发的出现，包括 案例学习和演示启发如何被掌握的例子。 •Multi-disciplinary team with some stakeholders unfamiliar with the risk scenario (e.g. clinical medical, marketing, human factors personnel). •如部分决策者不熟悉风险场景（例如临床药学，销售学，个别 人类特征）可采用多学科团队决策

	•A range of risk analysis and risk evaluation tools being available for use. •一系列的风险分析和风险评估工具被有效地运用。 •Emphasis placed upon data-rich information for risk assessment. •将风险评估的重点放在数据丰富的信息上。 •Favoring quantitative risk management tools furnished as much as possible with data driven approaches，as long as the data are considered reliable. •只要数据被认为是可靠的，支持定量风险管理工具提供尽可能多 的数据驱动方法。 •Pre-defined rules for brainstorming activities that are designed to minimize the adverse influences of the main heuristics (e.g. when brainstorming as part of risk assessment exercises，no member of the team should verbalize his or her score of a probability estimate until every contributor has time to think and record their own estimate). • 为旨在最大限度地减少启发的不利影响采用预先定 义的规则的头脑风暴（例如，当风脑风暴作为风险评 估的一部分练习时，团队的成员不应用语言表达他或 她的估计得分概率，直到每个参与者有时间思考和记 录自
Expert-Lay Bias *专家层级的偏见*	•Training and education of stakeholders recognizing this bias; include case studies and examples illustrating bias. •培训和教育可让决策者意识到这种偏见：包括 学习案例和偏见演示例子。 •Multi-disciplinary team with some stakeholders unfamiliar with the risk scenario (e.g. clinical， medical，marketing，human factors personnel). •如部分决策者不熟悉风险场景（例如临床药学，销售学，个别人类特征）可采用多学科团队决策。 • Several decision makers involved. • 多个决策者参与

4. Implementation Of The Quality Risk Management Process

质量风险管理的实施

Per ICH *Q9,* the main steps in the QRM process include:

根据 ICHQ9，质量风险管理过程的主要步骤包括：

• Initiating a quality risk management process (Section 4.1)

启动质量风险管理程序（4.1 节）

• Risk assessment (Section 4.2)

风险评估（4.2 节）

• Risk control (Section 4.3)

风险控制(4.3 节)

• Output/ result of the QRM process (Section 4.4)
质量风险管理过程的输出/结果（4.4 节）
• Risk review (Section 4.5)
风险回顾（4.5 节）
• Risk communication (Section 4.6)
风险沟通（4.6 节）

4.1 Initiating a Quality Risk Management Process 启动质量风险管理程序

QRM should include systematic processes designed to coordinate, facilitate and improve science based decision making with respect to risk. All QRM activities, whether they are prospective or retrospective in nature, should be adequately planned prior to initiating any risk assessments. The rigor in planning should be commensurate with the impact of the potential risks on product quality. Planning activities should include (depending on formality of assessment):
质量风险管理应包括协调、促进和提高风险相关的科学决策的系统过程。所有质 量风险管理活动，不论其本质上是前瞻性还是回顾性的，都应在启动任何风险评 估前进行充分的计划。计划的严密性应与潜在风险对产品质量的影响相一致。计 划活动应包括（取决于评估的正式程度）：

• Defining the problem statement, scope (in and out of scope), known assumptions, and expected outcomes
确定问题描述、范围、已知的假设和期望的结果
• Identifying the appropriate team of SMEs and an impartial (to the extent possible) trained facilitator
确定由专家组成的适当团队，以及一个公正（尽可能）、经过培训的协调人
• Determining the level of formality and selecting the appropriate tool(s) to deliver the expected outcomes
确定风险管理的正式程度，选择适当工具以获得预期结果
• Determining how the QRM activities will be documented
确定如何记录质量风险管理活动
• Identifying and collecting relevant background information， reference documents and data related to the potential risks or product and patient impact relevant to the risk assessment
识别并收集相关信息、参考文件和潜在风险或其对产品和患者影响的相关数据
• Specifying a timeline, deliverables and appropriate levels of decision making (and appropriate decision makers) for the risk management process
指定风险管理过程的期限、预期目标和适当的决策
• Defining a reporting and communication plan 确定一个报告和沟通计划

It is also important to appropriately document these planning elements and obtain management support for the QRM activities, including resource(s) allocation.
适当记录这些计划要素并获得管理层对质量风险管理活动的支持（包括资源分配）也是很重要的。

4.2 Risk Assessment 风险评估

Risk assessment is a part of QRM and an essential component of managing risks throughout the product lifecycle. The risk assessment process comprises risk identification, risk analysis, and risk evaluation.

风险评估是质量风险管理的一部分，也是产品生命周期中管理风险的根本组成部 分。风险评估过程由风险识别、风险分析和风险评价组成。

A risk assessment exercise may take a number of different forms, such as a technical or scientific rationale developed for a problem statement, an impact assessment, or the detailed application of a formal risk management tool or methodology. Irrespective of the type of risk assessment performed, the assessment should be documented, approved, archived, and retrievable from the Quality System.
一个风险评估活动可采用不同形式，例如针对一个问题开发的技术或科学理论、 一个影响评估或正式风险管理工具或方法的详细实施步骤。不论所采用的风险评 估类型如何，都应记录评估并得到批准，保存并可通过质量系统进行追溯。
The level of rigor and type of risk assessment should be commensurate with the potential impact and knowledge of risk associated with a risk question, problem description or problem statement.
严格的程度和风险评估的类型应与潜在影响、对相关风险的认识相一致。
Broadly, rigor and formality of the risk assessment should be commensurate with a combination of the potential for a direct adverse impact to the patient or product quality and the level of process and risk understanding. A direct and critical patient or product quality impact coupled with an incomplete or uncertain understanding of the hazard, process and risk, demands the highest level of rigor and formality.
一般来说，风险评估的严格和正式程度应与风险对患者或产品质量的潜在直接影 响以及对过程和风险的理解程度相对应。对患者或产品质量有直接和关键影响， 并且对危害、过程和风险的理解不完整或不确定，则风险评估的严格和正式程度 应最高。
Conversely, with no or minimal potential patient impact coupled with a very comprehensive and contemporary knowledge of hazard, process and risk can be supported by a lower level of rigor and formality. Where it is not possible to estimate the specific clinical implications of a risk to patient safety, evaluating the risk to product quality becomes an important surrogate.
相反，对患者没有和具有很小的潜在影响，并且对危害、过程和风险有非常全面 的认识，则所需的严格和正式程度较低。当无法估计风险对患者安全的特定临床 影响时，评估风险对产品质量的影响就变得很重要。

4.2.1Execution of Risk Assessments 风险评估的实施
Irrespective of the product, process, risk question, problem description, or problem statement all risk assessments require the same fundamental activities in a common sequence of events:
不管什么产品、过程、风险提问、问题描述或问题陈述，所有的风险评估都需要 进行一系列共同的基本活动：
• Identify the owner of the QRM process.
确定质量风险管理过程的所有者
• Identify the stakeholders of the QRM exercise, and the individuals responsible for its execution. The stakeholders should assist with identifying the audiences for subsequent risk communication activity, the actual content of the risk communication and the technical level at which to deliver the risk communication message.
识别质量风险管理活动的相关方以及具体执行人员。相关方应协助确定参与后续 风险沟通活动的人员，风险沟通的实际内容和风险沟通信息传递的技术级别。
• Identify the areas of expertise required for the exercise and build the risk assessment team. Ensure that the team members are credible and have the necessary level of expertise and

risk management training. For formal risk assessments, it is essential to have a trained facilitator guide the risk management process and cross-functional SMEs involved in assessing and managing the risks.
确定参与风险评估的专业人员，组建风险评估小组。确保组员是可信的，具有必 要的专业知识，经过风险管理培训。对于正式的风险评估，由一个受训的协调员 指导整改风险管理过程以及参与评估和管理风险的跨部门专家团队是非常必要 的。
• Describe the product, process, recipient, and mode of administration of product (where appropriate).
描述产品、过程、处方和产品用药途径（适当时）。
• Define the risk question, problem description, or problem statement.
提出风险问题，问题描述或问题陈述。
• Determine the appropriate risk management tools to employ. A variety of tools exist, each with a range of suitability for risk identification, risk analysis and risk evaluation. Table 4.2-1 compares a selection of the most commonly employed tools to assist in tool selection.
确定拟采用的风险管理工具。有不同的风险管理工具，进行风险识别、风险分析 和风险评价时，每个工具均有其适用范围。表 4.2-1 对最常用的工具的选用进行了 比较。
• Decide the means and criteria employed to assign values or surrogate descriptors to probabilities and severities for risk factors and the derivation of overall risk during risk analysis. It is valuable at this point to determine any pertinent assumptions or uncertainty associated with data used in the risk assessment process.
确定风险分析过程中为风险因素的可能性和严重性赋值或确定等级并推算风险 大小的方法和标准
• Identify criteria for risk evaluation.
确定风险评价的标准。
• Assemble background information and data on the potential hazard, harm, or human impact relevant to the risk assessment (e.g., design documents including drawings and specifications, supplier documentation, complaints, investigations, CAPA, trend analyses of monitoring and testing, audit results, information from related products, etc.).
收集与风险评估相关的潜在危害、伤害或对人体影响的信息和数据（例如，包括 图纸和设计要求的设计文件、供应商文件、投诉、调查报告、CAPA、监控和测 试的趋势分析、审计结果、相关产品信息等）。

All these elements should be formally documented.
所有这些要素都应有正式记录。
A risk assessment may range from a documented simple scientific rationale to a formal risk assessment methodology. A wide variety of tools and techniques are available to facilitate risk assessments， as recognized in ICH Q9 such as:
风险评估可以是一个有记录的简单科学原理，也可以是一个正式风险评估方法。 如 ICH Q9 中所述，可采用不同的工具和技术进行风险评估，如：
• Process mapping techniques 流程图
• Fishbone (Ishikawa) analysis 因果分析
• Risk ranking and filtering (RRF)风险排序和筛选
• Fault tree analysis (FTA)故障树分析
• Failure mode and effects analysis (FMEA)故障模式与影响分析
• Failure mode effects and criticality analysis (FMECA)故障模式、影响及关键点分析
• Hazard analysis and critical control points (HACCP)危害风险和关键控制点

• Hazard operability analysis (HAZOP)危害操作分析
• Preliminary hazard analysis (PHA)初步危害源分析

Each of these tools and techniques exhibits a number of inherent features that should be considered，together with the level of rigor and formality when choosing the most appropriate tool for a particular risk assessment exercise. Even simple informal risk tools can support particular objectives and their use may be considered acceptable. Table 4.2-1 provides a comparison of the features and characteristics for some of the common risk management tools.
在选择最恰当的工具时，应考虑每一工具和技术的内在特性、严格和正式程度。 即使简单非正式风险工具也可用于特定的风险评估。表 4.2-1 对部分风险管理工具 的特性进行了比较。

Table. 4.2-1 Comparison of Common Risk Management Tools 常用风险管理工具的比较

	Comparing common risk assessment tools 常用风险评估工具的比较				
	Fault Tree Analysis (FTA) 故障树分析	Preliminary Hazard Analysis (PHA) 初步危害源分析	Failure Mode and Effects (and Criticality) Analysis (FMEA/FMECA) 故障模式、影响（及关键点）分 析	Hazards Analysis and Critical Control Points (HACCP) 危害分析和关键控制点	Hazards and Operability Studies (HAZOP) 危害操作分析
Tool Concept 工具定义	Qualitatively identify all probable pathways for faults to occur, and then identify how to prevent the fault pathways from occurring. 定性地识别故障所有可能发生途 径，再确定如何防止其发生。	Preliminary identification and ranking of risks based on prior experience or knowledge. 根据以往经验或知识，初步识别 风险并进行排序。	Assess failure modes and then determine whether the failure could be detected and whether prevention, detection, and response controls are adequate. 评估故障模式，再决定是否可以 检测故障，预防、检测和响应控 制措施是否充分。	Identify and implement process controls that consistently and effectively prevent hazard conditions from occurring. 识别并实施过程控制措施，以一 致且有效地防止危害的发生。	Identify all possible process or design deviations and assess if controls are adequate. 识别所有可能过程或设计偏差， 评估控制措施是否充分。
Tool Approach 方法	Top-down approach that considers what causes a failure. Deductive and logical approach and outputs can also be used as a tool for deviation root-cause analysis. 自上而下的方法，考虑什么导致 了故障。也可用推理、逻辑方法 和输出作为偏差根本原因分析的 工具。	Prospective bottom-up approach that considers potential hazards, hazardous situations and events that may cause potential harm to product quality and / or patient safety. Approach identifies potential negative events and remedial measures for consideration. 前瞻性自下而上的方法，考虑可 能导致潜在产品质量和/或患者安 全伤害的危害、危害环境和事件。 可识别潜在不良事件以及纠正措 施。	Bottom-up approach that considers what could go wrong and what the related risks are. Methodically divides the analysis of complex processes into smaller manageable considerations to facilitate the assessment. While essentially identical to the FMEA, FMECA has additional capability to rank the criticalities of failure modes. 自下而上的方法，考虑什么可能 出错，以及相关风险是什么。可 将复杂过程分解以便进行评估。 尽管基本与FMEA 相同,FMECA 还有额外的功能，即对故障模式 的关键性进行排序。	Bottom-up approach that considers how to prevent hazards from occurring and / or propagating. Better for preventative applications rather than reactive. Emphasizes strength of preventative controls rather than ability to detect. 自下而上的方法，考虑如何防止 危害发生和/或扩散。最好作为预 防性应用而不是被动性应用。	Bottom-up approach that considers what could go wrong, the possible causes, and what the related risks or consequences are. 自下而上的方法，考虑什么可能 出错，可能的原因以及相关风险 是什么或后果是什么？
Risk Focus 关注的风险	Process faults (ex: deviation conditions that typically include terms such as “not”, “without”, “doesn’t”, “won’t”, etc.) 过程故障（如：偏差情况通常如“不”、“没有”、“不得”、“将不”，等)	Negative events-any combination of hazards, faults, failure modes, deviations, etc. 负面事件-危害、故障、故障模式、 偏差等任意组合。	Failure Modes (similar to faults) 故障模式（类似故障）	Hazards (contaminants, adventitious agents, dangerous conditions, etc.) 危害（污染物、外来试剂、危险 状况等）	Deviations from standard (design, specification, procedure, etc.) 偏离标准（设计、指标、程序等）
Similar Tools or Methods 类似工具或方法	Fishbone/Ishikawa/Cause & Effect diagrams 鱼刺图/石川图/因果图	FMEA 故障模式、影响分析	PHA, HAZOP 初步危害源分析、危害操作分析		FMEA 故障模式、影响分析

Stand-Alone vs Used with Other Tools 单独应用还是与其他 工具联用	Often used in conjunction with other tools since FTA has no capability to assess effectiveness of risk control. 通常与其他工具联用，因为 FTA 不能用来评估风险控制措施的有 效性。	Typically supplemented later by more detailed analyses with other tools (ex: FMEA) once risks are better understood. 在对风险有进一步理解，后期通 常采用其他工具（如故障模式、影响分析）进行更详细的分析	Typically used alone, though FMEA/FMECA inputs may be identified using other tools such as FTA or PHA. 通常单独使用，尽管也可采用其 他工具如 FTA 或 PHA 识别 FMEA/FMECA 输入。	Typically used alone, though HACCP inputs may be identified using other tools such as FTA. 通常单独使用，尽管可采用其他 工具如 FTA 识别 HACCP 的输入。	Typically used alone, though HAZOP inputs may be identified using other tools such as FTA. 通常单独使用，尽管可用 FTA 等 其他工具识别 HAZOP 输入。
Quantitative vs Qualitative 定量还是定性	Typically qualitative (May be used quantitatively if fault occurrence rates are well-known) 通常为定性（也可定量，如果很 清楚故障发生频次）	Semi-quantitative, Typically qualitative risk ratings leading to simple RPN calculations. 半定量，通常定性风险排序使 RPN 计算更简单。	Either depending upon application. Risk Prioritization Number (RPN) concept favors quantitative approaches to risk rating. 定性或定量，取决于具体应用。 定量方法更利于 RPN 计算。	Either depending upon application. Critical control points typically have quantitative control limits. 定性或定量，取决于具体应用。 关键控制点通常具有定量的控制 限。	Either depending upon application, though most applications are qualitative. 定性或定量，取决于具体应用。 尽管大多应用都是定性的。
Key Assumptions 关键假设	Assumes that some other tool or process will be used to determine effectiveness of risk controls for the fault conditions identified in the FTA. 假设采用一些其他工具或过程来 确定风险控制措施的有效性，这 些风险控制措施是为了应对 FTA 中识别的故障状态。	Assume SME input and /or prior experience is adequate to support successful assessment. 假设专家的意见和/或经验足以帮 助成功进行评估。	Failure modes are intuitive, well known, or have been previously identified. 故障模式是直觉的、熟知的或已 经识别过的。	Assumes comprehensive understanding of the process and controls used for the process. 假设对过程和过程控制措施有全 面了解。	Assumes that risk events are caused by deviations from established design or operating intentions. 假设风险事件由偏离设计或操作 造成。
Key Strengths 主要优点	Effective at showing how multiple factors may contribute to a given fault condition. Best tool for accommodating human elements such as non-compliance with SOPs, training, etc. Excellent tool for defining the scope of a large risk assessment. Effective in determining the root causes of faults or observed risk conditions. 能够有效地显示多个因素如何导 致一个特定的故障状况。处理涉 及人员要素（如不付合 SOP，培 训等）的最佳工具。确定大型风 险评估范围的极好工具。可有效 地确定故障或所观察的风险状况 的根本原因。	Able to be used when information is limited. Allows risks to be considered very early in the lifecycle. Useful to define scope of a complex system or process and for prioritizing hazards. 可在信息有限的条件下使用。可 在生命周期的早期进行风险评 估。可用于确定复杂系统或过程 的范围以及用于危害的排序。	Ability to rank risks and appoint effort accordingly. Wide acceptance in the industry, with many case studies available. Best method for prioritizing and ranking risks. Effectively summarizes modes of failure, the factors causing the failure, and their effects. 能够对风险进行排序并分配相应 资源。广泛应用于工业生产，有 许多案例研究。进行风险排序的 最佳方法。可有效地汇总故障模 式、影响因素及其作用。	Tool ensures that critical points in the process can be identified and adequately controlled. Great precursor or complement to process validation. 确保过程中关键点可识别并进行 充分控制的工具。工艺验证的很 好前提或补充。	Systematic and flexible tool that has much of the power of FMEA, but without heavy reliance on rating the ability to detect (a risk aspect that is typically challenging in complex processes and when dealing with human factors). Risk identification brainstorming is built into the HAZOP methodology. 同 FMEA 大多功能类似的系统性 和灵活应用的工具，但不过于依 靠对检测能力（风险的一个方面， 通常用于复杂过程，以及处理人 员因素）进行定级。用于风险识 别的头脑风暴是 HAZOP 的一部 分。

Key Limitations 主要不足	No means to assess effectiveness of risk reduction activities. Larger assessments can be difficult to format and communicate effectively. Qualitative nature of FTA often requires it to be paired with another tool that has quantitative analysis capabilities. No risk ranking or prioritization capability. 无法对风险降低措施的有效性进 行评估。不易进行大型评估的安 排和有效沟通。FTA 的定性本质 导致通常需要和能够定量分析的 工具联合使用。不能用于风险排 序或优先级别确定。	Generally requires additional follow-up analysis. Quality of results may be highly dependent on SME input rather than data. 通常要求额外的跟踪分析。结果 的质量可能取决于专家的贡献而 不是数据。	Forces the user to rate risks in terms that may not be well understood (ex: human factors or process anomalies are difficult to rate for probability of occurrence or the ability to detect). Analysis can be highly detailed and tedious for complex systems having multiple components. 迫使用户确定风险等级，即便是 对于没有很好认识的风险（如， 对于人员因素或过程异常，难以 确定发生可能性或检测能力的级 另 IJ)。对于多组件的复杂系统， 分析可能会非常具体、乏味。	Analysis is not effective or feasible unless the subj ect process and associated controls are well understood and well defined. Difficult to apply to new processes or rapidly evolving / developing processes. 除非过程和相关控制措施有很好 的理解，并明确界定，分析将不 会有效或可行。难以用于新过程 或快速发展的过程。	No risk ranking or prioritization capability since probability of hazard occurrence is not typically considered. No means to evaluate hazards involving interactions between different parts of a system or process. 因为通常不考虑危害发生的可能 性，故无法进行风险排序或确定 优先级。无法评价系统或过程的 不同部分有相互作用的危害。
Scope Management 范围管理	Scope must be actively managed- team must put assumptions and / or limitations in place to manage scope from becoming unnecessarily detailed. 必须积极地控制范围 - 小组必须 建立范围管理的假设和/或限制， 以避免过于详细。	Scope must be actively managed- team must put assumptions and / limitations in place to manage scope from becoming unnecessarily detailed or broad. 必须积极地控制范围 - 小组必须 建立范围管理的假设和/或限制， 以避免过于详细或宽泛。	Scope must be actively managed- team must put assumptions and / or limitations in place to manage scope from becoming unnecessarily detailed. 必须积极地控制范围 - 小组必须 建立范围管理的假设和/或限制，以避免过于详细。	Easier to manage- scope is determined by the process being assessed. 易于管理 - 范围可根据被评估的 过程确定。	Scope must be actively managed - team must put assumptions and / or limitations in place to manage scope from becoming unnecessarily detailed. 必须积极地控制范围 - 小组必须 建立范围管理的假设和/或限制， 以避免过于详细。
Risk Ranking Capability 风险排序能力	None if tool is used qualitatively- all faults are treated equally. For quantitative ranking, data is needed for rating probability of all faults. 无，如果定性地使用该工具 - 平等 对待所有故障。对于定性排序， 需要数据用于确定所有故障的发 生可能性的等级。	Yes- Risk Prioritization Numbers (RPN) commonly used to determine needs for subsequent risk controls and further risk assessment. 具有 - 通常用 RPN 确定是否需要 采取后续控制措施以及进一步的 风险评估。	Yes- Risk Prioritization Number (RPN) commonly used to correlate risk level to required mitigation effect. 具有 - 通常用 RPN 将风险等级和 所需风险降低效果关联起来。	Partial- Hazards are classified into significant vs. non-significant. Controls are classified as critical vs. non-critical. 部分 - 将危害分为重大和非重大。 控制措施分为关键和非关键。	Optional. A pseudo- RPN approach could be applied if desired. 可选的。需要时，可应用一种 RPN 类似方法。
Considers Probability of Occurrence? 考虑发生可能性？	Optional 可选的	Yes 是的	Yes 是的	Yes 是的	Partial- a deviation Credibility decision is required. 部分 - 需要确定偏差的可信性。
Considers Ability to Detect? 考虑可检测性？	Optional 可选的	Not traditionally, but may be added as an optional consideration 通常不，但也可作为选择项	Yes 是的	No- emphasis is on hazard prevention, not necessary detection and remediation. 不 - 重点在于防止产生危害，不在 于检测和纠正。	Yes, but not explicitly- if detection is used in the process control scheme, then it lowers the risk probability and / or severity. Detection also sometimes credited as a HAZOP "safeguard". 是的，但不明确 - 如果过程控制中

					用到检测，那么它可降低风险发 生的可能性和/或严重性。检测有 时也可作为一种 HAZOP 的安全 措施。
Considers Severity of Impact? 考虑严重性？	No 不	Yes 是的	Yes 是的	Yes 是的	Yes 是的
Ability to Process Interrelationships of Multiple Fault Modes 能够处理多种故障模 式的相互关系	Yes (by design) 是的（通过设计）	Not without creating significant complexity. 不，否则将特别复杂	Not without creating significant complexity. 不，否则将特别复杂	No 不	Not without creating significant complexity. 不，否则将特别复杂
Ability to Handle Human Factors/ Dynamics 能够处理人员因素/动 力	More capable 较能够	More capable 较能够	Less capable 较不能够	Less capable 较不能够	More capable 较能够
Output Format 输出格式	Graphical depiction 图形描述	Tabular 表格	Tabular 表格	Tabular 表格	Tabular 表格
Key Guidance Reference(s) 主要指导文件	IEC international Standard 1025 (also referred to as Standard 6025 IEC 国际标准 1025 (也可参考标 准 6025	Limited. Brief overviews can be found in ISO 14971 and IEC 60300 有限 。 概 述 可 见 ISO14971 和 IEC60300.	IEC International Standard 812 (also referred to as Standard 60812) IEC 国际标准 812 (也可参考标准 60812)	WHO Guideline, Quality Assurance of Pharmaceuticals, Chapter 5-NACMCF, Principles and Applications Guidelines for HACCP WHO 指南，药品质量保证，第 5 章-NACMCF，HACCP 原理和应 用指南	IEC International Standard 61882 IEC 国际标准 61882

4.2.2 Risk Identification 风险识别

Identifying potential hazards and harms, which may elicit an adverse impact on product quality or patient safety, is one of the most important activities in any risk assessment process. All subsequently performed risk assessment activities will relate to these identified hazards. Although a number of risk management tools are recognized, process mapping, fault tree analysis, and fishbone analysis are simple and structured techniques that are especially suited to risk identification.

识别可能对产品质量或患者安全造成不利影响的潜在危害和伤害，是任何风险评估过程中最重要活动之一。后续所 有风险评估活动都与这些识别的危害相关。尽管有许多风险管理工具，流程图、故障树分析以及因果分析是特别适 合风险识别的简单、有条理的风险管理技术。

Risk identification is the systematic use of information to identify hazards and potential harms relevant to the risk question or problem description. Risk identification addresses the question *"What might go wrong?"* and it includes identifying the possible consequences of hazards.

风险识别是通过对信息的系统利用，识别风险问题或问题描述相关的危害和潜在伤害。风险识别回答了“什么可能出 现问题”包括识别危害可能造成的后果。

Production processes typically involve six main components (13):

生产过程通常包括 6 个主要部分（13):

1. Equipment 设备
2. People 人员
3. Methods 方法
4. Environment 环境
5. Materials 物料
6. Measurements 测量

When the likely causes of potential adverse events are being identified, it is useful if each of these components is considered and taken into account. Salient information from which to identify hazards includes historical data, theoretical analysis, technical analysis, advice from technical experts and the concerns of stakeholders (including customers or their surrogates). 在识别了潜在不良事件的可能原因后，考虑每一部分的作用是有益的。用来识别危害的信息包括历史数据、理论分 析、技术分析、技术专家的建议、相关方关注点（包括顾客或其代理人）。

4.2.3 Risk Analysis 风险分析

Typically, risk analysis consists of estimating the risk associated with the identified hazards. It uses either a qualitative or quantitative process of linking the likelihood of occurrence (probability) and the severity of harms. In some QRM tools, the ability to detect the hazard (detectability) also factors into the estimation of risk. Derivation of the values (qualitative or quantitative) assigned to probability, severity and detectability can be prone to bias, errors in judgment, and problems of misperception.

风险分析通常包括估计已识别危害的相关风险。采用定性或定量的方法将发生的可能性（可能性）与伤害的严重性 结合起来。在使用部分风险管理工具对风险进行估计时，也考虑危害的检出能力（可检测性）。推算可能性、严重 性和可检测性的数值（定性或定量）容易出现偏差，导致判断失误。

Risk analysis is beneficial when conducted with a multi-functional team of SMEs. This assures that risks are analyzed from multiple perspectives. Team discussion is particularly useful so that different perceptions of the risk can be surfaced.

最好由多部门组成的专家团队进行风险分析。这保证了从不同角度对风险进行分析。团队讨论特别有用，这样可以 了解对风险的不同看法。

It is also important to recognize that an SME's perception of risk may differ markedly from that of other team members who may be unfamiliar with the process or product under study in the risk assessment.

一个专家对风险的看法可能与其他不熟悉所研究的过程或产品的组员存在明显区别。认识到这一点也很重要。

Generally, people tend to regard as "risky" any technology that is new, imposed on them, unfamiliar or

beyond their control. Given the highly technical nature of pharmaceutical manufacturing, these are important considerations to ensure that an effective risk analysis occurs. Appropriate strategies to combat these inherently human biases are detailed in the risk communication section.
通常，人们倾向于将任何新的、强加给他的、不熟悉的或超出其控制的技术归为“有风险的”。考虑到药品生产的高 技术特性，考虑到这点对确保有效的风险分析十分重要。在风险沟通一章详细列举了应对这些固有认知偏见所采取
的适当策略。
Numerical values (or alternative surrogate descriptors) (14) for probability, severity, and detectability are typically designated as singular discrete values (e.g., 1, 5, 10) or as qualitative descriptors (e.g., high, medium, low). While useful, these surrogate descriptors fail to encompass known variability or perceived uncertainty. The adoption of probabilisticdescriptors based on historical, process capability， or other relevant real-time data represents a more accurate but more complex means of accounting for this (15).
表示可能性、严重性和可检测的数值（或替代描述值）（14)通常指定为单一离散数值（如 1、5、10)或定性描述 (如高、中、低）。尽管具有一定作用，这些替代描述值无法包含已知变动或预计的不确定性。对此，采用基于历 史数据、过程能力或其他相关实时数据的逻辑性描述更加准确，但也更加复杂（15)。

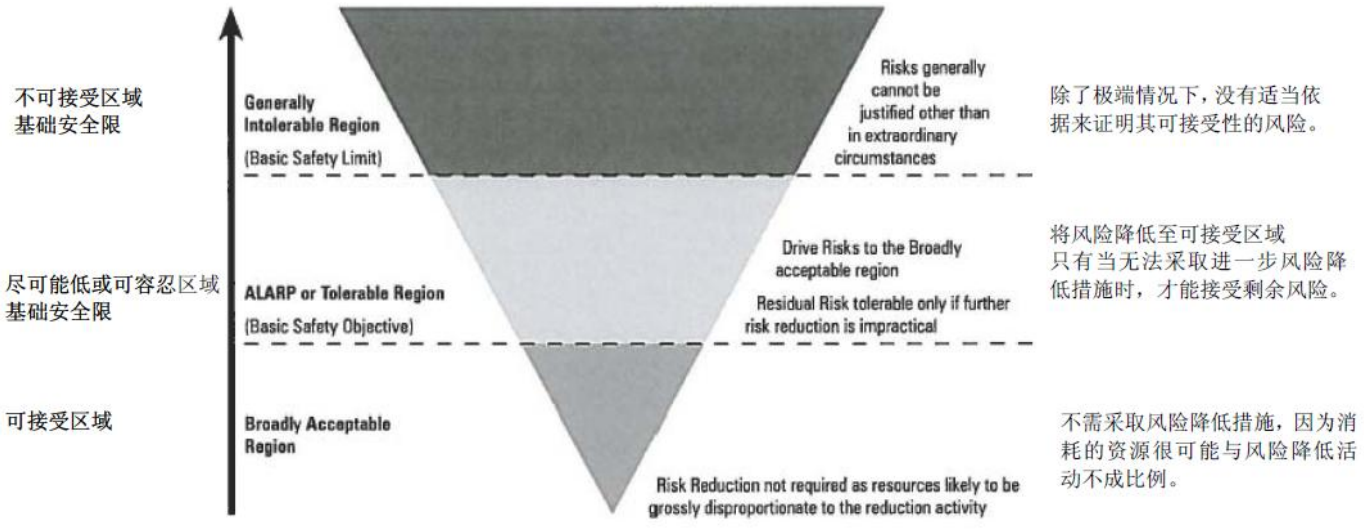
It is important also to recognize that probability of occurrence risk factor values are usually assigned numerical estimates that are expressed using ordinal scales, such as a scale of 1 through 5, where a value of "1" may represent a very low probability and "5" may represent a very high probability. The magnitude of the individual values is not necessarily meaningful in a numerical sense (16, 17). For example, an event with a probability of occurrence of "4" on an ordinal scale has of course a higher probability of occurring than an event with a probability of "2", but it is not necessarily twice as likely to occur. Furthermore, it is not strictly mathematically permissible to multiply ordinal scale values, and numerical operations such as (Risk = 3 x 4) or (Risk = 3 x 4 x 2) (18) have questionable validity. In this respect, surrogate descriptors (e.g., high, medium, low) may be more valid than numerical descriptors.
通常为风险因素发生可能性指定数值，以序数如 1到 5表示，其中 1代表可能性很低，而 5 代表可能性很高。单个数值 的大小并不一定具有数学上的意义（16,17)。例如一个事件发生可能性为 4，当然比可能性为 2的事件发生可能性要 高，但并不是说其发生次数是后者的两倍。而且，从严格的数学角度说，不允许将序数值相乘，数学运算如（风险 =3 x 4)或（风险=3 x 4 x 2) (18)的有效性是有疑问的。从某种意义来说，替代的定性描述（如高、中、低）可能 比数值更加有效。

4.2.4 Risk Evaluation 风险评价

During a risk evaluation, the identified and analyzed risks are compared against given risk acceptability criteria.
在风险评价过程中，将已识别和分析的风险与给定的风险接受标准进行比较。

Risk is typically categorized as broadly acceptable, as low as reasonably practicable (ALARP), or intolerable (See Figure 4.2.4-1). Broadly acceptable risks are those for which the severity of harm or likelihood of occurrence of harm (or both) is sufficiently low that adverse impacts are minimal. Broadly acceptable risks are considered acceptable with no further risk reduction.
风险通常分为大体可接受的、需要尽可能低（ALARP)或不可接受的（见图 4.2.4-1)。大体可接受的风险指那些危 害的严重性或发生的可能性（或两者都是）很低，造成的不良影响最小的风险。这种风险是可以接受的，不需进一 步的风险降低措施。

Figure 4.2.4-1 Classifications of Risks 风险的分类



Intolerable risks are those for which the combination of severity of harm and likelihood of occurrence of harm is so great that a significant impact to the quality of the product or to patient may result.
不可接受的风险指那些伤害的严重性和发生的可能性的组合较大，可能导致对产品质量或患者安全的重大影响。

Risks categorized as ALARP or Intolerable should be assessed from a risk / benefit perspective. Risk / benefit analyses answer a basic question: *Does the activity in* question *provide* benefits *to* the user *such that any residual risks are acceptable by* comparison? These analyses should be performed by individuals who are knowledgeable and experienced and are able to evaluate the technical, clinical, regulatory, and economical aspects of the decision to be made. The benefit of the activity in question should have been estimated (at an earlier point in time, by medical professionals) considering the expected
performance during clinical use, as well as, other potential treatment options. Examples of information used in this analysis include process / product data, literature searches, and survey information. Once completed, the risk / benefit analysis should be documented in a report, which is typically reviewed and agreed to by the company's senior management.
应从风险/效益的角度评估归类于尽可能低的风险或不可接受的风险。风险/效益分析回答了一个基本问题：所讨论的 活动是否给用户带来益处，残留风险是可接受的？这些分析应由知识丰富、有经验并能够对拟采取决策从技术、临 床、法规和经济角度进行评价的人员来完成。应评估所讨论活动的效益（由医学专业人员提前完成），并考虑临床 以及其他治疗应用时的预期表现。分析中所使用的信息包括工艺、产品数据、文献搜索和调查信息。完成后，应将 风险/效益分析记录在报告中，并由公司高层审核和批准。

Note that the quality of the outputs of a risk assessment exercise usually depend on the robustness of the data and on the assumptions and sources of uncertainty related to the exercise, such as gaps in the level of knowledge about the sources of harm and in product and process understanding.
注意风险评估活动的输出通常取决于数据的耐受性以及相关不确定度的假定和来源，如对危害根源以及产品和过程 的认识水平的差距。

The output of a risk assessment is usually a semi-quantitative estimate of risk (if a numerical probability factor is used), or a qualitative description of risk (e.g., high, medium, or low), when qualitative factors are used. These should be defined in as much detail as possible.
风险评估的输出通常是对风险的半定量估计（如果可能性采用了数值表示）， 或者是对风险的定性描述（如高中低）
(当采用了定性表述时）。这些都应尽可能详细地加以明确。
Sometimes a "risk score" is used to further define descriptors in risk rankings. When comparing risks associated with different scenarios, clearly defined risk acceptance thresholds should be employed. This demands that the same number of risk factors should be employed in each assessment along with using a consistent means of scoring. Evaluation of risk using scores based upon representative numerical values provides a suitable frame of reference and means of assessment, but the designation of a numerical level above which the risk is deemed "intolerable" (19) and requires responsive risk reduction, is often quite subjective. Risk is never zero nor is it an absolute certainty; rather, it exists along a continuum extending from a very low level of possibility through to a high level of certainty (20). Therefore, the selection of risk acceptance thresholds should be based on a clear scientific rationale, with consideration given to the confidence levels associated with the threshold value selected.
有时在风险排序中用“风险评分”进一步定义风险表述。当对不同方案的风险进行比较时，应清楚地确定风险接受限 值。这就要求进行评估时采用相同的分析表示方式，并采用一致的评分方法。根据典型数值用评分进行风险评价提 供了适当的参比框架和评估方法，但确定不可接受的风险限度水平（19)并采取风险降低措施，通常都是主观的。 风险不会为零，也不是个绝对确定的值；实际上，风险可以是一个很低的可能性到很高确定性的连续体（20)。因 此风险接受限值的选择应基于明确的科学原理，并考虑所选择限值的置信水平。

4.2.5 Supporting tools 辅助工具

Statistical tools can support and facilitate QRM activities. They can enable effective data assessment, aid in determining the significance of the data set(s), and facilitate more reliable decision-making.
统计学工具可用于质量风险管理活动，有效地进行数据评估，帮助确定数据组的重要性，并有助于进行可靠的决策。 Statistical tools commonly used in the pharmaceutical industry include:
制药行业通常使用的统计学工具包括：

- Control Charts, such as:

控制图如：

Acceptance Control Charts 接受控制图
Control Charts with Arithmetic Average and Warning Limits 带算术平均值和警戒限的控制图
Cumulative Sum Charts 累积和图 *Shewhart Control Charts* 修哈特控制图 *Weighted Moving Average* 加权平均

- Design of Experiments (DOE) 实验设计
- Histograms 直方图
- Pareto Charts 帕累托图

• Ishikawa diagrams (fishbone or cause-and-effect diagrams)石川图
• Process Capability Analysis过程能力分析

4.3 Risk Control 风险控制

Risk control activities attempt to reduce risk to acceptable levels by implementing controls based on risk scores. Risk control focuses on two activities: risk reduction and risk acceptance. After the completion of risk reduction activities the residual risks should be reviewed in a formal risk acceptance process where a risk /benefit analysis may be performed to answer the question, *"Does the overall* benefit *to the user outweigh the risks associated with the use of this product, process?"*
风险控制活动是根据风险评分实施控制措施，将风险降低至可接受水平。风险控制聚焦于两个活动：风险减低和风 险接受。在风险降低活动完成后，通过正式风险接受过程对残留风险进行回顾，进行风险/效益分析回答下述问题：“对用户的整体效益是否大于使用这一产品、工艺的所带来的风险？”

4.3.1 Risk Reduction 风险减低

Risk reduction focuses on reducing the severity and probability of occurrence by implementing appropriate product, process, and system controls. Each identified risk should be assessed to determine if it is broadly acceptable, as low as reasonably practicable, or unacceptable / intolerable. For unacceptable / intolerable risks, the risk reduction strategy should define the corrective and preventive actions to attempt to reduce the risks to an acceptable level. Risk reduction activities may be initiated and guided by addressing the following questions:
风险减低重点是通过适当产品、工艺和系统控制降低严重性和发生可能性。应对每一已识别的风险进行评估，确定 其属于可接受风险，需尽可能低风险还是不可接受风险。对不可接受的风险，风险减低策略应确定纠正预防措施，将风险降低至可接受水平。可通过回答以下问题，启动并指导风险降低活动：

• Is the risk above an acceptable level?
风险是否在可接受水平之上？

• Were the appropriate controls considered to reduce or eliminate the risk?
是否考虑了适当控制措施来降低或消除风险？

• Were unacceptable risks managed and / or reduced to acceptable levels?
不可接受的风险是否降低至可接受水平？

• How do we know the new controls are (or will be) effective?
我们如何知道新控制措施是（将会是）有效的？

• Have proposed risk controls been examined for new risks?
建议采取的风险控制措施是否会带来新风险？

Risk elimination may not always be possible or practical. For example, a company that manufactures hospital scanners (medical devices) may decide to not market their products in countries with unreliable power supplies. Their scanners may be resilient to spikes in the electrical grid, but technical safeguards may be either too costly or the risk of malfunction is considered unacceptable. Consequently the risk is avoided by not selling the product in these markets.
将风险完全消除并不总是可能或可行的。例如，一个生产医院用扫描仪（医疗器械）的公司可能决定不在电力供应 不稳的国家销售其产品。他们的扫描仪可能对电网的峰值具有一定弹性，但要么技术安全措施成本过高，要么故障 风险不可接受。结果该公司就通过不在这些市场销售产品来规避风险。

Risk reduction should first focus on reducing harm. This can be achieved, for example, by developing a contingency plan that will be executed should the risk materialize. In these circumstances it is essential to monitor and review the situation regularly or even continuously. However, it may not always be possible to reduce a risk by reducing harm. In such instances, reducing the probability of occurrence by adding preventive controls and increasing the detectability of hazard(s) by adding detection controls can provide other strategies for reducing risk. Risk reduction should preferentially focus on prevention rather than detection. Prevention can be achieved in several ways such as:
风险降低时首先应考虑降低伤害。这可以通过例如建立发生风险时采取的应急计划来达到。在这些情况下，必须定 期甚至持续对状况进行监视和回顾。但并不总是能够通过降低伤害来降低风险。此时，可通过增加预防控制措施来 降低发生可能性，通过增加检查控制措施提高危害的可检测性，这样也可降低风险。风险降低应优先考虑预防措施 而不是提高可检测性。预防措施可从以下几种方式考虑：
• Build in safety by design 通过设计提高安全性
• Add protective measures in product or manufacturing process 增加产品或生产工艺的保护性措施
• Add safety warnings 增加安全警示

A reduction in the probability of occurrence can be affected by removing or controlling the cause(s) of the hazard or failure mode through a product, process or system design change. Design and process changes can bring about a reduction in risk ranking by addressing either the occurrence of the cause of failures or the occurrence of the failure itself. A design / process change, in and of itself, does not imply that the risk will be reduced. Any changes(s) should be reviewed to determine the effect on the product and process. For maximum effectiveness and

efficiency, changes to the design / process should be implemented early in the development process. Studies to understand the sources of variation using statistical methods may be used; the knowledge gained may assist in the identification of appropriate controls including ongoing feedback of information to the appropriate operations for continual improvement and problem prevention.
通过产品、工艺或系统的设计变更，降低或控制危害或故障模式的根源，以减少发生的可能性。设计和过程变更可 针对故障产生根源或者故障本身的产生来降低风险等级。一个设计/过程变更本身并不意味着风险一定会降低。应对 任何变更进行审查，确定其对产品或过程的影响。为了使效果和效益最大化，应在开发过程尽早进行设计/过程的变
更。可采用统计学方法研究变动的来源；所获得的知识有助于识别适当的控制措施，包括操作的持续信息反馈，以 便持续改进和防止问题的发生。

Improvement of detection mechanisms can also be useful in reducing risks especially where prevention controls are insufficient. In general, improving/ enhancing detection requires knowledge and understanding of the significant/ dominant causes of process variation and any special causes. Increasing the frequency of inspections is usually not an effective risk reduction action and should only be used as a temporary measure to collect additional information on the process so that permanent corrective / preventive actions can be implemented.
检测机制的改进也可降低风险，尤其在预防措施不充分时。通常提高检测能力需要对过程变动的重大/主要原因和任 何特殊原因有一定知识和理解。增加检查频次通常不是一个有效的风险降低措施，只能作为临时措施来收集更多过 程相关信息，以便实施永久的纠正/预防措施。

Consider, for example a vial stopper application in which the failure mode is "vial not stoppered correctly." A preventive approach to precluding the failure mode would be to control the cause(s) of the failure. Some preventive actions could include improving the set-up procedure, and performance of annual preventive maintenance on the feed screws and universal joints and bearings. The incorporation of detection controls might include controls such as a periodic in-process inspection of vials, a 100% visual inspection at the conclusion of stoppering, monitoring of occurrence rates, or incorporating a qualified vision system with a feedback loop such that improperly stoppered vials would be removed from the process stream.
在西林瓶胶塞应用中一个故障模式为“未正确地加塞”。排除该故障模式的预防措施可以是控制故障产生的根源。部 分预防措施包括改进安装程序，并对进料螺杆、万向节、轴承进行年度预防性维护。检测控制可包括定期对西林瓶 进行中间控制检查，在加塞结束进行 100%目检，监视发生概率，或采用带有反馈回路的自动灯检系统，以便将未正 确加塞的西林瓶剔除。

Often these preventive and detective activities are implemented in a step-wise manner, reducing the risks incrementally until an acceptable level can be reached. Risk reduction does not necessarily remove the probability of harm entirely; it limits negative consequences of a particular event.
通常这些纠正预防活动以步进式的方式实施，逐步降低风险直到达到可接受水平。风险降低措施并不一定将危害发 生的可能性完全去除；它可以限制一个特定事件的负面影响。

4.3.2 Risk Acceptance 风险接受

Risk acceptance is a formal process in which decision makers review the risks associated with a specific activity, and determine whether the risks are acceptable or need to be reduced further. Risk acceptance reviews occur after all reduction strategies have been implemented and verified for effectiveness and the process have been evaluated to identify residual risks. Residual risks are those risks that remain after all control measures have been implemented or which may result from the implementation of a reduction strategy. For example, in the case of a vial not being stoppered properly a risk reduction measure might be to increase the force used to place the stopper. However, the increased force may result in an unanticipated new risk of cracked vials. This would be a risk that originated from the implementation of a reduction strategy.
风险接受是决策者审核特定活动相关风险的一个正式过程，并决定风险是否可以被接受或需要进一步降低。在所有 风险降低策略已实施，确认其有效性，并评估过程剩余风险后，进行风险接受审核。剩余风险是在所有控制措施已 实施后残余风险或因风险降低策略的实施而导致的风险。例如当西林瓶没有正确加塞时，一个可能的风险降低措施 可能是提高加塞的压力。但是增加压力可能导致非预期的新风险-西林瓶破裂。这就是由于实施风险降低策略而导致 的风险。

Risk acceptance levels are determined by an organization's policy on QRM, and may be influenced by many factors (e.g., societal, regulatory, scientific) typically unique to the organization and situation. It is essential that there is adequate documentation that describes what the acceptable levels are and who is empowered to set them. Preferably, there should also be documented rationale for the decisions.
风险接受水平可根据一个组织的质量风险管理方针来确定，并受组织和环境特定的多种因素影响（例如：社会的、
法规的、科学的）。必须有足够的文件描述可接受水平，以及由谁制订。最好应有决策的书面依据。

It is widely acknowledged that risk is rarely completely eliminated. Risk management practitioners attempt to reduce risk as much as possible and practical but recognize that a point of diminishing returns may be reached where further controls have a minimal impact on risk reduction. Thus a low level of risk may remain that does not significantly impact the activity being analyzed and therefore the quality of the product being produced. These risks are categorized as ALARP and may be accepted contingent on an acceptable risk /benefit analysis. High risks should normally be reduced without consideration of cost while those risks closer to the acceptable region offer greater flexibility to balance

the technical and economic aspects. Intolerable risks should not be accepted without further control measures being implemented or without a formal risk / benefit analysis being performed.
普遍认为风险很少能够完全消除。风险管理人员试图尽可能实际地降低风险，并知道可能达到一个收益递减点，更
多的控制措施对风险降低影响极小。这样就会存在较低的风险，但并不能显著影响被分析的活动，以及所生产产品 的质量。这些风险归类为应可能低的风险，根据风险/效益分析偶尔也是可接受的。高风险通常必须降低而不考虑成 本，尽管那些接近可接受区域的风险在平衡技术和成本方面具有更大的灵活性。在没有实施控制措施或进行正式风 险/效益分析前，不得接受不可接受的风险。

Risk acceptance decisions affecting patient safety and product quality must be made by appropriate decision makers and associated justification must be documented. These decisions may be made and/ or reviewed as part of a periodic management review meeting.
影响患者安全和产品质量的风险接受决定必须由适当的决策者做出，并书面说明理由。这些决定可作为定期管理评 审的一部分制订和/或审核。

4.4 Output/Result of the Quality Risk Management Process

质量风险管理过程的输出/结果

For expedient execution of formal QRM activities, relevant supporting data, salient information, and facts should be clearly documented and communicated. Risk assessment outcomes including risk reduction and risk acceptance decisions, level of residual risk and their acceptability; and risk review requirements should be documented and approved by the appropriate decision makers. QRM documents should be archived appropriately, and should be recoverable and accessible to ensure a com-
为了方便一个正式质量风险管理活动的实施，相关支持数据、显著的信息和事实应有清晰的记录，并在相关方之间 进行沟通。适当决策人员应记录并批准风险评估结果包括风险降低和风险接受决定、剩余风险水平及其接受与否， 以及风险回顾要求。质量风险管理文件应适当保存，并可获得以保证

4.4 Output/Result of the Quality Risk Management Process

4.4 质量风险管理程序的输出/结果

For expedient execution of formal QRM activities, relevant supporting data, salient information, and facts should be clearly documented and communicated.Risk assessment outcomes including risk reduction and risk acceptance decisions, level of residual risk and their acceptability; and risk review requirements should be documented and approved by the appropriate decision makers. QRM documents should be archived appropriately, and should be recoverable and accessible to ensure a communicated continuity of learning and continual improvement. The documents should also be current and actively maintained with respect to best available science, engineering, and product and process data accompanying the product and process lifecycle.
执行正式的 QRM 活动的权宜之计,相关支持数据,突出信息和事实应该清楚地记录和传达。风险评估结果包括减 少风险和风险接受的决定,残余风险水平及其可接受性;和风险评审需求应记录并经适当的决策者批准。QRM 文 档应该适当地归档,应可恢复和访问,以确保学习和持续改进的持续沟通。该文档应该保持现行版，并在产品和 工艺的生命周期内遵从可获得的最好的科学、工程，产品和过程数据来积极维护。

4.4.1 Risk Register

4.4.1

风险登记

Subsequent to the publication of ICH Q9, the concept of a risk register has been adopted for the pharmaceutical industry. While these documents are common outside the pharmaceutical industry， they have not been commonly used within it. The expectation for these risk registers was created in mid-2010 within the United Kingdom's Medicines and Healthcare Products Regulatory Agency (MHRA) in their "GMP- Quality Risk Management: Frequently Asked Questions" document. The MHRA laid out an expectation that every manufacturing site should have a formal risk register, which is a list that provides for planning and remediation of the manufacturing site's high-level risk items. Most regulatory agencies have explicit or implicit requirements for the use of risk management, so the requirement for a risk register may be seen as a natural progression in the maturity of the use of risk management in our industry.
随着 ICH Q9 的出版,注册风险的概念已经被制药业所采用。虽然这些文件在制药行业之外是普遍存在的,但这些 文件没有被普遍使用。这些风险注册的期望成立于 2010 年代中期，在英国药物和保健产品监管机构(MHRA)他们的“GMP 质量风险管理:常见问题”文档中首次出现。MHRA 制定了一个期望,每个制造公司应该有一个正式 的风险登记表,这是一个提供计划和修复生产基地的高级风险项目列表。多数监管机构明确或隐含要求使用风险 管理,所以注册风险的要求可能可以被视为风险管理在我们的行业被成熟使用的自然发展的结果。
While most companies have collections of risk assessments performed at their sites, many of them do not have a system to manage all these risk assessments in such a way that an overall view of the risks and hazards are clearly
laid out.

虽然大多数公司都有收集在其公司内部执行风险评估的资料,但他们中的许多人没有系统地管理这些风险评估， 即将风险和危险清晰地列出作一个全面的审核。

The risk register summarizes significant risks at a manufacturing site in a high- level document; it also provides an explanation of the remediation of those risks. The risk register should also point to or list out the individual risk assessments that identified the significant risks for that site.
风险登记用高级别的文件总结生产基地的重大风险;它还提供了一个补救这些风险的解释。风险登记也应该指出 或列出确定内部重大风险的个案风险评估。

The benefit in the use of a risk register is two-fold:
使用风险登记的好处是双重的：

1. It provides a summary document for the regulators to review during inspections.
1. 它为监管机构在检查期间提供了一个审查总结文档。

2. It provides site management a fairly dynamic view of the overall risk for the site and a communication tool to share with the site in general.
2. 一般来说，它为现场整体风险地管理提供了公平的动态观点，是与现场分享和沟通的工具。

A risk register is a great tool to incorporate into your risk management program to facilitate and encourage risk review and risk communication.
风险登记是纳入风险管理程序一个有用的工具,可以促进和鼓励风险审查和风险沟通。

4.5 Risk Review
4.5 风险审核

Risk review is the review or monitoring of output /results of the risk management process considering (if appropriate) new knowledge and experience about the risk (2). The QRM process is not complete once the outcomes of the risk assessment have been summarized and reported, and risk reduction measures have been implemented. Risk management is an ongoing process whereby risk assessments are reviewed and monitored to determine if any new risks or changes have been introduced.It is important that risk assessments are an integral part of a company's Quality System to continuously assess whether current controls are satisfactory for existing processes or if original risk management decisions have been impacted by new risks or changes to existing risks or risk control mechanisms.
风险回顾是鉴于风险的新知识和经验(如果适用的话)，对风险管理过程的输出/结果进行回顾或监视(2)。当风险 评估的结果被总结出来并报告,而且风险减少措施已经实施时，QRM 过程并没有完成。风险管理是一个持续的 过程,凭借风险评估和监控,以确定是否引入了任何新的风险或变更。很重要的是,风险评估是一个公司的质量体 系的组成部分,用以不断评估当前控制措施是否符合现有工艺的要求，或者原来的风险管理决策是否被新的风险 或存在的风险的变更或是风险控制机制所影响。

Risk assessments should be current and reviewed throughout the lifecycle of a product, process, or system. To keep risk management "living," there are two types of triggers that might require review and updates to existing risk management measures and decisions: 1) event-based reviews or 2) schedule-based reviews.
风险评估在产品、工艺或系统的整个生命周期中应该是现行的并经审核的。为了让风险管理“有活性”,有两种类 型的事件可能会引起对现有的风险管理措施和决策做出审查和更新:1)基于事件的审核或 2)基于日程的审核。

4.5.1 Event-Based Reviews
4.5.1 基于事件的审核

There are a number of event-based, incidental triggers that would present an opportunity for a riskreview. Examples of these event-based drivers and a brief discussion follows。
有很多基于事件地偶然触发,给风险评估提供了一个契机。这些基于事件驱动的例子,下面有一个简单的讨论。

4.5.1.1 Deviations or Non-Conformances 4.5.1.1
偏差或不符合项

Deviations in processes and systems should be an immediate trigger to review a risk assessment. One should evaluate and determine the root cause for the deviation as well as those controls that should be put in place to prevent the event from recurring. Additionally, deviation trends are an indication that the risk profile may have changed. A current and up-to-date risk assessment is one of the fundamental tools for an effective CAPA system.
工艺和系统的偏差应该立即引起风险评估地审查。公司应该评估和确定偏差的根本原因，并且这些控制措施应 该执行到位,以防止事件的再次发生。此外,偏差趋势表明风险概况可能已经改变了。当前和最新的风险评估是 一个有效的 CAPA 系统的基本工具之一。

4.5.1.2 Product Complaints, Returns, or Patient Safety Related Events 4.5.1.2 产品投诉、退货或与病人安全相关的事件

Though product complaints, returns, or patient safety related events are lagging indicators that represent failure of some element of the Quality System, they should be used as key input in ensuring that a risk review activity is triggered both at initial knowledge of the event and when the root cause has been identified. The risk management activities that follow such an event should:
虽然产品投诉、退货或者与病人安全相关事件是代表质量系统的某些元素失败的滞后指标,但它们应该作为确保 风险评估活动在两种情况下被触发的主要输入，即在事件发生的初始阶段和根本原因被确认时。接着这种事件 的风险管理活动应该包括以下内容：

- Determine controls to immediately protect the patients who may have been exposed to the defective product.
•确定控制措施，以及时保护可能已经暴露于有缺陷产品下的患者。

- Evaluate impact to other lots of product that may be available in the market.
•评估对其他市场上可能用到批号的产品的影响。

- Evaluate whether the risk is common to similar products or activities.
•评估风险在类似的产品或活动中是否普遍。

- Use information from the root cause analysis to identify controls that should be established to prevent recurrence.
•利用对根本原因分析的信息来识别控制措施,并应建立防止再次发生的控制措施。

4.5.1.3 Data Trends
4.5.1.3 数据趋势

The regulatory requirement for process monitoring and annual reporting provides an opportunity for continual improvement. This has been codified in the guidance and statements on Process Validation by regulatory authorities. Concurrent with this process, when unexpected data trends are detected a proactive response is not only necessary but also a wise business practice. A risk assessment and risk control strategy is useful to troubleshoot and identify any new or modified process controls necessary for remediation.
过程监控的监管要求和年度报告为持续改进提供了一个机会。这被监管当局编写到指南和工艺验证的声明中。与工艺要求一样，当意想不到的数据趋势被发现时，积极的响应不仅必要,而且是一个明智的商业惯例。风险评 估和风险控制策略在诊断和识别过程控制方面是有用的，即修复所必需的任何新的或改善的过程控制。

4.5.1.4 Change Control
4.5.1.4 变更控制

Continual improvement via effective changes to our processes is a key element of the PQS. Changes are inevitable and a part of the lifecycle of a product from initial development through marketing to divesture。 A best practice is to develop the risk assessment early in development and transition to the next lifecycle phase with appropriate updates. The risk assessment then becomes a powerful knowledge management tool that is kept alive throughout the life of the product.
通过有效的变更来对我们的工艺进行持续改善是 PQS 的一个关键元素。变更是不可避免的,是一个产品从最初 开发到进入市场到退市整个生命周期的一部分。最好的操作方式是在开发早期引入风险评估，并在转移到下一 个生命周期阶段时作适当地更新。然后风险评估将成为一个强大的知识管理工具，可以使产品在整个生命周期 中保持活力。
For existing processes, a risk assessment provides value in the management of ongoing operational risks, and can be created retrospectively after validation. These assessments have the added benefit of being built from historical data and real experience as data-based inputs into the process.
对于现有的工艺，风险评估在管理现行的操作风险方面提供价值，并可以在验证后建立回顾性审核。这些评估 可以基于历史数据和实际经验的建立来增加价值,即将实际经验用数据的形式输入到工艺流程中。

Once the process is qualified, the process transitions to one of continuous verification and improvement. Changes are implemented with the intent to improve and evolve into more robust processes. For each change it is important to assess the process and determine the following:
一旦工艺验证合格，工艺转移到下一步的持续验证和改善活动中。变更作为提高和演变成更稳定的工艺的目的 被执行。对于每一个变更，评估工艺是很重要的，并需确定以下内容：

- Does the change introduce a new risk or change the profile of an existing risk?

•变更是否引入新的风险或改变现有风险的概况？

- Are there sufficient controls in place with the implementation of the change or do new controls need to be introduced?

•变更的实施是否有有效地控制措施或是否需要引入新的控制措施？

- Does the change eliminate or reduce the effectiveness of existing controls?

•变更是否消除或减少现有控制措施的有效性？

- Does the change impact the validated state of the equipment or process?

•变更是否影响设备或工艺的验证状态？

Assessment of changes and review of the risk assessment should be an integrated part of the change control process throughout the product lifecycle.
在整个产品生命周期中评估变更和审查风险评估应该是综合变更控制过程的一部分。

4.5.1.5 Audits and Inspections
4.5.1.5 审计和检查

Audits, internally or externally driven, provide an opportunity for an outside and independent assessment of the Quality System and compliance with regulatory requirements.It is also an excellent time to assess the completeness of risk management activities (and documents, if applicable), and identify any potential gaps that could lead to potential audit or inspection observations.When challenged, the risk assessment would be an excellent tool to demonstrate that sufficient controls are in place and that the risks associated with the gaps are acceptable.Conversely, audits and inspections may identify a new or previously unrecognized hazard that needs to be addressed.Again, the risk assessment can be used as a tool to systematically address the observation and required controls. Potential regulatory commitments will be focused only on the hazard and required controls, avoiding unnecessary and excessive non-value work.
审计,由内部或外部驱动的,提供了一个外部的机会来独立地评估质量体系是否符合监管要求。这也是一个很好 的机会来评估风险管理活动(和文件,如适用)的完整性,并识别任何可能导致潜在的审计或检查观察的潜在漏洞,。当受到挑战时,风险评估将是一个很好的工具来证明已有足够的控制措施而且相关的风险缺口是可以接受的。相 反,审计和检查可能会识别出一个新的或以前未识别的风险,需要解决。同样的,可以使用风险评估作为一种工 具来系统地论述观测到的情况及所需的控制措施。潜在的监管承诺将只关注风险和所需的控制措施,避免不必要 的和过度的没有价值的工作。

Some caution should be taken when committing to doing risk assessments in response to audit or inspection observations. QRM is not a substitute for good science and data. A risk assessment should never be used to deviate from regulations, justify bad practices, or defend practices that need to be corrected. Compliance with current Good Manufacturing Practices (cGMPs) is a mandate. Risk assessments provide the tools to proactively align with clear regulatory expectations and industry standards, and appropriately direct / prioritize efforts and resources based on impact of the risks.
在对审计或检查观察做出回应时，提交风险评估应采取谨慎应对的方式。QRM 并不能代替良好的科学和数据。 风险评估不应该被用于偏离法规,证明不良操作,或保护需要纠正的操作。符合现行良好生产质量管理规范
(cGMPs)是强制性的要求。风险评估为主动结合明确的监管期望和行业标准提供工具，并根据风险的影响，适当 直接地/优先地安排努力方向和资源。

Additionally, regulatory intelligence is important to identify， new and emerging regulations. It can also serve to identify observations and gaps found at other facilities that may be similar to one's own operations. Use of these external triggers is another proactive way to update risk assessments and avoid unnecessary regulatory observations.
此外，识别新的和新出现的法规监管情报是很重要的。它也可以通过识别可能类似于自己操作的其他公司的检查 结果和差距来获得。利用这些外部的触发事件是另一个更新风险评估和避免不必要的监管检查的积极方式。

4.5.2 Scheduled Reviews
4.5.2 计划性审核

Periodic, scheduled reviews provide another mechanism for integrating QRM into the PQS, operations and supporting business processes. Worldwide, several regulatory agencies require a periodic review of processes, systems, and operations. The principle is that some review and assessment is required periodically to ensure that these systems remain in a validated state (e.g. , facilities， equipment, and processes). Additionally, Annual Product Reviews / Product Quality Reviews are a regulatory expectation. Incorporating a review of the corresponding risks assessments and risk control strategies in these reviews provides efficiencies, a more effective review process, and ensures ongoing risk management. Furthermore, the frequency of these reviews may be varied and established based upon the level of risk and the product lifecycle

phase. The early lifecycle phase may require more frequent reviews of data gathered after launch of the commercial process in comparison to a mature process.
定期的计划性审核为将 QRM 融入到 PQS、操作流程和支持性业务流程提供另一种机制。在世界范围内，几个监 管机构要求定期审核工艺、系统和操作规程。原理是某些检查和评估需要定期进行，以确保这些系统仍然处于验 证状态(例如：设施、设备和工艺)。此外，产品年度审核/产品质量评估是一个监管的预期。将相应的风险评估和 风险控制策略的回顾整合到这些回顾当中提高了效率，以一种更有效的工艺审核形式，确保持续的风险管理。此 外，这些回顾的频率可以是不同的，并可以基于风险的级别和产品生命周期的阶段来定。与成熟的生产工艺阶段 相比，生命周期的早期阶段即开始商业化生产之后可能需要更频繁的回顾数据。

4.6 Risk Communication
4.6 风险沟通

Risk communication is the sharing of information about risk and risk management between the decision makers and other stakeholders. Effective communication through the correct vehicle and means enables effective risk management decision-making.
风险沟通指风险和风险管理的信息在决策者和其他利益相关者之间进行分享。通过正确的工具和手段的有效沟 通可以令风险管理决策流程有效地运行。

Communication of the exact systems, processes, individual and collective roles and responsibilities should be clear; systematic, disciplined, methodical, and timely conveyance of information is imperative. Equally, the processes and exercise of communications should be effective and an essential component， bridging each step of QRM. Effective communication in this context permits rational, factual , and science-based decision-making, permitting an organization to take the appropriate actions commensurate with the evaluated risk.
确定系统、流程、个人和集体在沟通中的角色和职责应该是清晰的；系统的、自律的，有条理的和及时传达的信 息是必要的。同样的，沟通的过程和活动应该是有效的，是将 QRM 的每一步拼接起来的重要组成部分。在这种 情况下有效的沟通允许合理的、基于事实的和以科学为基础的决策，允许组织采取与风险评估工作同样重要的适 当行为。

Communication activities are recognized as fundamentally important to the risk management process outlined in the ISO Risk Management Standard, ISO 31000(21). This is underlined by the recognition that a high performance in risk management activities is associated with organizations that have a high level of regard for continual and timely communications with external and internal stakeholders(21).
ISO 风险管理标准,ISO 31000(21)中列出的风险管理流程，交流活动被公认是风险管理中最重要的。大家都承认， 在风险管理活动中有高执行力的组织机构，在与内部和外部利益相关者的持续和及时的沟通也是高水平的(21)。

The communication of responsibilities, information, activities and data is implicit in ICH Q9, which defines risk communication as "the sharing of information about risk and risk management between the decision makers and others." (2) It is considered to be the exchange of information about risk and its management. It can be regarded as a two-way process in which properly informed decisions can be made about the level of risks and the need for risk control against properly established and comprehensive risk criteria(21). Ultimately risk communication should culminate in decisions and disclosure of residual risks.
沟通的责任、信息、活动和数据隐含在 ICH Q9 中，其对风险沟通的定义是“在决策者和其他利益相关方之间共 享风险和风险管理的信息。”(2)这一句话被认为是风险及其管理信息的相互交换。风险沟通可被看作是一个双 向过程,正确明智的决定取决于对风险水平的分级和制定风险控制措施的必要性，即根据之前已建立的全面风险 标准得出的控制措施(21)。最终的风险沟通应该在做出决策和揭开残余风险时达到最高潮。

ICH Q9 does not give definitive description for how risk communications should be executed， but does recognize that "parties can communicate at any stage of the [quality] risk management process" and that "the output / result of the QRM process should be appropriately communicated and documented. "(2) It is imperative that risk communication begins during the early phases of development in order to design products and processes with inherent safety features embedded in the product's design. ICH Q9 provides some examples of originators, recipients and stakeholders, and states that the information that might be communicated might relate to the “existence，nature, form, probability，severity, acceptability, control, treatment， detectability， or other aspects" of risks to quality (2).
ICH Q9 并没有明确地描述应该如何执行风险沟通,但认识到“相关方可以在【质量】风险管理过程的任何阶段进 行沟通”,和“QRM 过程的输出/结果应该被适当地传达和记录”。（2)风险沟通最好在研究的早期阶段就开始,以达 到在产品和工艺的设计阶段将固有的安全特性嵌入到产品设计中。ICH Q9 为发起者,接受者和利益相关者提供 了一些例子，并说到需要沟通的信息可以包括风险质量的“存在情况、本质、形式、概率、严重性、可接受性、 可控制性、处理方式、可检测性,或其他方面”（2)。

4.6.1 Essential Elements of Risk Communication 4.6.1 风

险沟通的重要因素

There is probably no single vehicle or mode of communication sufficient to cover all communication requirements throughout the QRM process. Similarly, there is no single tool， process or technique that mitigates inherent human bias associated with communication. Quality System elements (as defined in ICH Q10) and QRM documentation (as defined by ICH Q9) should operate in concert to ensure that all information between each step is exchanged expediently, ensuring minimal human bias and no gaps or miscommunication leading to an erroneous decision. An effective QRM program should clearly document and inform all stakeholders and their management of their individual and collective responsibilities.
可能没有单一的媒介或沟通方式足以涵盖整个 QRM 过程所有沟通的需求。同样的,没有单一的工具、过程或技 术可以减轻相关沟通中人类固有的偏见。质量体系元素(正如 ICH Q10 中定义的)和质量风险管理 QRM 文档(正 如 ICH Q9 中定义的)应该协同操作，以确保每一步的所有信息被方便地交换,确保最低限度的人类偏见和没有差 距或误解导致一个错误的决定。一个有效的 QRM 程序应该清楚地记录并告知所有的利益相关者他们管理下的 个人和集体的责任。

The risk register provides a mechanism to drive periodic review of risks and can ensure that the content is reappraised as an essential vehicle for sustaining risk communication. Any scheduled risk review cycles and non-scheduled event triggers for risk review (see Section 4.5， Risk Review) should be clearly established within the Quality System and appropriately communicated as part of QRM activities to ensure timely administration of these activities. Risk communication should also include the incorporation of salient information, risk assessment output and decisions into the management review processes and schedules. See Table 4.5.1-1 for a summary of essential communication elements to describe the processes and responsibilities within a QRM program.
风险注册为驱动定期的风险检查提供了一种机制,并可以确保其内容作为维持风险沟通必不可少的工具得到了 重新的评估。任何计划好的风险审查周期和触发风险评估的非正常事件（参见 4.5 节：风险审查)应该在质量体 系中明确规定并适当地沟通，将其作为 QRM 活动的一部分，以确保及时管理这些活动。风险沟通应该还包括 将突出信息、风险评估结果和决策整合到风险审核流程管理和时间表中。详见表 4.5.1-1 在 QRM 程序中描述流 程和责任的重要沟通元素的总结。

Table 4.6.1.1 Summary of Essential Information Conveyed to Ensure an Effective and Sustainable QRM Program 表 4.6.1.1 确保有效和可持续的 QRM 程序需传送的重要信息总结

QRM process Step QRM过程的步骤	Information Conveyed 需传递的信息	Information Recipient 信息接收方	Purpose 目的
Risk Management Initiation 风险管理的发起阶段	• Owner of the QRM process •QRM过程的所有者 • Description of the product or process type •描述产品或工艺的类型 • Who makes resources available •谁提供资源 • Stakeholders •利益相关者 • Who makes decisions •谁做决策 • Who monitors process •谁监控过程 • Plan • 计划 • Scope •范围 • Assumptions •假定条件 • Methods • 方法	• Stakeholders • 利益相关者 • Decision makers • 决策 者 • Risk assessment Participants •风险评估参与者 • Originators of information for risk assessment •风险评估信息的 发起者	• Ensure the right problem statement and scope are identified. 保正确的描述 问题和识别的范 围 • Ensure best use of resources in conducting risk management. This includes but is not limited to: 确保在执行风险 管理时最好地利 用资源。这包括 但不限于以下内 容 Set expectations 制定预期目标 Define roles/responsibilities 定义角色/职责 Ensure preparation activities are executed 确保预备的活动被执行 Ensure personnel are adequately trained 确保人员受到充分地培训 Gather data 收集数据 Ensure QRM process is executed 确保 QRM 流程被执行
Risk Assessment 风险评估	• Description of the risk identification, risk analysis and risk evaluation tools. •描述风险识别，风 险分析和风险评估的 工具 •Means of assembling background information and/or data on the potential hazard, harm ， or human impact relevant to the risk assessment. This may include background information from related products.	• Risk assessment participants •风险评估的参与者 • Originators of information for risk assessment •风险评估的原始信息	•The systematic application of tools and techniques to make obj ective，data driven assessment and record the assessment. •系统运用工具和技术来做客观、基于数据的评估，并记录评估过程。 • Ensure decision makers are advised and make decisions. •确保决策者被建议并做决策。

QRM process Step QRM过程的步骤	Information Conveyed 需传递的信息	Information Recipient 信息接收方	Purpose 目的
	•收集关于风险评估的潜在危险、危害，或者对人类的影响等 的背景信息和/数据。 包括相关产品的背景 信息。 • Titles, roles and areas of expertise of the assessment team. •评估小组专家的专长，角色和区域 • Who defines competencies and competent personnel. •谁定义胜任的条件和胜任的人选 • Criteria for categorizing risk • 风险分类的标准 •Means of communication of the risk analysis output. •风险分析结果的沟通方式		
Risk Control 风险控制	•Alternative means for controlling risk. •风险控制可选择的方式 •Balance between risk reduction cost and the benefit/ magnitude in risk reduction. •平衡风险减少的费用和风险减少的利益/量级这两方面 • Reduction plan, acceptance decision, justification, residual risk profile. •减少风险的计划，可接受的决策，理由，残余风险的概况	• Stakeholders •利益相关者 • Decision makers •决策者 • Other relevant management •其他相关的管理方	•To ensure that stakeholders understand how risks are reduced or controlled to an acceptable level. •确保利益相关者理 解如何减少风险或控 制到一个可接受的水 平 • To ensure reductions are implemented and to enable informed decision-making. •确保减少风险的措施被执行并已通知决策者
Risk Review 风险审核	•Frequency of planned/ scheduled review. •计划/日常风险审核的频率 •Triggers for initiating repeat risk analysis. •启动再次风险分析的事件 •Means of communication of	• Stakeholders •利益相关者 • Decision makers •决策者 • Risk assessment participants •风险评估的参与者 • Originators of information for risk assessment •风险评估的启动信	• Ensure that a lifecycle approach is sustained and that all risk management activities are maintained in a state of currency. •确保维持生命周期法，所有的风险管理活动保持在现行版的状态

QRM process Step QRM过程的步骤	Information Conveyed 需传递的信息	Information Recipient 信息接收方	Purpose 目的
	the risk review. •风险审核沟通的方式	息	• Ensure risk profile has not changed based on monitoring of post-production data streams. • 根据监控前期产品的数据流确保风险概况没有发生改变

4.6.2 Difficulties with Risk Communication 4.6.2
风险沟通的困难

Risk perception， and the management of risk perception, plays a significant role during QRM activities. Risk perception issues can lead to subjectivity and uncertainty in the outcomes of QRM exercises, because, as ICH Q9 states， "each stakeholder might perceive different potential harms, place a different probability on each harm occurring and attribute different severities to each harm."(2)
风险感知和风险感知的管理在 QRM 活动中扮演着重要的角色。风险感知问题可能导致 QRM 操作过程中产生 主观的和不确定的结果，因为,正如 ICH Q9 所描述的,"每个利益相关者可能感知不同的潜在危害,对每个危害发 生的概率有不同的意见，对每个危害的严重性也有不同的意见。"(2)

Traditionally, communication has been behavioral in nature, driven by the individual, and dialoguebased; verbal communication therefore presents inherent opportunities for failure, and should not be overly relied upon when performing formal QRM activities. Furthermore, in the context of regulated environments, the communication of information throughout and along the QRM process should:
传统意义上,沟通行为是个体的自然行为，由个体发起、基于会话的形式；当执行 QRM 活动时，不应该过分地 依赖口头交流，因为口头交流有导致交流失败的特性。此外,在监管环境的背景下，贯穿整个 QRM 过程中，信 息的沟通应该做到以下几点：

- Be clear and unambiguous.
- 是清晰和明确的。
- Be intuitive enough to avoid misunderstanding (heuristics).
- (启发式)足够的直观,以避免误解。
- Facilitate unbiased and objective risk analysis and evaluation.
- 促进公正和客观的风险分析和评估。
- Convey the appropriate amount of detail and content to facilitate its purpose.
- 传达适当数量的细节和内容,以促进其目的。
- Possess defined and recognizable originator and recipient(s).
- 具有定义好和可识别的发起者和接收者(们)。
- Be traceable and auditable based upon GMP expectations.
- 根据 GMP 的要求，具有可追溯性和可审计性。
- Permit recipients to execute their responsibilities and duties.
- 允许接收者们执行他们的责任和义务。
- Ensure preservation of institutionalized knowledge.
- 确保保留制度化的内容。

ISO 31000 states that confidence in the determination of the level of risk and its sensitivity to preconditions and assumptions should be considered in the analysis and communicated effectively to decision makers and, as appropriate, other stakeholders(21). It is imperative that the correct decision makers and stakeholders are informed to be fully aware of any insensitivity or bias of the risk assessment process. Risk perception is an important issue acknowledged in ICH Q9, which may result in stakeholders perceiving different origins of risk, levels of harm, probabilities of occurrence, and severities. ISO 14971, which sets out risk management activities for the design and manufacture of medical devices, also recognizes that different views，

opinions， and values associated with probability of occurrence, and severity (i.e. , risk perception) have the potential to bias, and should be taken into account especially when deciding acceptability of risk (22).
ISO 31000 说到，决定风险水平及严重性的可信程度的前提条件和假设是，应考虑其分析能力并与决策者，如 适用的话，其他利益相关者进行有效的沟通(21)。重要的是正确的决策者和利益相关者被告知要充分认识到任何 不敏感或偏见的风险评估过程。感知风险在 ICH Q9 中是一个重要的观点，这可能可以让利益相关者感知不同 来源的风险，危害的水平，发生的概率和严重性。ISO 14971,它为医疗设备的设计和制造制定了风险管理活动，也 认识到不同的观点、评论和价值观，与风险发生概率和严重性（例如：风险感知）的评估有潜在偏见的影响， 因此当做风险接受性决定时，特别需要将这种偏见考虑在内。

5.0 How To Use Quality Risk Management As An Enabler 如何将质量风险管理作为推动力使用

QRM is most valuable when fully integrated into the product lifecycle and its supporting systems (2). QRM should be applied throughout the supply chain for a product from raw materials through manufacturing, release, distribution, and delivery to the patient. Effective integration of QRM provides improved decision-making based on sound science for the entire Quality System and enables continual improvement of Quality System processes such as:
当质量风险管理完全融入产品生命周期及其支持系统中时最有价值。质量风险管理应该应用于从原料经过生产、 放行、分销和然后交付患者使用的整个产品的供应链中。质量风险管理的有效融合为整个质量系统提供了基于 完全科学的改进的决策并推动质量系统流程如下方面的持续改进：
• Quality System Elements (e.g., documentation, training, quality defects, auditing, periodic review, change control, continual improvement)
质量系统要素（如文件、培训、质量缺陷、审计、定期回顾、变更控制、持续改进）
• Product Design and Development (e.g. , Quality by Design, process validation, continual improvement activities, documentation of product and process knowledge)
产品设计和开发（如质量源于设计、工艺验证、持续改进活动、产品和工艺知识文件）
• Facilities, utilities, and equipment (e.g., design of facilities / equipment, housekeeping, qualification of facility / equipment/utilities， cleaning of equipment and environmental control, calibration /preventive maintenance)
厂房、设施和设备（如厂房/设备的设计、厂房/设备/设施的确认、设备清洁和环境控制、校验/预防性维修）
• Materials management (e.g., assessment of suppliers and contract manufacturers, starting materials, storage, logistics, and distribution conditions)
物料管理（如供应商和合同生产商的评估、起始原料、储存、物流和分发条件）
• Production (e.g., validation, in-process sampling and testing, production planning)
生产（如验证、过程取样和测试、生产计划）
• Laboratory control and stability studies (e.g., out-of-specification results, periodic retesting)
实验室控制和稳定性研究（如超标结果、定期复验）
• Packaging and labeling (e.g., design of packages, selection of container closure system, label control, instructions for use (IFU), medication guide, Risk Evaluation and Mitigation Strategy [REMS])
包装和贴标(如包装设计、容器密闭系统的选择、标签控制、使用说明书、用药指南、风险评估和降低策略[REMS]。
Many processes already incorporate a risk-based approach that is inherent in the process principles. Other processes can gain from the addition of proper application of QRM. In each case, application of risk management activities that are relevant to the type and level of risk inherent in each process will enable product realization, establish and maintain a state of control, and facilitate process improvement.
许多工艺本身就已经整合了基于风险的方法。其他工艺可以从另外的质量风险管理合理应用中获益。在不同情 况下，与每个工艺本身风险的类型和水平相关的风险管理活动的实施将推动产品实现、建立和维护控制状态并 促进工艺改进。

5.1 QRM Application during Process Validation Lifecycle 质量风险管理在工艺验 证生命周期中的应用

The FDA guidance entitled process validation: General Principles and Practices embraces international harmonized guidance published in ICH Q7, ICH Q8 (R2), ICH Q9, and ICH Q10. FDA's guidance proposes a three stage lifecycle approach to Process Validation (23):
FDA 发布了题为“工艺验证：一般原则和实施方法”的指导原则，其中包含了 ICHQ7、ICHQ8(R2)、ICHQ9 和 ICHQ10 的内容。FDA 的指导原则提出了工艺验证生命周期三阶段的方法（23）：
1. Process Design 工艺设计
2. Process Qualification 工艺确认
3. Continued Process Verification 持续工艺验证
Though this terminology is specific to this guidance document, the lifecycle concept is generally accepted worldwide by regulatory agencies. It advocates for more emphasis on process development, defining process boundaries, and better use of statistical tools to monitor and assess process performance. As defined in the guidance, process validation is "*the collection and evaluation of data， from the process design stage*

through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality products.' QRM provides the tool to define what really is critical to patient safety and product quality, gain process knowledge and understanding throughout the product lifecycle, and focus resources. As discussed in Section 5. 1.4, QRM Applied to Stage 3 Continued Process Verification, validation strategies have historically incorporated elements of risk, recognized or not.

尽管这个术语专属于本指导性文件，但是生命周期的理念普遍被世界各地的法规部门所接受。该指导原则提倡 更加强调工艺开发、确定工艺边界点和在工艺性能监测和评价中更好的应用统计学工具。在本指导原则中工艺 验证被定义为"用于建立科学的可以证明工艺能够持续地生产出符合质量要求的产品的证据的来自工艺设计阶 段到工业化生产阶段的数据的收集和评估"。质量风险管理提供工具去确定什么是对于患者安全和产品质量是 真正关键的，在整个产品生命周期中获取工艺知识和工艺理解并集中资源（在关键点上）。如在 5.1.4 节中讨论 的一样，质量风险管理应用于第三阶段持续的工艺验证，验证策略已经历史性地整合了意识到或未意识到的风 险的要素。

5.1.1 Quality Risk Management Applied to Stage 1 Process Design 质量风险管理应 用于第一阶段工艺设计中

Every manufacturing process begins in a developmental mode during which the system/ equipment design and process parameters are examined. The objective of process development is to define the commercial process that will consistently deliver a safe and efficacious drug product. The outputs are the master production and control records and a control strategy that will ensure product is consistently produced to meet all of its required quality attributes.

每个生产工艺都开始于开发模式，在这个期间应该检查系统和设备设计及工艺参数。工艺开发的目标是确定能 够持续生产出安全和有效的药品的工业化生产工艺。其输出是主生产和控制记录以及一个可以确保产品能始终 产生符合所有其需要的质量属性的控制策略。

The first step in the process is to define the Quality Target Product Profile (QTPP) (3). An early risk assessment is instrumental in defining the product with respect to its potential CQAs and the acceptable ranges for those attributes that provide targets for process design and optimization.

该过程的第一步是确定质量目标产品概况（QTPP) (3)。早期的风险评估有助于确立可以为工艺设计和优化提供目标的产品潜在的关键质量属性（CQAs)及其可接受的范围。

Based on this assessment, effective and efficient developmental studies (e.g., Design of Experiments) can be executed to develop knowledge regarding the process boundaries and estimate the likelihood of process failures. These risks can either be removed by design or reduced through processing controls. Based on these experiments， CPPs and their ranges are defined to ensure CQAs are maintained within appropriate limits. This information is then used to update the risk assessment and finalize the CQAs and CPPs that define the commercial process. The control strategy provides the rationale and blueprint for ensuring process control and how each lot will conform to these CPPs and CQAs.

基于此评估，有效和高效的开发研究（如实验设计）能够实施用来开发关于工艺边界的知识和用来判断工艺失 败的可能性。这些风险不仅可以通过设计移除，也可以通过工艺过程控制来降低。基于这些实验，关键工艺参 数及范围被确定用来确保关键质量属性维持在适当的限度内。然后这些信息用来更新风险评估并最终确定工业 化生产工艺的关键质量属性和关键工艺参数。控制策略为确保工艺控制和每个批次如何能符合这些关键工艺参 数和关键质量属性提供基本原理和蓝图。

Development is customarily performed on a small scale so the transition to commercial operations may not be predictable. Uncertainties and risks such as variability associated with commercial quantities of raw materials and components, mixing and heat transfer may occur during scale-up(23).These risks can be better understood and reduced by developmental studies but never fully eliminated. Prior knowledge and engineering principles can increase our understanding of scale-up and reduce these risks.

工艺开发通常小规模地开展所以向工业化大生产转移可能是无法预测的。不确定性和风险如与原料和辅料的工 业化数量、混合和热交换相关的变化可能在工艺放大阶段出现。这些风险可以通过工艺开发研究被更好的理解 和降低但无法彻底消除。已有知识和工程学原理可以增加我们对工艺放大的理解并降低这些风险。

Risk management tools such as a process FMEA, risk ranking and filtering, decision trees, or Ishikawa diagrams may be useful to assess these potential uncertainties and their effect on product quality. An FMEA can help the team make the most optimal decisions about where and what controls are necessary to reduce risks. It also helps the team understand the residual risks that are acceptable and that cannot be eliminated.

风险管理工具如工艺失效模式与影响分析、风险排序和筛选、决策树或鱼骨图对于评估这些潜在的不确定性及 其对产品质量的影响是有用的。失效模式和影响分析可以帮助团队作出为了降低风险在哪里用哪些控制措施是 有必要的最优决策。也可以帮助团队理解残留风险可以被接受但不能被消除。

5.1.2 Quality Risk Management Applied to Stage 2 Process Qualification 质量风险管理应用于第二阶段工艺确认

According to the FDA guidance, Stage 2 Process Qualification is the step where the process design is evaluated to confirm whether the process is robust and suitable for commercial processing. QRM has a critical role in the evaluation, which encompasses two elements:

遵照 FDA 指导文件，第二阶段工艺确认是工艺设计被评估来确认工艺是否针对工业化大生产工艺耐用和稳定的 步骤。质量风险管理在评估中起到关键作用，包含两个要素：

1. Qualification of the facility design, utilities and equipment 厂房设计、设施和设备的确认
2. Process Performance Qualification (PPQ) 工艺性能确认

During the execution of utility and equipment qualification, QRM may be used to assist in differentiating criticality and achieving efficiencies by eliminating redundant or non-value added testing. The extent and scope of testing and documentation during qualification should be appropriate and commensurate with the level of risk (See Section 5.2, QRM Application during Facilities, Manufacturing and Control Systems Lifecycle).

在设施设备确认的实施过程中，质量风险管理可以用来帮助区分关键性和通过消除多余或不增加价值的测试赢 得效率。测试的程度和范围和确认过程中的文件应当适当并与存在的风险水平相适应。（见 5.2 节，质量风险 管理应用于厂房、生产和控制系统的生命周期中）

ASTM E2500-007 provides guidance on a risk-based approach to commissioning and qualification activities, designated as verification (24). Per the guidance, risks to product quality and patient safety should govern the scope and extent of verification activities for manufacturing systems. SMEs have the responsible for these verification activities; ownership is not just defined organizationally. Verification activities are defined initially and updated throughout the system lifecycle to assure robust manufacturing controls.

ASTM E2500-007 为将运行和确认活动定为验证基于风险的方法提供指导。按照这个指导文件，产品质量和患 者安全的风险决定了生产系统的验证活动的范围和程度。相关领域的专家负责这些验证活动；业主不仅仅是组 织意义上的的定义。验证活动首先被定义并在整个系统生命周期中不断更新来保证稳健的生产控制。

Subsequent to utilities and equipment qualification, Process Performance Qualification (PPQ), formerly known as process validation, should be performed. PPQ covers the initial demonstration of process / product performance and again incorporates the principles and practices of QRM.

继设施和设备确认之后，以前被称之为工艺验证的工艺性能确认（PPQ)应当被实施。工艺性能确认既包含了 工艺和产品性能的最初证明，又整合了质量风险管理的基本原则和方法。

The control strategy and previous process risk assessments serve as inputs for determining the scope and required number of batches for PPQ. However, it should be noted that some Health Authorities still require three consecutive batches for each drug product image, independent of process understanding, development activities, or risk assessments.

控制策略和以前的工艺风险评估充当确定工艺性能确认的范围和需要批数的输入条件。然而，应该注意的是一 些卫生当局仍然要求每个药品工艺做三个连续批次，并不受工艺理解、工艺开发活动或风险评估支配。

PPQ deliverables include the validation protocol and the validation report. Analytical testing, in-process monitoring, and demonstration of critical process controls should be linked to the process risk assessment. PPQ provides the opportunity to verify that controls are effective and process CPPs and product CQAs will be consistently met.

工艺性能确认的交付物包括了验证方案和验证报告。分析检验、过程监控和关键工艺控制的证明应该与工艺风 险评估相关联。工艺性能确认提供机会去证明控制是有效的，工艺关键工艺参数和产品关键质量属性将始终如 一地符合。

Many protocols contain "worst case" scenarios (e.g., hold times, microbial control) in order to learn more about the limits of the process so that risks can be better predicted and reduced by implementing proper controls. PPQ activities may include increased sampling frequency over routine sampling requirements. Multiple samples are typically taken across the manufacturing lot to demonstrate intra-lot consistency. Additionally, the protocol may include criteria for acceptance of the process that are more stringent than the product release criteria. Examples of this practice include content uniformity during blending, mixing and filling, and weight control during compression and filling. The rationale is demonstration that tighter than minimally required values during the PPQ effort, reduces risk in route operations.

为了获悉更多关于工艺限度的信息很多方案中都包含了 “最差条件”的场景（如存放时限、微生物控制）以便 能够更好的预测风险并通过实施适当控制降低风险。工艺性能确认活动可以包含超过日常取样需求增加取样频 率。为了证明批间一致性多次取样常常选择在大生产中进行。此外，方案中也可以包含严于产品放行标准的工 艺可接受的标准。实践的例子包括混合、配料和填充中的含量均匀度和压片和填充过程中的重量控制。基本原 理是证明在工艺性能确认阶段比最低限度要求值更严则在日常生产中就能降低风险。

5.1.3 Quality Risk Management Applied to Sterilization and Cleaning Validation

质量风险管理应用于灭菌和清洁验证

During Stage 2, other processes are qualified including sterilization and cleaning. Both processes include application of risk management principles with respect to validation study design and testing. Many sampling regimens for sterilization are designed to examine areas of the equipment or batch that represent potentially "worst case" scenarios. Typically, penetration thermocouples and biological indicators are placed in the coldest locations during the sterilization studies. Also, biological indicators utilize organisms that are the most resistant and most likely to

survive the specific sterilization process that is being challenged. Use of these resistant biological indicators as "worst case" surrogates for process bioburden is incorporated into the design of the sterilization process. Demonstrating their inactivation during PQ essentially reduces the risk of bioburden survival during routine sterilizations of the equipment， provided that the same operating conditions are maintained.
灭菌和清洁过程等其他工艺过程在第二阶段进行确认。这两个工艺过程都包含了风险管理基本原则关于验证研 究设计和测试方面的应用。灭菌的许多取样规则都被设计用在设备的检查区域或代表潜在“最差条件”情景的 批次。通常在灭菌工艺研究中渗透热电偶和生物指示剂都被放置在最冷点。另外，生物指示剂需要使用在挑战 的特定的灭菌工艺中最有抗性和最有可能存活的微生物。替代工艺生物负载作为“最差条件”的这些抗性的生 物指示剂的使用是灭菌工艺设计的一部分。在工艺确认中证明生物指示剂可以失活实质上降低了生物负载在提 供相同操作条件的设备日常灭菌过程中存活的风险。
Sampling regimens and locations selected for cleaning validation can also be risk-based with respect to identifying area that pose a higher risk for residue carry-over after cleaning. Locations selected for PQ sampling are locations that are at high risk for process residuals to accumulate (i.e., "worst case" locations that are the most difficult to clean and dry in the processing equipment). Criteria for site selection can also be expanded to include detection and the likelihood that process residues will be detected by routine visual inspections. One may improve detection via use of boroscopes, cameras, viewing mirrors, or disassembling the equipment where feasible (e.g., piping elbows and transfer panels). Consideration of both the probability of residue soil accumulation and the likelihood of detecting it on routine inspection will help to focus resources on sampling areas that pose the greatest risk to residual carryover. Finally, one could also include the concept of severity in this assessment by considering the toxicity/potency of the drug product. For highly potent compounds, more sample locations may be selected for testing, particularly those of moderate risk for product accumulation and limited visibility during routine inspection.
清洁验证中选择的取样规则和取样点也可以基于风险选择相对于清洁后残留物残留风险最高的标识区域。性能 确认取样点应该是工艺残留物积聚风险最高的点（如工艺设备中最难清洁和最难干燥的“最差条件”点）取样 点选择的标准也可以扩大至包括可检测性和工艺残留物在日常目视检查中被监测到的可能性。提高可检测性的 方法之一是通过使用内孔表面检测仪、照相机、观察镜或可拆卸设备拆开检查（如管道弯头和转换板）。在日 常检查中残留物积聚可能性和检测可能性的考虑将帮助集中资源在形成残留风险最大的区域取样。最后，在评 估中可以通过考虑药品的毒性和生物活性来考虑严重性。对于高活性的化合物，可以选择更多的取样点监测， 尤其那些产品积聚中度风险和日常检查中视线受限的区域。
Prior to qualification, emphasis should always be to reduce the risks of residue carryover through process design. Clean-In-Place (CIP) systems should be considered versus manual cleaning processes. If there are areas in the piping system where water or residues can accumulate and cannot be thoroughly removed by flushing (dead legs), design and piping changes should be made to remove them from the system. Risk is best managed through elimination in process design; increased sampling should not be the operative control for poor design.
在确认之前，重点应该是通过工艺设计来降低残留物风险。相对手工清洗过程在线清洁系统（CIP)应该优先 考虑。如果在管路系统中存在水或残留物积聚完全不能通过冲洗去除的地方（盲端），应该通过设计和更改管 路避免。风险最好在工艺设计阶段就消除，增加取样不应当作为不好的设计的有效的控制。

5.1.4 Quality Risk Management Applied to Stage 3 Continued Process Verification

质量风险管理应用于第三阶段持续工艺验证

The longest segment of the product lifecycle is typically the commercial production phase. The goal of Continued Process Verification is to assure that a process remains in a state of control during this commercial phase. Once a process has gone through Process Qualification, an ongoing program should be established to collect and analyze product and process data that relate to product quality. The process risk assessment should be updated with the data from the PPQ, when necessary, and serve as an input to developing an on-going monitoring program.
产品生命周期中最长的阶段通常是工业化大生产阶段。持续工艺验证的目的就是保证工艺在大生产阶段处于受 控状态。一旦工艺通过了工艺确认就应该建立一个持续的项目去收集和分析产品质量相关的生产和工艺数据。 必要时，工艺风险评估应根据从工艺性能确认得到数据进行更新，并作为开发持续监控项目的依据。
Fundamental to process control is identifying the sources of variation, detecting this variation, understanding the impact of the variation, and then controlling variation in a manner commensurate with the risks it represents. Statistical tools such as Statistical Process Control (SPC), control charts, and multivariate analysis can be used to assess this process variation and monitor process performance. Subsequent to completing Process Qualification, heightened testing and sampling of process parameters and quality attributes is expected until statistically significant estimates of variability can be established. Statistical techniques are also used to identify trend limits, alert limits, action limits, and rejection limits; however, identification and response to these limits should also be based on a good understanding of risks and controls.
工艺控制的基本原理是识别变化的来源、检测变化、理解变化的影响，然后使用与其相关的风险相适应的方式 来控制变化。统计学工具如统计过程控制（SPC)、控制图和多变量分析可以被用来评估工艺变异和监控工艺 性能。继完成工艺确认后，在建立变异的统计学上显著评价之前加大对工艺参数和质量属性的检测和取样都是 被期待的。统计学技术也被用来确定趋势限、警戒限、行动限和拒绝放行限。然而这些限度的识别和响应也应 该基于对风险和控制的良好的理解。
Prior to the new guidance, process evaluations were generally limited to the Annual Product Review (US)/Product Quality Review (EU).

Additionally, periodic assessments of equipment， utilities, and other process systems were based on an organization's particular needs， risk threshold, and regulatory requirements (e.g., sterilization processes re-qualified at least annually, as a minimum). Depending upon process changes, criticality, and a firm's risk tolerance, the interval and the extent of the assessment (also called re-qualification or re-validation assessments) varied for these other systems. Under the new guidance, product reviews are more frequent with the expectation that controls are in place for more immediate actions. The goal is to detect and correct adverse process shifts sooner, before product quality is impacted.
在新的指导文件出台前，工艺评估普遍局限于年度质量回顾（美国）/产品质量回顾（欧盟）。此外，设备、设 施和其他工艺系统的定期评估以前都是基于其他机构特殊的要求。依赖于工艺变更、关键性和企业风险承受力， 这些系统的评估（也称作再确认或再验证评估）也是多样化的。在新的指导文件下，产品回顾更为频繁并期望 工艺控制是在线的即时行为。目的是更快的检测到错误并在产品质量受影响前及时纠正错误。
Monitoring of CPPs and CQAs would continue throughout the lifecycle as documented in the control strategy. However, process monitoring is intended to provide assurance that a process is operating in a validated state and is not solely dependent upon monitoring process parameters and attributes. The process risk assessment and process capability data are important inputs to determine the scope and frequency of monitoring. For example, parameters that are high risk due to their impact on product quality may have more frequent process monitoring than other parameters. Monitoring activities would also include facilities and equipment controls, the manufacturing environment, and critical utilities. Decisions related to within or between batch monitoring could be supported by understanding the level and scopes of risks. Process monitoring should also include identification of adverse trends, enhancing process knowledge and supporting process improvements. 关键工艺参数和关键质量属性将按照文件中的控制策略在整个生命周期中持续进行监控。然而工艺监控的目的 是保证工艺在验证状态下持续操作而不仅仅依赖于监控工艺参数和质量属性。工艺风险评估和工序能力数据是 确定监控范围和频率的重要依据。例如对产品质量影响高风险的参数比其他参数应有更频繁的工艺监控。监控 活动也将包括厂房和设备控制、生产环境和关键设施。对风险水平和范围的理解可为决定是在批次内还是批次 之间实施监控提供支持。工艺监控也应包括不良趋势的识别、优化工艺知识和支持工艺改进。
The data gathered during Stage 3 should be used to improve and optimize the process. When warranted, the knowledge gained should drive updates to risks assessment and the control strategy.
从第三阶段获取的数据应当用于改进和优化工艺。当被批准时，获取的知识应当去驱动更新风险评估和控制策
略。
System performance will always vary, but the overall goal in manufacturing should be to strive for excellence. Incorporating risk assessments and risk reviews into a firm's Quality System, business processes, whether event-based or scheduled, helps provide the mechanism to achieve this goal of manufacturing excellence.
系统性能总是变化的，但是生产的总体目标应该是力争卓越。不论是基于事件还是基于计划，将风险评估和风 险回顾融入进质量体系和商业过程中为实现生产卓越这一目标帮助提供了作用机制。

52 QRM Application during Facilities, Manufacturing and Control Systems Lifecycle 质量风险管理应用于厂房、生产和控制系统的生命周期中

As part of implementing a lifecycle strategy it is important to evolve from "evidence-based" compliance to include "science- and risk-based" compliance. This enables continual control and improvement through focus on those aspects of the manufacturing operations that are deemed critical for process control and product quality (24). QRM should be applied iteratively throughout the lifecycle of facilities, manufacturing, and control systems for the following activities:
作为实施生命周期策略的一部分从基于证据的法规符合性到包含了基于科学和风险的法规符合性的演变是重 要的。通过聚焦于生产操作中被认为对于工艺控制和产品质量关键的方面推动持续控制和改进。质量风险管理 应在厂房、生产和控制系统的整个生命周期中以下活动中应用：
- Facility， manufacturing and automated control systems planning, design, build, verification / qualification, maintain, and retire phases.
厂房、生产和自动控制系统规划、设计、建造、验证/确认、维护和退役阶段；
- Consideration of dedicated vs. multi-product risks and controls in designing facility, equipment, and cleaning validation.
单一品种和多品种风险和在设计厂房、设备和清洁验证上的控制方面的考虑；
- Development of equipment commissioning and qualification plans.
设备运行和确认计划的开发；
- Assurance of control of the qualified state and drive for continual improvement.

确认状态控制的保证和力求持续改进。

5.2.1 Lifecycle Strategy 生命周期策略

Risk assessments should be initiated as early as the planning phase during development of user requirements and should be revisited / updated during the design, build, test and routine operation phases to ensure that risks in the design and operation of a process or system are either eliminated (mainly during design) or reduced such that a continued state of control is maintained (See Figure 5.2.1-1). Roles and responsibilities should be clearly defined for system owners, manufacturing, engineering, and quality / validation leads to ensure appropriate risk-related decision-making throughout the lifecycle. 风险评估应该在用户需求的开发的规划阶段尽早开始，并在设计、建造、测试和日常操作阶段回顾和更新以确 保在工艺或系统设计和操作上的风险能够消除（主要在设计阶段）或降低从而保持一个连续的控制状态（见图

5.2.1)。系统业主、生产、工程和质量/验证部门的角色和职责应该清晰的定义以确保在整个生命周期中能够 做出合适的风险相关的决策。

Figure 5.2.1-1 Systems Lifecycle 图 5.2.1-1 系统生命周期

Figure 5H1 Systems Lifecycle

Plan

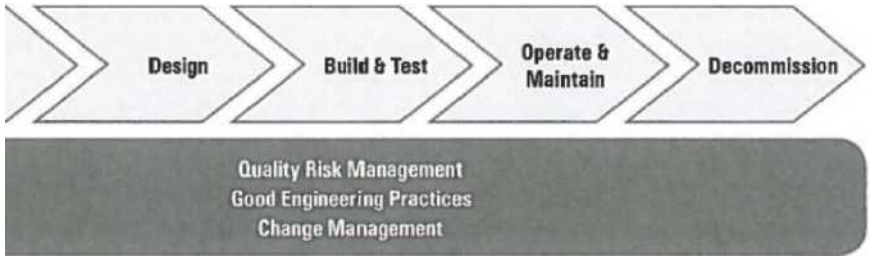


图 5.2.1-1 系统生命周期

计划	设计	建造和测试	操作和维修	停止运行
质量风险管理 良好的工程规范 变更控制				

During the early conceptual or planning phase of the lifecycle, risk assessments are mostly qualitative in nature. This initial risk assessment is typically applied to the development of User Requirement Specifications (URS). The objective of the risk assessment is to identify potential hazards that may need to be addressed during the design phase of the project. Performing risk assessments early in the lifecycle allows significant opportunities to design the system with appropriate controls such that risks can be eliminated or reduced to the lowest possible level.
在生命周期的早期概念或规划阶段，风险评估本质上是质量最高的。最初的风险评估一般都在用户需求说明书 的开发中应用。风险评估的目的是识别可以在项目的设计阶段就能够处理的潜在的危害。提早在生命周期中执 行风险评估意味着有更大的机会通过设计恰当的控制将系统的风险消除或降低至尽可能最低水平。

During the design phase of the project, both qualitative and semi-quantitative risk assessment approaches may be considered. As more information is developed by SMEs and stakeholders, the risk assessments can become more detailed. The objectives of risk assessments during design are to ensure the identification of risks directly related to critical aspects, to eliminate or reduce these risks to an acceptable level through system design, and to identify other procedural risk control mechanisms (e.g., operational SOPs, maintenance procedures). Design controls are preferred over procedural controls whenever feasible. It is important to ensure that the requirements specifications and requirements traceability matrix incorporate relevant controls for management of any identified potential risks to product CQAs and CPPs.
在项目的设计阶段，可以考虑使用定性和半定量的风险评估方法。一旦相关领域的专家和利益相关者发展了更 多信息，风险评估可以变得更详细。设计阶段的风险评估的目标是保证与关键方面直接相关的风险的识别，通 过系统设计消除风险或降低风险至可接受水平,并确定其他程序上的风险控制机制(如操作SOPs，维修程序）。 不论是否可行设计控制被认为比程序控制要更好。重要的是要将需求说明书和需求跟踪矩阵与管理识别出的与 产品关键质量属性和关键工艺参数相关的潜在风险相关的控制措施相结合。

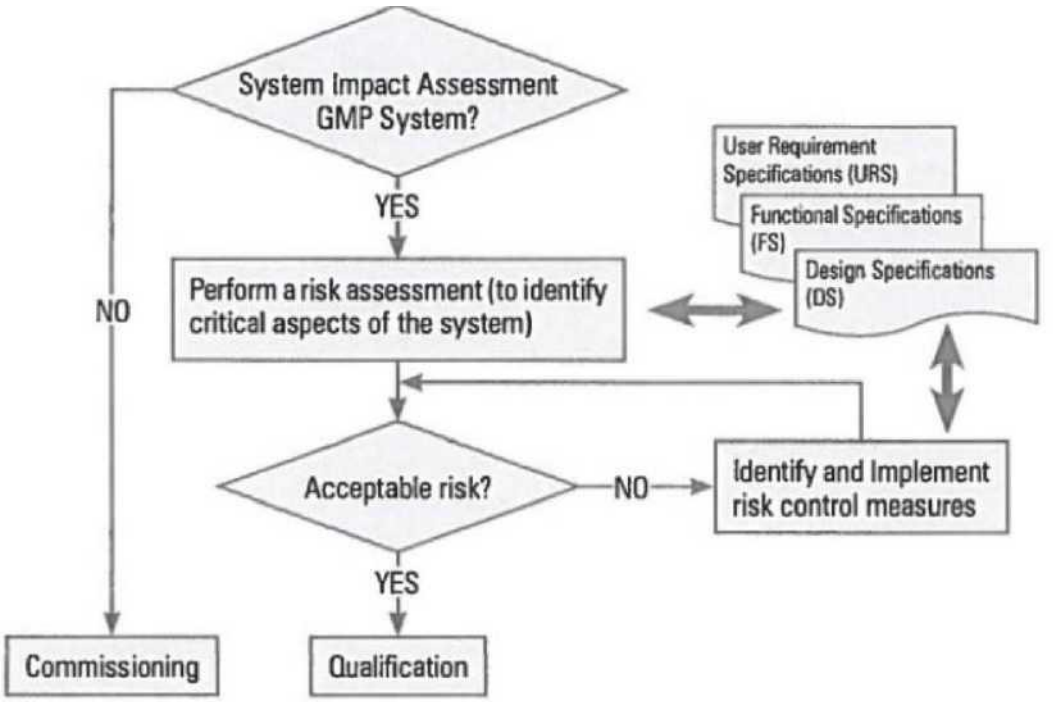
Design reviews should provide assurance on how the system design effectively meets the user, functional, and design requirements for the system including critical aspects by providing a structured framework to evaluate and manage risks to acceptable levels. Risk assessments should be approved at the end of design to signify that the design and risk control measures identified have been implemented into the design of the system. Outcomes from the risk assessment should also be used to determine testing requirements for the system.
设计评审应该通过提供一个评估和管理风险至可接受的水平的结构框架来证明系统设计是如何有效满足用户 需求、系统的功能和设计需求的。风险评估应当在设计结束时批准以表示设计和识别的风险控制措施已经在系 统设计中实施。风险评估的结果也应被用于确定系统的测试要求。

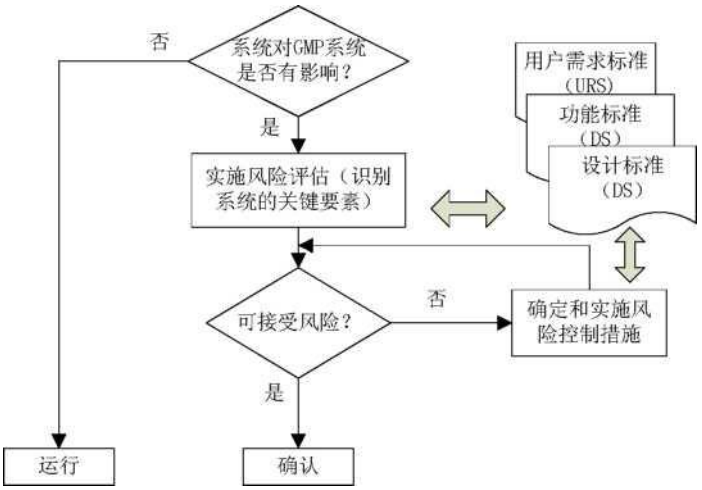
Risk assessments should be conducted and updated throughout the operational phase of the system lifecycle, especially to evaluate the impact of events such as deviations, investigations, CAPAs, unplanned maintenance activities, and proposed changes to ensure that a validated state of control is maintained.
风险评估应在系统生命周期的操作阶段实施和不断更新，特别是用来评估如偏差的事件的影响、检查、纠正预 防措施、非计划性的维护活动和提出的变更以确保控制的验证状态得到维护。
There should be an appropriate flow of information between QRM and other facilities / equipment project activities to ensure that any impact to the risks, risk controls, system design, project budget, or schedule are identified in a timely manner and communicated to and approved by the appropriate parties. For example, a value engineering decision may create a new risk or increase an existing risk. Conversely; quality risk assessments may identify the need for a previously unforeseen risk control measure, which may impact the project budget or schedule.
应当用质量风险管理和其他厂房设备相关项目活动之间的恰当的信息流来确保风险的任何影响、风险控制、系统设 计、项目预算或项目排期。例如，价值工程决策可能产生新的风险或增加额外的风险。相反地，质量风险评估可以 识别出以前未预测到可能影响项目预算或项目排期的风险的控制措施的要求。
Risks should also be assessed when decommissioning or retiring a system. The risk assessment can be used to address potential impact such as data migration and long-term retention of data or other records that support system operations and the products that were produced from that system. System lifecycle documents including risk assessments should be under appropriate change management and updated as needed throughout the lifecycle.
当设备停止运行或退役时风险也应该评估。风险评估可以用来处理支持系统运行及该系统生产出的产品的数据 移交和数据长期保留或其他记录的潜在影响。包括风险评估的系统生命周期文件应该处于恰当的变更管理之下 并在整个生命周期中根据需要更新。

5.2.2 Quality Risk Management Application to System Qualification Activities 质量 风险管理应用于系统确认活动

QRM can provide the basis for determining the level of rigor necessary for system lifecycle deliverables including testing. Risk assessment and risk control considerations should be included in the preparation, review, and execution of equipment commissioning, qualification or verification test plans, and test scripts. These should also be compared against the requirements / acceptance criteria that should have already incorporated the risk considerations appropriately. Testing therefore becomes a means to verify that risk control measures are implemented and effective. The rigor and extent of qualification should be commensurate with the level of risk. See Figure 5.2.2-1 for an approach that can be used for incorporating QRM in the determination of testing requirements.
质量风险管理可以为确定系统生命周期交付包括测试的严格的必要水平提供基础。风险评估和风险控制应在设 备运行、确认或验证测试计划和测试脚本的准备、评审和执行过程中考虑。这些也应与已整合了适当风险考虑 的需求/可接受标准进行比较。测试因此成为验证风险控制措施可以有效实施的一种方法。确认的严格程度应与 其风险相适应。见 5.2.2-1 可以用于整合质量风险管理于确定检测要求的的一种方法。

Figure 5.2.2-1 Approach for QRM Application to Determine System Testing Requirements
图 5.2.2-1 质量风险管理应用于确定系统测试要求的方法





5.2.3 QRM Application to Facility and Equipment Operation, Maintenance and Continual improvement 质量风险管理应用于厂房、设备操作、维护和持续改进

No system or its environment remains stagnant and unchanged for prolonged periods of time. QRM should be applied throughout the operational phase of the system lifecycle to monitor and assess system performance and changes, to ensure that the system and associated operations are maintained under a state of continuous control. The level of risk control activities should be balanced with the level of residual risk.

没有系统或者其所处的环境会长时间维持停滞不变。为了确保系统及其相关的操作能维持在持续控制的状态质 量风险管理应在整个系统生命周期的运行阶段用来监控和评估系统性能和变更。风险控制活动的水平应与残留 风险的水平相平衡。

The approach to demonstrating ongoing control of the validated state through periodic review or requalification has not been well understood past initial delivery, installation and qualification of systems. Requalification of systems typically involves repeating the qualification test protocols and comparing the results to the original data. "Over time, the industry has been moving towards primarily relying on periodic review of discrepancies, changes, unplanned maintenance, and ongoing monitoring trends to assure maintenance of the validated state, with

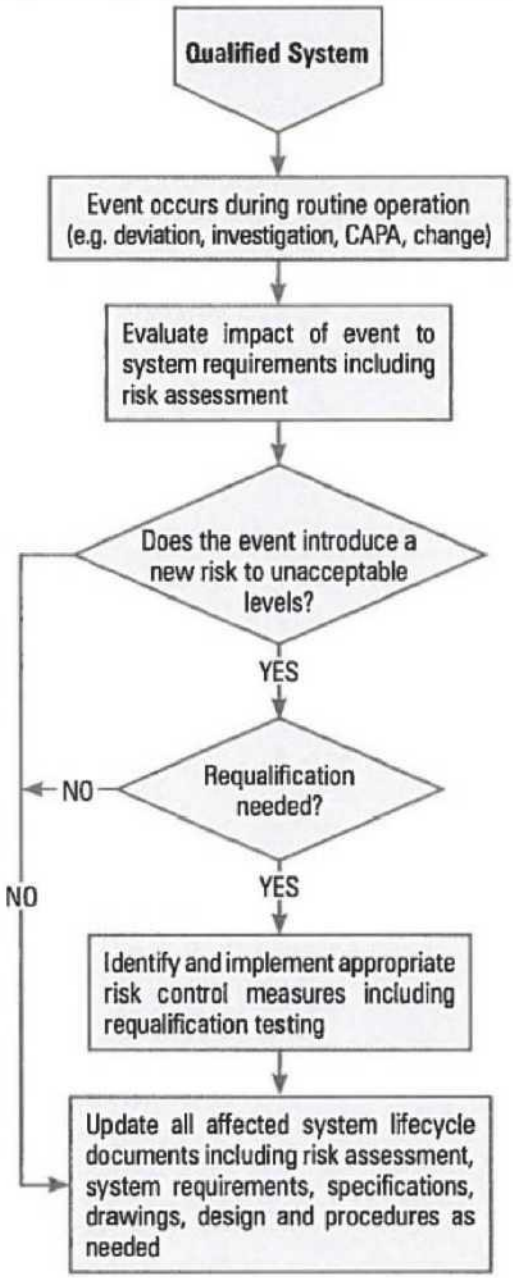
requalification only being performed when required by regulatory expectations. Understanding the criticality of systems and their robustness to change are fundamental in the application of QRM to periodic review and requalification. Effective calibration and maintenance programs are additional preventive measures to ensure that the facility and systems are continuously maintained to specifications. The risk assessment can be used to identify critical instruments or components for a system and the appropriate maintenance and/ or calibration frequency for these critical elements.

通过定期回顾或再确认来证明验证状态的持续控制的方法已经不能很好的理解以前系统最初的交付、安装和确 认。系统再验证通常涉及重复确认测试方案和比较原始数据和结果。过时了，行业已经趋向主要依赖于对差异、 变更、非计划性维修和持续监控确实的定期回顾来确保验证状态的维持，仅仅当为了满足药监当局的期望时才 开展再确认。理解系统的关键性及其对变更的耐用性是对定期回顾和再确认应用质量风险管理的基础。有效的 校验和维护项目是确保厂房和系统持续保持符合标准的附加预防措施。风险评估可以用来为系统识别关键仪表 或组件并为这些关键要素确定恰当的维修和/或校验频率。

The Quality System should ensure robust and effective management of deviations, investigations, changes, CAPAs, unplanned maintenance events, or adverse data trends to ensure that the existing profile of risks for the system does not reach an unacceptable level. Incorporating QRM in these instances can help define criticality, acceptability， resolution timing, and review frequency. The outcomes of the risk assessment should be used to drive appropriate control of any potential new risks or changes to existing risks or risk control measures that may be associated with the deviation, investigation, change, CAPA, unplanned maintenance activities, or adverse data trends. Low-risk changes may require little to no additional testing or evaluation, whereas high risk changes are likely to require sufficient testing to verify the suitability and effectiveness of the change.

为了确保系统存在的风险不会达到不可接受的水平质量系统应保证偏差、调查、变更、纠正预防措施、非计划 性维修事件或不良数据趋势得到强而有效的管理。整合质量风险管理进这些事件中可以帮助确定关键性、可容 许性、解决时间和回顾频率。风险评估的结果可以用于推动对每个潜在新风险进行恰当的控制或推动对偏差、 调查、变更、纠正预防措施、非计划性维修活动或不良数据趋势相关的风险或风险控制措施进行变更。低风险 变更可能完全不需要额外的测试或评估，反之高风险的变更可能需要充分的测试来证明变更的适宜性和有效性。

See Figure 5.2.3-1 for an example of how QRM can be integrated into the operation and maintenance activities for facilities and equipment.
见图 5.2.3-1 质量风险管理如何被整合入厂房和设备的运行和维修活动中的例子 Figure 5.2.3-1 QRM Application during Operation and Maintenance Activities 图 5.2.3-1 质量风险管理在运行和维修活动中的应用



5.2.4 Facility and Equipment Design: Dedicated Versus Multi-Product Facilities 厂房和设备设计：单一品种和多品种厂房

Per ICH *Q7, Good Manufacturing Practice for Active Pharmaceutical Ingredients, "Building and facilities used in the manufacture of intermediates and APIs should be located, designed, and constructed to facilitate cleaning, maintenance, and operations as appropriate to the type and stage of manufacture. Facilities should also be designed to minimize potentia1 contamination. Where microbiological specification have been established for the intermediate or API, facilities should also be designed to limit exposure to objectionable microbiological contaminants , as appropriate." (25)* Product and process requirements should drive the design strategy for facilities, manufacturing, control, and support systems.

依照丨 CHQ7，原料药良好的生产质量规范，‘‘用于中间体和原料药生产的建筑和厂房应根据生产的类型和状态 进行选址、设计和建造并利于清洁、维修和操作。厂房也应设计来使潜在污染最小化。必要时，中间体或原料药建立了微生物指标的地方，厂房也应设计来限制会引起微生物污染的暴露。产品和工艺需求应推动厂房、生 产、控制和支持系统的设计策略。

QRM can be used to proactively identify， and manage multi-product risks as a product is being transferred to a facility. A risk- and science-based evaluation of a process takes into account the potential for cross-contamination, the impact on product quality, and the intended use of the product(26).This includes addressing risks for highly potent/ sensitizing (e.g., cytotoxic) materials. These risks are managed by conducting manufacturing operations in a control1ed environment. This approach is especial1y critical for multi-product facilities and equipment trains that are used to produce different APIs, intermediate products, or finished products.

当一个产品被转移至一个厂房时质量风险管理可以用来主动识别和管理多产品共线的风险。基于风险和科学的 工艺评估要考虑潜在的交叉污染、对产品质量的影响和产品的预期用途。这也包括了寻找高活性或高致敏性（如 细胞毒性）物料。这些风险通过在控制环境下执行生产操作来管理。这种方法对于应用生产不同品种原料药、 中间产品或最终制剂产品的多产品公用的厂房和设备组特别关键。

The concepts of segregation and contamination control practices to manage multi-product risks are described in regulations, guidance, and reference standards such as ICH Q7 and EudraLex Volume 4 Chapter 3 "Premises and Equipment." These concepts include:

用于管理多品种风险的隔离的理念和污染控制方法被描述在法规、指导文件和相关标准中，如 ICHQ7 和 Eudralex 第四卷第三章“厂房和设备“。这些理念包括：

• Understanding of the process, biohazard and contamination issues and related concerns
对工艺、生物危害和污染事件及其相关关注点的理解。

• Segregation of APIs and intermediates by design (spatial) or practice (temporal). Segregation is further delineated as primary, secondary, environmental, or process design; some examples include:
对原料药和中间体在空间上设计隔离或操作时暂时隔离。隔离措施进一步可以描述为主要的、次要的、环境或 工艺设计。实例包括：

Primary: Separate clean rooms that are dedicated to specific process equipment and process steps including equipment arrangement.
主要的:专门用于特殊工艺设备和包含了设备布置的工艺步骤的单独的洁净间

Secondary: A multi-product environment where each product is campaigned and separated with a rigorous / validated change-over cleaning, or many products at once in separated trains, or separating upstream from downstream process steps.
其次的:多产品共线环境的每个产品都分阶段生产并严格的经过验证换产品清洁或许多产品立刻分开生产 或将上下游工艺步骤分开。

Environmental: Clean room pressure cascade from the most critical operating zone to the least critical zone (i.e., clean to dirty).
环境：从最关键操作区域到最不关键区的洁净间梯度压差（如干净区到脏区）

Process Design: Closed versus open system.
工艺设计:密闭与开放式系统

• Controlling process, material, waste, and personnel flows to reduce the impact of cross-contamination
控制工艺流、物流、废弃物流和人流来降低交叉污染

• Designing, constructing, and operating control 1ed (e.g., clean room) environments that are suitable for the type of manufacturing activities being performed.
设计、建造和操作适合于生产活性物质类型的控制环境（如洁净间）

• Cleaning, decontamination, and disinfection practices 清洁、
净化和消毒行为

• Steam /water sanitization and sterilization procedures 蒸汽/
水消毒和灭菌程序

• Changeover procedures
转移程序

• Viral clearance by reduction and inactivation 通过降
低或灭活来清除病毒

• Gowning and hygiene practices 更
衣和卫生行为。

• Environmental controls and monitoring practices to detect and control potential contaminants
用于监测和控制潜在污染物的环境控制和监控措施。

Proactive QRM will ensure that appropriate multi-product controls exist not only for the product that is being transferred to the facility but also for products that are already produced in that facility.

主动的质量风险管理可以确保正在转移到工厂的产品和工厂内原有产品都存在多产品共线方面恰当的控制。

53 **Quality Risk Management Application During Technology Transfer** 质量风险 管理在技术转移中的应用

Technology transfer includes transfer of product, process, technology, or analytical methods throughout a product lifecycle (until discontinuation) including:
整个产品生命周期（一直到中止）中包含产品、工艺、技术或分析方法转移的技术转移包括：

• New product transfers from development to ful1-scale commercial manufacturing
从开发至大规模工业化生产的新产品转移

• Transfers of clinical and marketed products within or between manufacturing and testing sites 在生产和实验场地之间或之内的临床和市售产品的转移

The development of a new product and the associated manufacturing process requires the acquisition and management of process and product knowledge. The transfer of processing technology from development to production is a critical step in the product lifecycle. Technology transfers for existing processes are also common as many products are manufactured at multiple sites or outsourced.
新产品的工艺开发及其相关生产公司需要获得和管理工艺和产品知识。从开发到生产的工艺技术转移在产品生 命周期中是关键步骤。当许多产品在不同地点生产或者外包时现有的工艺的技术转移也是一样的。

Knowledge management is a key supporting enabler for effective QRM. It supports the development of a robust and reliable production process that will reproducibly deliver product that is safe, pure, and efficacious. Such knowledge needs to be transferable and thus requires tools for managing data, information, and ultimately knowledge. Even risk assessments performed at an early stage in the product lifecycle will have to be understood and interpretable years later when the commercialization step is reached. QRM thus requires forward planning, so processes, methods, and knowledge can be safely transferred.
知识管理是有效开展质量风险管理的关键的驱动因素。它支持一个稳定可靠的可以重复生产出安全的、纯的和 有效的产品的生产工艺的开发。这些知识需要可转化，因此需要工具去管理数据、信息和基本知识。当工业化 生产多年后在产品生命周期早期实施的实际的风险评估将不得不被理解和解释。因此质量风险管理需要预先计 划，所以工艺、方法和知识可以安全的转移。

Technology transfers are generally associated with potential risks for incomplete transfer of knowledge and would need to be managed adequately where the company is not directly in control of manufacturing (e.g., use of a contract manufacturing organization [CMO]). A successful technology transfer will result in each process step being fully understood, controlled and largely optimized, with potential risks being controlled to acceptable levels prior to the transfer. The participation of SMEs such as va1idation, production, development, engineering, and quality personnel is crucial to the success of the transfer.
为了完成知识的转移技术转移通常是与潜在风险有关系，并在在企业不能直接控制生产的地方（如合同生产组 织[CMO])将需要充分的管理。一个成功的技术转移将带来每个工艺步骤都被完全的理解、控制和大部分都已 优化、在转移之前潜在风险已经被控制在可接受水平。相关领域的专家如验证、生产、工艺开发、工程和质量 人员的参与对转移的成功至关重要。

QRM can be app1ied throughout the technical transfer process starting with the site selection. A risk assessment should be performed to determine the risk with choosing a particular site to ensure that the best sourcing decision is made (e.g., evaluate risks with the options of contract manufacture, a new company owed facility; or retrofitting an existing company owed facility). Each site has separate risk profiles, which should be taken into consideration.
质量风险管理可以在开始于场地选择的整个技术转移过程中应用。在为保证做出最好的供货决定（如评估一个 缺厂房的新公司选择合同生产的风险或一个缺厂房已有的公司改造）而确定选择特定的生产场地的风险时应该 实施风险评估。每个生产场地都有应该考虑不同的风险情况。

After the site has been chosen a risk assessment can be performed to assess the risks associated with a particular site (e.g., types of equipment, scale, raw materials, and personnel). For instance， if a contract manufacturer has been chosen questions arise such as:
在生产场地已经选择后风险评估可以实施用来评估特定的生产场地相关的风险（如设备的类型、尺寸、原料和 人员）。比如：如果选择合同生产商可以提出以下问题：

. What are the differences or similarities between the donor and recipient sites in the facilities and equipment that is used to produce the product?
用于生产此产品的厂房和设备供方和接收方之见有哪些不同或相同？

. What is the level of manufacturing experience with a particular product class (e.g., recombinant protein versus small molecule)?
特定的产品类别（如重组蛋白质和小分析）的生产经验水平是什么样的？

Assessment of risks associated with these differences or changes as part of change control activities can ensure that unacceptable risks are not introduced due to the differences or changes.
作为变更控制活动的一部分的这些不同或变更相关的风险的评估可以确保不可接受的风险不会被引入这些不 同或变更。

Another factor to consider is the type of facility (i.e., is it a multi-product or multi-host facility?). If so, then special considerations should be made for cleaning and change-over procedures, managing cross-contamination or material/product mix-up risks (see Section 5.1.3, QRM Applied to

Steri1ization and Cleaning Validation and Section 5.2.3, Facility and Equipment Design: Dedicated versus Multi-Product Facilities for more information). Risks for storage and transportation, especially if manufacturing is divided among multiple sites, should also be assessed and appropriate risk control measures identified.
另外一个考虑的因素时厂房的类型（如是多产品或多客户共用厂房吗？）。如果是，在清洁和转换品种程序、 管理交叉污染或物料和产品混淆的风险方面需要做出特殊考虑（更多信息见 5.1.3 节质量风险管理应用于灭菌和 清洁验证和 5.2.3 节，厂房和设备设计：专用和多品种共用厂房）。储存和运输的风险尤其是生产被分开在多个 生产场地进行时也应评估并确定恰当的风险控制措施。
The technology transfer should not only ensure a successful transition from product development to product operations or a new site, but should do so in a manner that results in a process that can be validated to reliably produce high quality product. The more comply the process is, or the higher the level of residual quality risk is inherent to the process, the more appropriate it will be to conduct additional evaluative studies to ensure that the process is in an adequate state of control. QRM can be used to identify, how much validation is required, or where revalidation is not necessary, including assessment of the number of batches required for validation.
技术转移不仅要确保从产品开发向产品生产或新生产场地成功的转移，也应以结果是一个工艺能被验证确实是 可以生产出高质量的产品的方式进行。工艺越符合或工艺固有的残留质量风险越高，为确保工艺处于足够的控 制状态实施额外的评估研究将越合适。质量风险管理可以用来识别需要多少验证或哪儿不需要再确认，包括验 证需要的批次的评估。
Conducting engineering studies or production of test batches prior to conducting validation activities can be an effective method to identify, and appropriately manage risks that were not identified during development or transfer planning. During the transfer of an existing manufacturing process, there is the added benefit of historical data availability (including an understanding of CQAs, CPPs and process controls) that provides a knowledge baseline useful for QRM application during the technology transfer. Risk assessments should be completed and high / unacceptable risks reduced to acceptable levels prior to producing qualification lots that support the technology transfer.
为了识别和恰如其分地管理在开发和转移计划过程中未识别出的风险一种有效的方法可能在实施验证活动之前执行 工程研究或实验批次。在已生产的工艺的转移过程中历史的可用的数据（包括对关键质量属性、关键工艺参数和工 艺控制的理解）在为技术转移中用于质量风险管理的应用提供知识基础方面有更多效益。在生产支持技术转移的确 认批次前风险评估应已完成并且高风险和不可接受风险应被降低至可接受的水平。
Finally, QRM can be applied during technology transfer to assess considerations for bridging stock and support appropriate management of the overall plan and logistics for the transfer. As emphasized throughout this document, QRM is an iterative process and the risk assessments performed in support of the technology transfer should be reviewed and revised as appropriate.
最后质量风险评估在技术转移期间的应用可以用来评估考虑为库存牵线搭桥，用来支持为转移做的整个计划和 物流的做适当管理。正如贯穿于本文件始终强调的一样，质量风险管理是一个反复的过程，支持技术转移的风 险评估应该根据需要不断回顾和更新。

5.4 Quality Risk Management Application in Materials Management
质量风险管理应用于物料管理

The globalization of the pharmaceutical industry has increased the complexity and challenges of vendor qualification including assurance of materials quality and integrity. A dependable source for active, inactive, and other raw materials and components is one of the prerequisites for successful manufacturing. While globalization has increased the number of available suppliers, it has also increased quality risks. Thus, pharmaceutical companies need to invest in improved supplier qualification and materials management programs in order to manage the risk of assuring quality of materials from all suppliers. Selection of suppliers should primarily be based on their ability to consistently deliver material per specifications. Cost may be a factor but should not be the primary driver.
制药工业的全球化增加了包含了保证物料质量和完整性的供应商确认的复杂性和挑战。活性、非活性和其他原 料和辅料的可靠的来源是成功生产的先决条件之一。当全球化已经增加了有效供应商数量时，质量风险也增加 了。因此，为了管理在保证从所有供应商的物料的质量中的存在的风险，制药企业需要在改进供应商确认和物 料管理项目上投资。供应商的选择首先应当基于始终如一的实现物料的每一项质量标准。成本可以是选择因素 之一但不应该是主要的因素。
QRM helps pharmaceutical manufacturers assure the safety of their active, inactive, and other raw materials through the establishment of a risk-based effective supplier assessment and qualification program. The supplier qualification program has to be part of the Quality System in order to provide assurance that the drug substance / drug product and services that are purchased will consistently meet specifications and expectations for compliance with the regulations. This process builds quality into the supply chain and the manufacturing process, and reduces the likelihood of producing a nonconforming product. QRM can help prevent recalls, health authority enforcement actions, bad publicity, damage to a company's integrity and reputation, and most importantly negative impact to patient health. QRM aids manufacturers in being knowledgeable about their suppliers in order to build control systems to prevent the purchase of materials from unscrupulous re-packagers or wholesalers.
质量风险管理通过建立基于风险的有效供应商评估和确认项目来帮助制药生产企业确保他们活性、非活

性和其他原 料的安全。为了为购买的原料药/制剂产品及其服务将始终满足其质量标准和遵守法规的期望提供保证供应商确认项 目必须是质量系统的一部分。此过程将质量建立于了供应链和生产过程中，并降低产生不合格产品的可能性。质量 风险评估将帮助预防召回、卫生当局的强制措施、负面宣传、对公司诚信和声誉的损害和最重要的对患者健康负面 影响。为了建立控制系统去预防从不讲道理的分包商或批发商购买物料质量风险管理有助于生产商在他们的供应商 面前聪明。

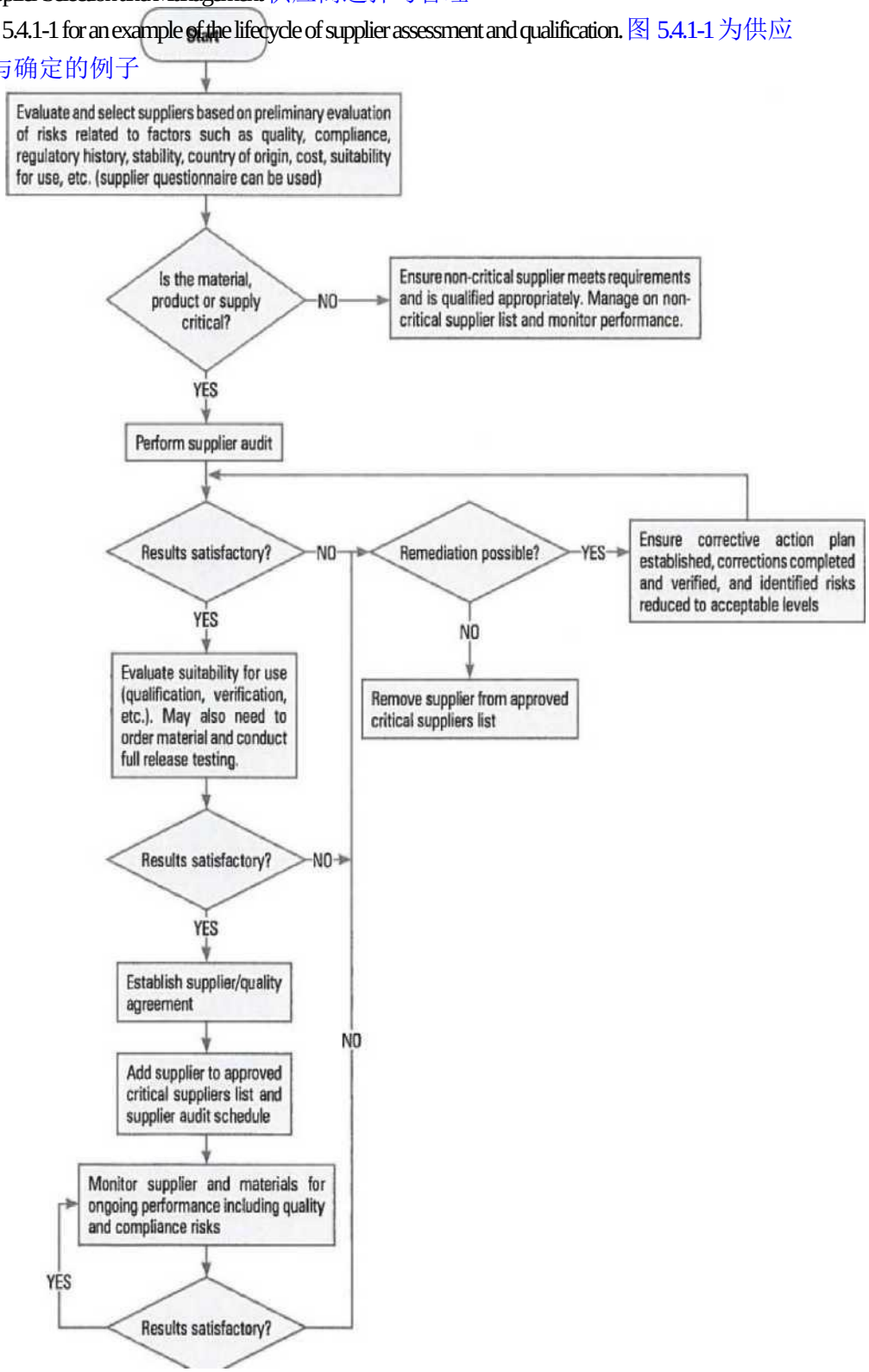
5.4.1 Supplier Selection and Management 供应商选择和管理

See Figure 5.4.1-1 for an example of the lifecycle of supplier assessment and qualification.

见图 5.4.1-1 供应商评估和确认的生命周期的实例

5.4.1 Supplier Selection and Management 供应商选择与管理

See Figure 5.4.1-1 for an example of the lifecycle of supplier assessment and qualification. 图 5.4.1-1 为供应商评估与确定的例子



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5.4.2 Risk Controlfor Suppliers

5.4.2 供应商风险控制

Ideally.vendor selection begins with the establishment of the raw material attributes and specifica- tions_ Manufacturers need to clearly de specification requirements and understand how those requirements contribute to the quality of the product _ Experiments with different sources and differ- ent standards of components may be necessa to understand the effects on the finished product.

理想状态下，供应商的选择从物料属性与标准的建立开始。生产者需要清晰地定义标准需求并且理解其对 产品质量的作用。使用不同来源不同标准的物料进行实验，对于理解其对最终产品的影响是必须的。

While most companies rely on API or cipients that have speccations recognized by compendial monographsit may be necessary to investigate the need for tighter or additional specmcations for these materials due to their performance in the specific dosage form being developed. The risks of these raw materials should be assessed right om the start with a view to product development and commercialization.

尽管大多数公司依靠 API或者辅料本身具有符合法定个论的标准，但因其对制剂表现的影响，有必要进行调查以紧缩或者增添标准。在产品开发以及商业化的过程中，物料的风险必须从一 开始就进行评估。

While it may be preferable to deal with a manufacturer of the APIraw materialsor components directlymost companies have to purchase om a distributor or wholesaler network.
Some of the factors that should be considered when evaluating risks and selecting a supplier (le.manufacturers and distributors) include:

尽管直接从生产商处购买 API，物料或者组份更好，但大多数公司不得不从分销商或者批发商处购买。评价 风险与选择供应商（如生产商、分销商）需考虑以下因素：

- Quality of raw materials i.e. compendial monograph material and the ability of the supplier to provide Certificates of Analysis [COAsavailability of material with different specmcations).
物料质量（法定标准物料，供应商提供分析证明的能力，提供不同标准物料的能力）
- Consistency of supply (e.g.reliance of the vendor on secondary or tertiary suppliers).
供应持续性。（如对二级、三级供应商的依赖）
- Registration inspection and compliance status of supplier_
供应商注册、检查及相符性情况
- Willingness of the supplier to enter into an agreement or contractincluding willingness to be audited.
供应商达成协议与合同的意愿，包括接受审计的意愿
- Willingness of supplier to share information (e.g.Quality System containers closures and distribution channels).
供应商分享信息的意愿（如，质量系统，容器，密闭包材以及分销渠道）
- Uniqueness of Material (e.g. considerations for biotechnology raw materials such as bovine spon giform encephalopathy [BSE] and transmissible spongiform encephalopathy [TSE]virus,micro- biological contamination, endotoxin levels,leachable/extractable ,variability risks etc.).
物料的独特性（生物技术物料对于如对疯牛病[BSE]以及传染性海绵状脑病[TSE]的考虑，病毒，微生物污染，内毒素水平，浸出/提取，变异风险）
- Counterfeiting potential of the material.
假冒的可能
- Country of origin and location of manufacturing plant
来源国家与厂区地址
- Black market sources of the materials.
物料的黑市来源

In addition to the quality and compliance of vendors manufacturers need to assess the manufac- turer /supplier's reliabty to provide the material on a timely and dependable basis.
QRM looks at the lifecycle of the productnot just the immediate need during a particular step in the lifecycle. The geo-political and geophysical environment impacts the potential risk to drug substance / drug product availabty and quality.Regulatory oversight is an important aspect of supply chain integrity especially as it relates to assuring that

counterfeit and substandard materials do not enter the supply chain.

此外，生产商需要去评估供应商按时提供物料的可靠性与依据。QRM 观察产品的整个生命周期，而不仅仅 是其中某一步的特殊需求。地缘政治和地理环境对药物物料、产品的可用性和质量有潜在风险。法规符合 性是供应链完整性的重要方面，特别是关乎保证假冒伪劣物料无法进入供应链。

See Table 5.4.2-1 for an example of how risk management can help determine the audit equency for a supplier. This example illustrates a modelwhich can present varied audit frequencies based on variations in supplier risk rating.

表 5.4.2-1 是风险管理用于决定供应商审计频率的例子，依据供应商风险等级的不同决定审计频率

Table 5.4.2.1 Example of Risk Management Application to Determine Supplier Audit Frequency

		Material and Supplier Criticality Assessment 1		
		Low	Medium	High
Supplier Performance Rating	Excellent	Audits every 4 years		

In the above example suppliers are evaluated based on the two parameters of past performance and criticaty of suppliers/ materials. The resulting cell in the 9-block diagram provides the recom- mended equency for supplier audits.

		与供应商重	t要性评估	
		低	中	高
过往表现	极好	每四年	每四年	每三年
	好	每四年	每三年	每两年
	一般	每三年	每两年	每年

在以上案例中，通过两个指标来评价供应商：过往表现以及物料与供应商重要性评估。在矩阵中提供 了推荐的供应商审计频率。

The first parameter Supplier Performance Rating is determined based on objective criteria of past performance. A performance level of Excellent Good or Standard is determined based on a pre- defined check list risk assessment with scoring for various elements such as quality of supplier's past performance percentage of non-conformances per lot on-time deliveryetc.

第一个指标：过往表现由供应商之前的表现的客观标准决定。极好、好、一般由之前定义不同方面的 的风险评价分数来决定，如每批不合格品率，按时到货情况等。

The second parameter across the top is determined based on the criticality of the material and the supplier's delivery of that material.The criticality level of Low Medium or High is determined based on a pre-defined checklist risk assessment of criticality of the material and the supplier's ability to provide the material.Elements that contribute to the criticality assessment inc1ude aspects such as where the material is used in the process the supplier's ability to provide material of the quality level that meets requirement supplier's internal Quality System their technical capabilities etc.

第二个指标：物料与供应商重要性评估由物料以及供应商物流的重要性决定。低、中、高由之前定 义的重要性风险评价分数来决定，物料的重要性以及供应商提供物料的能力。影响因素有：工艺中 物料使用处、供应商提供质量符合要求的物料的能力、供应商质量系统、供应商技术能力等。

This model can be defined in procedures within a company's Quality System. Inputs to determine the levels should be provided from across multiple functionswith quality parameters being weighted the highest. The resulting level should be refreshed periodical1y (e.g.annual1y)incorporating the most recent data and experience.

该模型可以在公司的质量系统中规定流程。由交互的多种功能提供数据来决定水平，质量指标被认为是 最重要的。水平结果应该根据最新数据与经验定期更新（如每年）。

Audit frequency is illustrated but the tool can be applied for other cross-functional purposes as well. For examplenew business could onybe given to suppliers with "excellent" or "good" performance rating. New suppliers can be given an initial rating of "standard" until data becomes available to incorporate in the annual refesh. For suppliers that have significant open CAPAs there should be a focused effort applied to move the suppliers up in their rating or out of the list of approved suppliers.

审计频率如图所示，该工具还可用于其他有交互作用的功能。例如，新业务只能给极好或者好的评级 的供应商。新供应商可以给予“标准”的初始评级，直到数据可用于年度更新。供应商有大的显著的 CAPA 时，应该专注于提高供应商评价或者从批准供应商列表中移除。

Risk control measures should apply to the entire supply chain not just testing on receipt. Incoming material need to be in accordance with a statistically based sampling scheme and the samples tested without compositing.

风险控制应该应用于整个供应链而不仅只是检查发票。新到货的物料应该按统计学设计的取样计划 而且在合成前进行检测。

One of the greatest risks is receiving a material that has been contaminated with a substance that can cause serious harm to the patient and is not identified during incoming inspection. If QRM is used to evaluate every aspect of the supply chain risks could be managed earlier during the selection of suppliers. As testing and specifications can onIy address and look for ingredients and lmpurities that are either knOW11 or expected there is always the risk of an unknown substance going undetected. For that reason it is necessayto consider the entire supply chain when considering the risk to product quality.QRM applied as a holistic approach can reduce the risk of substandard or harmful materials being purchased through the supply chain.

接收物料被可能会对患者造成极大危害的成分污染并且在检查中没有发现是最大的风险。如果质量风险 管理被应用于评价供应链的每个方面，在供应商选择阶段就能有效管理。因为检测只能发现已确定成分 或杂质，不明成分的混入是一直存在的风险。在考虑产品质量风险时有必要考虑整个供应链，质量风险 管理可以整体应用于减少从供应链引入非标准或者有害物质的风险。

5.4.3 Quality Agreements

Quality and Supply Agreements can function as useful and integral elements of a supplier risk man agement program. In some countries， Quality Agreements are required by regulation. These agreements are considered contracts between suppliers and manufacturer that dearly define roles and responsibilities and quality requirements. The fd1owing are elements of a typical Quality Agreement that help provide greater assurance of product quality and supply continuity:

质量与供应协议是供应商风险管理程序的重要组成部分。在一些国家，法规要求质量协议。质量协议是指定义供应商与生产者角色与责任的合同。以下为典型的质量协议元素以保证 产品质量与供应的连续性：

- Identity of the supplier 供应商身份
- Identity of the deliverables 可交付的成分
- Intended use of the component or service 组份或服务的预定用途 Allspecifications for the component or service 组份或服务的标准
- Description of the roles and responsibilities of the contract giver and contract receiver: 合同给出与接收者角色与责任描述

Responsibilities as they relate to cGMPs cGMP 相关责任

- Responsibility related to validation (e pre-approval of validation protocols by the contract giver) 验证相关责任（例如合同给出者提供批准前验证方案）
- Responsibilities related testing and release

检验与放行责任

- Responsibilities for the supplier to inform the manufacturer of any proposed changes such as changes to the manufacturing processequipment facility analytical methods standard operating procedures key personnel and any key secondary or tertiary supplier

供应商通知生产者变更的责任(如生产工艺、设备、设施、分析方法、标准操作规程、关键人员与二级三级分销商)

- Responsibilities for the supplier to inform the manufacturer of anyerrors deviations and out-of-spedfoation results that did or may have impacted the product quality

供应商通知生产者可能影响产品质量的差错、变更、OOS 结果的责任

- Possibility to participate in supplier's investigations

参加供应商调查的可能性

- Description of the manufacturing storage and distribution processes

储存与分发流程的描述

- Requirements for product release quarantine and potential destruction

产品放行要求与潜在破坏

- Requirements for shipment conditions 运输条件要求
- Requirements for the contract giver to audit the contract receiver

合同给出者对接收者审计的要求

- Requirement for the supplier to share the results of regulatory agency inspections.

供应商分享法规部门检查结果的要求

The task of controlling risks to drug substance / drug product is not over once the supplier has been identified and qualified. There still remains the activity of protecting the components during shipment and storage to ensure that quality is not compromised prior to being received at the manufacturer. The extrapolation of these measures to non-product components would increase the confidence in the materials received through the global supply chain.

Pharmaceutical manufacturers can increase their confidence in the shipment of their drug substance / drug product by working with their suppliers in the fol1owing methods:

制药生产者可以通过药物与产品风险控制的任务不仅仅是供应商的确认，还包括在运输和储存过程中，生产者 接收前物料质量不受影响。这些分产品成分的测量可以增强通过国际供应链提供物料的信 心。

与供应商协作增强其对药物产品运输的信心：

- Incorporation of anti-counterfeiting measures in packaging and labeling 包装贴签不良监测
- Use of tamper evident seals on containers

容器使用抗破坏密封

- Use of unit level identification systems (e.g.Radio Frequency Identification [RFID] tags2D-bar codes)

使用单位水平识别系统（如无线射频识别技术、二维码技术）

- Use of seals

使用密封

- Use of common carriers that do not bear the branding of the manufacturer

使用不标明生产商商标的普通容器

- Container level tracking and data col1ection (e.g.Global Positioning System [GPS])

容器级别跟踪与数据收集（如全球定位系统 GPS)

- Temperature /humidity data loggers

温度湿度数据

Increased confidence impacts the risk level and indirectly the risk to product quality. Purchasing sub stances locally does not assure that the material was manufactured locally or even in the same country '.Purchasers can take an active role in reducing this risk by establishing:

自信的增强影响风险水平而且间接影响产品质量。在当地购买物料并不能保证物料在当地 生产，甚至不在本国生产。交易者可以在减少风险方面起到积极作用，通过建立：

- Origin of the material 物料来源
- Integrity and compliance status of the original manufacturer
原始生产者的完整性与合规状态
- Distribution route of the material
物料分销路线
- Integrity and compliance of the links in the distribution chain
分销链完整性与合规性
- Manner in which the material was shipped and handled until its receipt by the manufacturer
物料接收前运输与处置方式

5.5 Quality Risk Management Application for Contract Services

5.5 质量风险管理应用于合同服务

Contract services is a broad term that can refer to many different steps in the overall manufacturing process from raw material manufacturing laboratory testing contract sterilization calibration /maintenance services packagingfinished dosage form or device manufacturing. The use of CMOs in some part of the drug manufacturing process has become increasingly prevalent in recent years. With the increasing complexity of products and processes specialization is sometimes necessary as manufacturers seek out specific skillstechnology experience or a means to reduce costs or improve efficiency. while the decision to use a contract supplier can be highly advantageous the risk associated with the loss of direct control should be considered and controlled adequately through a risk-based lifecycle approach that emphasizes the need for communication and clarity on roles and responsibilities. The selection process for a supplier and the qualification process of the supplier are key elements for adequately controlling the associated risk. See Section 5.5.1Supplier Selection Initiation and Technology Transfer.

在生产中合同服务应用于原料生产、实验室检验、合同灭菌、校验/保养服务、终产品包装、 设备生产。CMO 在生产工序中的应用在近些年越来越广泛。随着产品与工艺复杂性的增加， 有时需要生产者去寻找特殊技能、技术、经验以减少成本提高效率。尽管使用合同服务优 势明显，应该考虑不能直接控制的风险，强调通过沟通以及明确的角色与责任进行足够的 风险控制。供应商的选择与确认是控制相关风险的重要因素。查看 5.5.1 部分：供应商选择、 起用与技术转移。

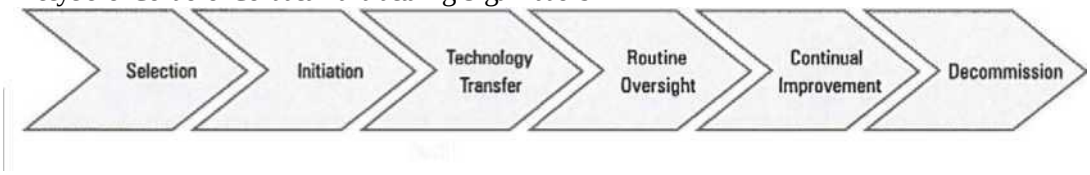
When a supplier is utilized by a sponsor company for any or all portion(s) of the activity which are undertaken within the product and process lifecycle it is critical to ensure that all parties involved participate in executing a comprehensive QRM strategy. The sponsor and supplier(s) should clearly define and apply QRM.

当一个供应商被发起公司用于参与产品及工艺生命周期中的一部分，要确保所有部分同一 QRM 策略。发起者与供应商需定义和应用 QRM。

Use of a supplier or a contract factory also follow a lifecycle concept (see Figure 5.5-1) which provides opportunities for the application of QRM at each stage as discussed in the following sections.

供应商或者合同工厂的使用需要遵照生命周期概念（看下图 5.5.1)，这位 QRM 在各步的使 用提供了机会 。

Figure 5.5-' Lifecycle for Control of Contract Manufacturing Organizations



5.5.1 Supplier SelectionInitiation and Technology Transfer

5.5.1 供应商选择、起用与技术转移

Selection of the supplier should be a systematic process that assesses the capabilities and experience of staff to support product quality. To apply a risk-based approach to supplier selection the initial asessment should take into account at a minimum the following supplier attributes:

供应商的选择是一个系统的过程，需要评估员工的能力与经验来支持产品质量。将基于风 险管理的方法应用于供应商选择，起用评估应该至少考虑供应商的以下内容：

- Availability per critical selection parameters 各关键选择参数的可行性

- Physical facty and equipment including geographic proximity to sponsor

实体设施与设备，包括地理上接近赞助商

- Quality System and inspection history

质量系统与检查历史

- Experience with process or similar complexity of process

工艺或相同复杂性工艺的经验

- Applicability and transfer of previous regulatory commitments (e.g. post-marketing commitments)

之前法规承诺的应用与转移（例如上市后承诺）

- Initiation and technology transfer considerations including comparabty of product(s) between manufacturing sites. See Section 5.3 QRM Application During Technology Transfer

项目启动与技术转移方面的考虑，包括生产场地产品的比较。详见 5.3技术转移中的质量风险管理

- Hazards from other manufacturing processes (e.g. cross contamination in a multi-product facility) 其他生产工艺的伤害（比如多产品设施的交叉污染）
- Control of suppliers

供应商控制

- Communication (linguistics considerations between all affected parties)

交流（各受影响部门的语言方面的考虑）

The supplier's Quality System and how it encompasses QRM is of particular interest. Lack of open two-way communication between the supplier and the contract giver may result in increased risks due to incomplete information and incorporation of feedback on Quality System elements.

最关注的是供应商的质量系统以及 QRM 的实施。供应商与合同给出者缺乏双向沟通会因信息不对称 以及质量系统因素回馈导致风险增加。

5.5.2 Routine Oversight of Supplier

5.5.2 供应商日常监测

Many suppliers have a long-term relationship with the contract giver and this is also where QRM and the lifecycle approach should be applied. Oversight is a risk-reducing activity and is directly linked to the actual risk posed. As the inputs to the risk assessment change (e.g. history of compliance change of deliverables)the control measure(s) may also need to change.

许多供应商与合同给出者有着长期的合作关系，QRM 与生命周期都应该被使用。监测是减少风险的 活动，与实际风险直接相关。风险评估输入的改变（如合规性历史、物料变化），控制手段也需要随 之改变。

The example in Table 5.5.2-1i11ustrates the concept of utilizing a more robust strategy and controls as the risk and complexity level of operations performed by a CMO increase. It is not intended to define the exact strategy to be used during routine oversight of the CMO's operations. The exact method and controls to be used by the sponsor company should be defined appropriately on a case-by-case basis based on the overall risk and complexity of the product process and relationship with the CMO(s).

如表 5.5.2-1所示，由于 CMO操作的风险和复杂性的上升更耐用的策略与控制的应用。定义 CMO明确 的监控策略并不是本意。赞助者确切的方法与控制，应该由总风险、产品工艺的复杂性、与 CMO的 关系来具体确定

Table 5.5.2-1 Example of QRM Application to Ensure Sufficient CMO Oversight 5.5.2-1 QRM用于保证对 CMO足够的监察的例子

Risk/Complexity Level	Oversight Method (Controls)
High	In addition to medium and low risk controls, routine sponsor Person in Plant (PIP|, review *b* approval of manufacturing
Medium	In addition to low risk controls, periodic audits conducted by sponsor and increased testing frequency.
Low	Use of shared quality metrics, key performance indicators (KPIs), and reduced inspection frequency.

风险/复杂 性	检测方法（控制）
高	在低与中的基础上，安排日常人员在厂，进行批记录检查与放行
中	在低的基础上，增加阶段性的审计，增加检验频次
低	使用分享的质量矩阵，关键表现指标 KPI，减少检查频次

In addition to the oversight methods noted in Table 5.5.2-1 the sponsor and CMO(s) should define in writing the routine methods and frequencies to be used to facilitate sufficient and timely communications and exchange of required information and data to jointly manage and control the GMP operations.

除表 5.5.2-1 所示之外，赞助者与 CMO 应该明确日常监测的方法与频率，进行充分的和适时的沟通，进 行所需信息和数据的交流以进行管理与控制 Gmp 操作。

For examplea Quality Agreement can be used to define a schedule and participants roles to ensure exchange of data and documentation (such as change control records deviations complaints adverse events CAPA). In some instances change control oversight for certain critical changes or deviations may require the sponsor's pre-approval (See Section 5.4.3 Quality Agreements).

例如质量协议可被用于定义数据与文档（变更记录、偏差、投诉、不良事件、CAPA)交流的日程与角 色。在一些例子中，重大变更以及偏差的检测需要赞助者的批准（参照 5.4.3 质量协议）

5.5.3 Continual lmprovement

5.5.3 持续改进

In line with ICH QI0 a contract giver should encourage continual improvement in the supplier's process The supplier's ability to continue improve feeds into the QRM approach. Measurement of KPIs or other quality metrics may be needed to manage and control this process. Systems that facilitate continual improvement include:

与 ICH Q10 同步，合同给出者应该鼓励供应商对工艺的不断改进。供应商不断改进的能 力回馈到质量风险管理中去。KPI 的测量或者其他质量矩阵来管理和控制该工艺。系统 的持续改进包括：

Annual Product Reviews / Product Quality Reviews

产品年度报告/产品质量审核

- Management review of Quality System

质量系统管理审核

- Trending/monitoring of internal and external factors that can affect product or process

影响产品或工艺的内外部参数的监测与趋势

- Periodic trending of process data to establish control levels and process capability

过程数据的周期性趋势，建立控制水平和工艺能力

- Change control

变更

- Deviations and investigations

偏差与调查

- CAPA effectiveness monitoring CAPA 有效性监测
- Process Analytical Technology (PAT) improvement opportunities

在线监测技术改进的机会

Review of Key Performance Indicators (KPI) and improvement metrics

KPI 报告与改进矩阵

- Assessments by external parties (regulators third party auditors)

外部评估（监管部门、第三方）

5.5.4 Supplier Decommissioning

5.5.4 供应商终止

When a product or process is to be retired QRM should be employed to develop a strategy to suitably manage the proper steps to be taken to avoid impact to product quality supply and continuity. When decommissioning/retiring a product or process from a facility it is important to first determine if the product or process will be ceased all together (e.g. withdrawn from market) transferred to another facility. or have a new generation of product or process implemented in lieu of the previous. Based on this, a suitable strategy can be deployed utilizing knowledge management and QRM.

当一个产品或者工艺要停用的时候，应当应用质量风险管理来为避免影响产品质量与保 证持续供应安排合适的策略步骤。当从设施中终止一个产品或者工艺时，首先要决定是 否要把产品集中到一起（如从市场撤回），转移到其他设施，还是新一代的产品与工艺 来代替之前的。依据这些，应用知识管理与质量管理风险的得以安排合适的策略。

For transfer of product or process to another facility see Section 5.3QRM Application During Tech-nology Transfer.

当转移产品或工艺到新的设施时，参照 5.3 部分，技术转移的质量风险管理。

The following are some key points to consider when developing a joint QRM strategy for retiring a product and /or transferring from a CMO(s) organization:

以下是终止和/或从 CMO 转移产品技术的 QRM 衔接策略需要考虑的要点：

• Avoid a disruption in supply of a medically necessary product or material.
避免在医疗上必要的产品或材料的供应中断。
• Communicate findings that could impact the quality or safety of previously distributed material or products (e.g. records complaints failed validations).
影响之前分销的物料或产品的质量或安全性的沟通记录（如记录、投诉、失败的验证）
• Transfer key information to support product quality at the new facility.
支持新设施产品质量的关键信息
• Re-execute specific qualification studies e.g. sterilization to meet annual revalidation requirements.
再执行特别的确认研究，例如年度再验证需要的灭菌
5.6 Knowledge Management 5.6
知识管理
During the execution of risk assessment exercises .it is essential to obtain accurate data informed opinion and expert judgment to identify potential negative events , failure modes, their probabilities, Severities and subsequent risk evaluations. Orderly logical comprehensive documentation and ready accessibility to information benefits the decision and assessment processes. Generally the more information that is communicated to participants, the less likely they are to exhibit overconfidence in making accurate decisions and judgments (8,27). The clear communication by documentary evidence and preservation of such information is imperative to assist not only in accurate decision-making but also to record for future reference and other related risk assessment activities. Three important factors that might influence the ability of experts to make reliable assessments on subject areas or issues with a high level of uncertainty are:
在风险评估实践的执行中，获得准确的数据、观点和专家评价对于鉴别潜在的负面事件、 失败模式、可能性、严重性以及随后的风险评价都是非常重要的。有序逻辑详尽的文档 和随时可用的信息，对决定和评估程序都是有益的。提供参与者越多的信息，他们越不 会在做出决定和判断中过于自信（8，27)。通过书面证据和保存这些信息的清晰的沟 通是必要的，不仅有助于准确的决策更用以供将来参考以及其他相关的风险评估活动。 可能影响专家对学科领域或问题做出可靠的评估能力的三个重要因素是：
Availability of a well-developed and established scientific theory for the area under study
所研究领域已建立的完善科学理论的可用性
Availability of precise measuring techniques in that area of study.
所研究领域精确的测量技术
Availability of pre-specified procedures, criteria and guidelines for decision-making.
决策用已明确的步骤、标准与指南的可用性
To ensure expert opinion is of the highest caliber, data-based and as free from conjecture as possible the science and engineering information associated with the area of risk assessment should be clearly documented. Equally important, all information regarding measurement certainty, accuracy and precision, together with clearly communicated and documented decision criteria should be achieved.
为了保证专家的意见是最优秀的，以数据为基础，穷尽猜想，风险评估领域相关的科学 和工程信息应明确记载。同样重要的是，应达到有关测量确定性、准确性和精确性，以 及清楚地传达和记录决策标准。
6.0Conclusions 6.0 结论

QRM is fast becoming an expectation in the pharmaceutical industry and justifiably so.
Patient protection is paramount and the ultimate goal of QRM. While risk management practices and risk-based decision-making are not novel concepts doing so in a structured documented and practical manner is novel for the pharmaceutical industry. This represents a paradigm change in behavior and approach used for proactively identifying and preventing risks as early in the lifecycle as possible. Implementation of QRM is still a young field for the pharmaceutical industry and can be established in many ways. The information presented in this report and the cases studies provided in companion documents is based on practical experience and is not intended to be either all inclusive or exclusive.

质量风险管理已经迅速在制药工业风靡起来。对患者的保护是至高无上的，是应用 QRM 的终极目标。尽管风险管理实践、以风险为基础的决策并不是全新的概念，但以建设好 的、文件化的、实用的方式进行风险管理在制药界是全新的。这代表着生命周期中尽可 能早地用于主动识别和防范风险的行为和做法的转变。QRM 的实施在制药工业中仍是 一个不成熟的领域，可以通过多种方式来建立。本报告提供的信息，相关文档中提供的 案例研究基于实践经验，并无意全包或独占。

Effective management of product quality risks and patient protection throughout the product fe- cycle including manufacturing operations requires integration of QRM into the PQS and routine operations. QRM cannot be managed as a separate element or process of the Quality System, but integration is not easy to accomplish. QRM requires a mindset shift building quality in as early as reasonably possible effective transition and knowledge management between the different product lifecycle phases adequate resources and the entire organization's commitment to implement. Additionally, the role of decision makers
and senior management in ensuring effective implementation of QRM cannot be overemphasized.

在整个产品生命周期中有效的质量风险管理包括在生产操作中，在 PQS 以及日常操作中 需要完整的 QRM。QRM 不能只作为质量系统中孤立的要素或者过程，整合并不容易做 到。QRM 需要心态的转变，尽可能早地引进质量建设，不同产品生命周期阶段之间合 理有效的过渡和知识管理，足够的资源和整个组织承诺的执行。此外，决策者和高级管 理人员在确保有效实施质量风险管理中的重要作用再怎么强调都不过分。

The broad practical range and flexibility in QRM application provided by ICH Q9 can become a double edged sword; that is, the utility and benefits of QRM can be lost when activities are completed as "check the box" exercises(i.e. used to justify non-compliance with regulatory expectations or as a substitute for science / data)or if outcomes from quality risk assessments cannot be acted upon in a timely manner. The ultimate objective of all QRM activities must remain patient safety by producing safe efficacious and pure pharmaceutical products

ICH Q9 提供的 QRM 实际应用的宽泛性和调节性是一把双刃剑，当这一行动沦为“勾选”行为时（例如用来证明不符合监管预期或用以替代科学/数据），或者从质量风险评估 的结果不能及时采取行动，质量风险管理的效用和收益可能会丢失。质量风险管理的终 极目标一定是生产安全有效高纯度的药品来保证患者的安全。