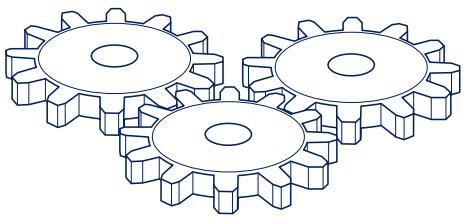
Technical Report No. 29 (Revised 2012)

Points to Consider for Cleaning Validation

PCMO℠

Paradigm Change in Manufacturing Operations℠

2012



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本书（TR29 Points to consider for Cleaning Validation (2012)）翻译工作由蒲公英制药技术论坛 www.ouryao.com 布克_41 发起主持。自 2013.09.16 发布 PDA TR29 翻译招募之日起，得到蒲友们的积极响应。热情参与本书的翻译工作，至今日 2014.128 日终于完成本书的翻译版并面世。全本近 100 页，历时 100 多天。对各位的利用业余时间进行翻译工作表示至真至诚的感谢!!

在此特别感谢以下参与翻译工作人员！

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PDA Task Force on Technical Report No. 29 (Revised 2012): Points to Consider for Cleaning Validation

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Points to Consider for Cleaning Validation

Technical Report No. 29 (Revised 2012)

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Paradigm Change in Manufacturing Operations (PCMO[SM])

PDA launched the project activities related to the PCMO program in December 2008 to help implement the scientific application of the ICH Q8, Q9 and Q10 series. The PDA Board of Directors approved this program in cooperation with the Regulatory Affairs and Quality Advisory Board, and the Biotechnology Advisory Board and Science Advisory Board of PDA.

Although there are a number of acceptable pathways to address this concept, the PCMO program follows and covers the drug product lifecycle, employing the strategic theme of process robustness within the framework of the manufacturing operations. This project focuses on Pharmaceutical Quality Systems as an enabler of Quality Risk Management and Knowledge Management.

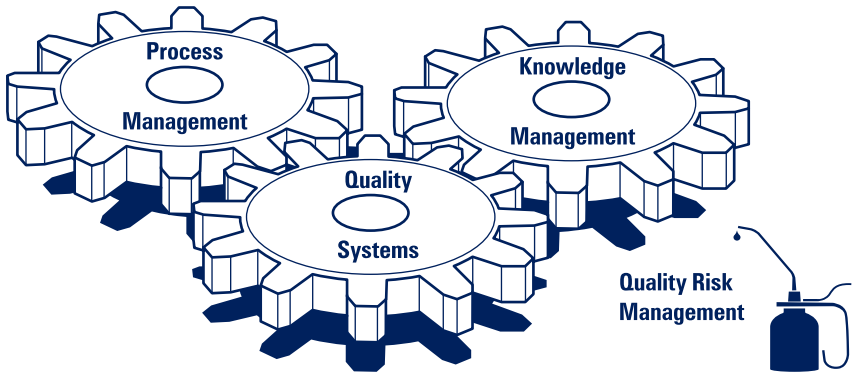
Using the Parenteral Drug Association's (PDA) membership expertise, the goal of the Paradigm Change in Manufacturing Operations Project is to drive the establishment of 'best practice' documents and /or training events in order to assist pharmaceutical manufacturers of Investigational Medicinal Products (IMPs) and commercial products in implementing the ICH guidelines on Pharmaceutical Development (ICH Q8, Q11), Quality Risk Management (ICH Q9) and Pharmaceutical Quality Systems (ICH Q10).

The PCMO program facilitates communication among the experts from industry, university and regulators as well as experts from the respective ICH Expert Working Groups and Implementation Working Group. PCMO task force members also contribute to PDA conferences and workshops on the subject.

PCMO follows the product lifecycle concept and has the following strategic intent:

- Enable an innovative environment for continual improvement of products and systems
- Integrate science and technology into manufacturing practice
- Enhance manufacturing process robustness, risk based decision making and knowledge management
- Foster communication among industry and regulatory authorities

The Product Life Cycle



For more information, including the PCMO Dossier, and to get involved, go to www.pda.org/pcmo

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1.0 Introduction

引言

Cleaning validation plays an important role in reducing the possibility of product contamination from pharmaceutical manufacturing equipment. It demonstrates that the cleaning process adequately and consistently removes product residues, process residues and environmental contaminants from the manufacturing equipment/system, so that this equipment/system can be safely used for the manufacture of specified subsequent products (which may be the same or a different product). As used in this Technical Report, "product" may be a drug product, active pharmaceutical ingredient, intermediate, or another type of formulation. If "drug product" is intended, that terminology will be utilized. Principles and practices given in this report may apply to a variety of manufacturing situations. It is incumbent on the reader to decide the appropriateness of those principles and practices to his/her specific situation.
清洁验证对于降低来自生产设备的药品污染的可能性有着重要作用。它证明了合适的清洁工艺可以持续充分除去生产设备上/系统中产品残留、工艺残留和环境污染，所以该设备/系统可以安全地生产后续产品（相同或不同产品）。在本技术报告中，"产品"可以是制剂、药物活性成分、中间体或其他处方类型。如果仅针对"制剂"，我们将用"制剂"这个术语。本报告给出的原则和规范可以用于各种生产情况。读者应自行决定这些原则和规范是否适用他/她的具体情况。

This report builds on the 1998 *PDA Technical Report No. 29, Points to Consider for Cleaning Validation* ***(1)***. This report also has utilized principles and specific wording from the 2010 *PDA Technical Report No. 49, Points to Consider for Biotechnology Cleaning Validation* ***(2)***. The authors of this revised Technical Report#29 would like to thank the members of the Task Forces who were responsible for those two earlier documents for making our job easier.
本报告建立在 1998 年 PDA 技术报告第 29 号"清洁验证要点"***(1)***的基础上。该报告还利用了 2010 年 PDA 技术报告第 49 号"生物技术清洁验证要点"的原则和具体内容***(2)***。本修订版技术报告第 29 号作者非常感谢这两个较早版本的工作组成员，使我们的工作变得更容易。

This revised Technical Report presents updated information that is aligned with lifecycle approaches to validation and the International Conference on Harmonisation (ICH) guidelines Q8 (R2) - *Pharmaceutical Development,* Q9 - *Quality Risk Management* and Q10 - *Pharmaceutical Quality System* ***(3,4,5)***. Also, this report aims to assist readers who want to create or benchmark a cleaning validation program for their equipment and facilities.
本修订版技术报告提出了更新的信息，即结合了生命周期的验证方法和国际协调会议（ICH）的指导原则 Q8 (R2) -药物开发、Q9-质量风险管理和 Q10-制药质量体系***(3,4,5)***。此外，这份报告也有助于读者建立或评估自己的设备、设施的清洁验证计划。

This Task Force was composed of European and North American professionals from pharmaceutical manufacturers, cleaning chemical suppliers, and consulting companies. The report has undergone a global, technical peer review to ensure concepts, terminology, and practices presented are reflective of sound science and can be used globally.
该工作组是由欧盟和北美的制药专家、清洁化学品供应商和咨询公司组成。该报告经过了一个全球性的技术同行评审，确保概念、术语、规范科学、合理，可在全球范围使用。

1.1 Purpose/Scope
目的/范围

This Technical Report covers all facets of cleaning validation for pharmaceutical manufacturers, including both manufacturers of APIs and drug products. It also applies to biotechnology manufacturing; however, the reader should consult *PDA Technical Report No. 49, Points to Consider for Biotechnology Cleaning Validation* for more detail and specifics for biotechnology manufacturing ***(2)***. We have included a lifecycle cleaning validation approach, including design/development of the cleaning process, process qualification (including the protocol runs), and ongoing validation maintenance. While the document discusses risk-based approaches, it does not provide details about risk-based manufacturing. PDA has formed a Task Force to write a Technical Report on that topic.

本技术报告涵盖了药品生产商清洁验证的各个方面，包括药物活性成分和药物制剂生产商。也可以用于生物制药，但读者应该查阅 PDA 技术报告第 49 号“生物技术清洁验证要点” ***(2)***，获得生物技术制造方面更多的细节和特性。我们采用了生命周期的清洁验证方法，包括清洗工艺的设计/开发、工艺确认（包括方案实施）和持续验证维护。尽管采用了基于风险的方法，本报告没有详细论述基于风险的生产。PDA 已经成立了撰写该主题技术报告的工作组。

We cannot emphasize enough how important risk analyses are in the selection of and validation of cleaning processes and their validation. This includes the traditional risk analysis based on effects on product quality and on patients. It also includes business risk considerations, such as steps taken to minimize lost product from contamination (even if detection systems are in place to prevent release of that contaminated product for consumer use).

我们怎么强调风险分析在清洁工艺的选择和验证过程中的重要性也不为过。这包括传统的基于对产品质量和对患者的影响的风险分析。也包括商业风险的考虑，例如采取措施将产品污染损失降至最低（即使有检测系统防止受污染的产品被放行）。

These practices and the associated guidance in this Technical Report are based on technical considerations and should be applicable in all regulatory environments. However, the intent of this Technical Report is not to provide a detailed plan or roadmap for a pharmaceutical manufacturer to perform cleaning validation. Rather, as the title suggests, it presents “points to consider” as one designs a cleaning validation program for process equipment based on an understanding of one’s manufacturing and cleaning processes. In cleaning validation, there are generally *multiple* ways to accomplish the same goal of a compliant, scientifically sound and practical cleaning validation program. Where options are given, the rationales for such options are also generally given. Examples are not meant to be prescriptive or limiting; they merely illustrate a certain practice. Actual acceptable practices should not be considered limited by the discussion in this Technical Report. Based on an understanding of the unique nature of any individual situation, different approaches or additional issues should also be considered. Sound science based on an understanding of the cleaning and manufacturing processes may lead to other equally acceptable practices. The Task Force that developed this document hopes that the report will be used in this spirit and will not be solely used as a checklist.

本技术报告中的这些规范和相关指南是基于技术考虑并可以用于所有监管环境。但是，本技术报告的目的不是为药品生产商进行清洁验证提供详细的计划或路线图。相反，正如标题所示，本报告提出了“清洁验证需考虑的要点”，基于对生产和清洁工艺的理解进行工艺设备清洁验证计划的设计。在清洁验证中，通常有多种方式来建立合规的、科学合理的和切实可行的清洁验证计划。大凡选择就有选择的理由。所举的例子并不意味着规范或限制，他们只是列举了某种做法。实际可接受的做

法不应被本技术报告中讨论所限制。基于对任何单个情况独特性的理解，不同的方法或其他问题也应考虑。对于清洁和制造工艺的合理、科学理解可能会导致其他同样可以接受的做法。制定本文件的工作组希望该报告的使用应本着这一精神而不仅仅作为一个检查清单使用。

This report should be considered to be a resource to help guide the development or evaluation of a cleaning validation program. It is not intended to establish mandatory standards for cleaning validation. It is intended to be a single-source overview for pharmaceutical manufacturers that complements existing regulatory guidance and other documents referenced in this document. The reader should also be aware that a specific topic may be discussed in several sections of this Technical Report. Therefore, a more complete perspective may be obtained by considering all relevant sections about a certain topic. Furthermore, while many approaches are presented here, specific approaches utilized for a given cleaning process should be selected based on a good understanding of that process, as well as the appropriateness of the selected practice for that specific situation. It is not enough to merely say that the practice is mentioned as an acceptable one in PDA Technical Report No. 29; each firm should be prepared to defend why the selected approach is a valid one for its operations *(1)*.

该报告应被视为一种资源，以帮助指导清洁验证计划的开发或评估。它的目的不是建立清洁验证的强制性标准。希望它作为唯一的综述，为药品生产企业提供现有的监管指南和本文档中引用的其他文件的补充。读者也应该知道，一个特定的主题可能会在这个技术报告的几个章节中讨论。因此，一个更完整的观点可以通过关于某个主题的所有相关章节获得。此外，虽然这里介绍了许多方法，对于一个给定的清洁工艺中使用的具体的方法的选择应该基于对清洁工艺的很好理解，以及在该特定情况下所选择的方法的合适性。只说“这种操作在 PDA 技术报告第 29 号是作为一个可以接受的操作”是不够的，每个企业应该准备回答为什么所选择的方法是一个有效的方法*(1)*。

2.0 Glossary of Terms

术语集

Acceptable Daily Exposure：A dose that is unlikely to cause an adverse effect if an individual is exposed, by any route, at or below this dose every day for a lifetime.
可接受的日暴露量：指通过任何途径，在等于或低于此剂量时一个人终身接触都不可能造成不利影响的剂量。

Acceptable Daily Intake：An amount of a substance consumed on a daily basis that is considered at a safe level.
可接受的每日摄入量：每日摄入某种物质被认为是安全水平的剂量。

Acceptance Criteria：Numerical limits, ranges, or other suitable measures for the acceptance of test results.
可接受标准：接受测试结果的数值限度，范围，或其它合适的测量值。

Acceptance Limit：The maximum amount of residue allowed in a product, in an analytical sample, or as an amount per surface area.
可接受限度：产品中允许的最大残留量，以分析样品中残留含量或每表面积残留数量表示。

Active Pharmaceutical Ingredient (API) orDrug Substance：Any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product and when used in the production of a drug, becomes an active ingredient of the drug product (also called “drug substance”).
药用活性成分（API）或原料药：用于制备制剂的任何物质或混合物质，如果用于生产药品，该物质或混合物就为制剂的一个活性成分（也称为“原料药”）。

Analyte：Substance (usually a residue) for which an analysis is being performed.
分析物（待测物）：将要被分析的物质（通常是指残留物）。

Blank：Analytical sample taken to establish backgroundvalue for the analytical measurement which may be subtracted from an experimental value to determine the “true” value.
空白对照：用于分析测量建立背景值的分析样品，可将实验测试结果减去该背景值以确定“真”值。

Campaign：Processing of multiple lots or batches of the same product serially in the same equipment.
阶段性生产：多个批次的同一产品在同一设备连续加工。

Changeover：The steps taken for switching multiproduct equipment from the manufacture of one product to themanufacture of a different product.
切换生产：指在多品种生产设备上从一个产品的切换至另一产品的制造所采取的步骤。

Clean：Having product residues, process residues, and environmental contaminants removed to an acceptable level.

清洁：将产品残留、工艺残留和环境污染物去除至可接受的水平。

Clean Hold Time：The time from the end of the cleaning process until the equipment is used again (which may be product manufacture, autoclaving, or a steam in place (SIP) cycle).
清洁保持时间：指从清洁工艺结束至设备再次使用（也可以是产品生产、高压灭菌或在线蒸汽灭菌（SIP）。

Cleaning Agent：The solution or solvent used in the washing step of a cleaning process. Examples of cleaning agents are water, organic solvent, commodity chemical diluted in water, and formulated detergent diluted in water.
清洁剂：清洁工艺中用于清洗步骤的溶液或溶剂。清洁剂有水、有机溶剂、用水稀释的日用化学品和用水稀释的配方洗涤剂。

Cleaning Procedure：The documentation that assures any product and process-related material introduced into equipment as part of the manufacturing process stream is removed and the equipment is adequately stored.
清洁规程：指保证随生产引入到设备中的所有产品及工艺相关的物料被除去，设备被适当地存放的文件。

Cleaning Process：A process that is used to remove any product, process-related material and environmental contaminant introduced into equipment as part of the manufacturing stream.
清洁工艺：指清除因生产而引入设备的任何产品、工艺相关的物料和环境污染物的过程。

Cleaning Validation：Documented evidence with a high degree of assurance that a cleaning process will result in products meeting their predetermined quality attributes throughout its life cycle.
清洁验证：指一个清洁工艺能够确保产品在其生命周期内满足预定质量属性的有效证明文件。

Cleaning Verification：A one-time sampling and testing to ensure that specified equipment has been properly cleaned following a specific cleaning event.
清洁效果确认：一次性取样和测试以确保所指定的设备在清洁后已得到适当清洁。

Contamination：An undesired residue or residue level on cleaned equipment surfaces or in a manufactured product.
污染：指在已清洁的设备表面或生产的产品中不期望的残留物或残留水平。

Coupon：A small, generally flat portion of a defined material of construction (such as stainless steel or PTFE) and of a defined surface finish, typically used for laboratory cleaning evaluations and/or for laboratory sampling recovery studies
材质试样：一块小的、通常是平整的特定材质（如不锈钢或 PTFE）样品，经过特定表面处理，主要用于实验室清洁评估和/或用于实验室取样回收率研究。

Dedicated Equipment：Equipment used exclusively for the manufacture of only one drug product, bulk drug substance, or intermediate.
专用设备：专门用于一种制剂、原料药或中间体生产的设备。

Degradation：Breakdown (usually chemical) of material during manufacture (including during and after the cleaning process).
降解：在制造过程中（包括清洁过程及清洁后）物质的分解（通常是化学的）。

Dirty Hold Time：The time from the end of product manufacturing until the beginning of the cleaning process (also called “soiled hold time”).
生产后保持时间：生产结束至清洁过程开始的时间（也叫“脏污保持时间”）。

Dry Equipment：No visible water in the equipment or line when viewed under appropriate lighting conditions.
干燥的设备：在适当照明条件下观察设备或生产线无可见水分。

Equipment Train：The sequence of equipment through which a product is produced or processed.
设备组：按照产品生产或加工流程排列的一组设备。

Free Drained Equipment：No visible water pool in the equipment or line when viewed under appropriate lighting conditions (but may contain water droplets).
自排水设备：在适当的照明条件下观察设备或生产线无可见积水（但可能含有水滴）。

Grouping Strategy：A strategy for establishing similar cleaning processes, usually based onsimilar products or similar equipment, and to validate the cleaning process based primarily on validation data for a representative of the group.
分组策略：是指根据同类产品或类似设备建立类似的清洁工艺的策略，主要根据代表性的产品/设备的验证数据来验证该清洁工艺。

Highly Hazardous Drug Active：A drug active that can cause serious adverse effects at typical doses. Those adverse effects are generally not related to the main therapeutic activity of the drug, and includes effects such as carcinogenicity, mutagenicity, genotoxicity, reproductive hazards, allergenicity, and cytotoxicity.
高度危险的药物活性成分：指在常用剂量下可导致严重副作用的药物活性成分。这些副作用通常与药物治疗的主要功能是不相关的，包括致癌性，致突变性，基因毒性，生殖危害，致敏性和细胞毒性。

Investigational Medicinal Product：A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial.
临床用药品：活性物质或安慰剂的药物制剂，用于临床试验的测试或对照。

LD_{50}：The dose of a material which results in 50% mortality in an animal test
半数致死量：动物实验中导致 50%死亡的剂量。

Limit：A value for a residue above which a cleaning process would not be acceptable
限度：指一残留物水平，超过该数值，则该清洁工艺不符合要求。

Marker：Component of a product or a cleaning agent used as an analyte to quantitate the total amount of product or cleaning agent present.
标记物：一个产品或清洁剂的成分，作为分析物对产品或清洁剂总量进行定量。

Mock Soil：A soil which is used in place of the manufactured product during a cleaning validation protocol (also called a “surrogate” soil).
模拟污物：清洁验证中用于替代所生产产品的污物（也叫“污物替代物”）。

Mock Soiling：A process of soiling the equipment for a cleaning validation protocol in which soil is applied to the equipment surfaces to simulate the condition of the soil on those surfaces following typical product manufacturing.
模拟脏污：清洁验证方案中弄脏设备的过程，即将污物涂布至设备表面以模拟常规产品生产后设备表面上脏污状况。

Normal Dose：The therapeutic dose of a product as given on the approved product labeling.
正常剂量：指经批准在产品标签上列出的产品治疗剂量。

Product Changeover：Procedural steps taken forswitching from the manufacturing of one product to another product.
产品切换：从制造一种产品切换到另一种产品所采取的程序。

Recovery Study：A laboratory study combining the sampling method and analytical method to determine the quantitative recovery of a specific residue for a defined surface.
回收率研究：结合取样方法和分析方法确定特定表面上残留物定量回收率的实验室研究。

Residue：Chemical or microbiological material remaining on equipment surfaces after a cleaning process.
残留物：清洁后残留在设备表面的化学物或微生物。

Soil：The chemical or microbiological materials left on process equipment after completion of process manufacturing, but before initiation of the cleaning process.
污物：生产结束之后清洁开始之前遗留在工艺设备上的化学或微生物物质。

Worst-Case Process Condition：A condition or set of conditions encompassing upper and/or lower processing limits and circumstances, within standard operating procedures, which pose the greatest chance of product or process failure when compared to ideal conditions (such conditions do not necessarily induce product or process failure).
最差工艺条件：指在标准的操作程序中包含工艺限度和工艺条件上下限的一个或一组工艺条件。与理想条件比较产品或工艺会产生最大的失败机会（这些条件不一定会引起产品或过程失效）。

Worst Case Soil：A soil that is the most difficult to clean from production equipment based on knowledge generated from laboratory studies, scientific properties, and/or production experience.
最差污物：指基于实验室研究、科学性质和/或生产经验等知识确定的最难从生产设备上清洁的污物。

2.1 Definition of Acronyms 首字母缩略词

AA: AtomicAbsorption
AA:原子吸收

ADE: Acceptable Daily Exposure
ADE:可接受的日暴露量

ADI: Acceptable Daily Intake
ADI:可接受的每日摄入量

API: Active Pharmaceutical Ingredient
API:药物活性成分

CAPA: Corrective and Preventive Actions
CAPA:纠正与预防措施

CBER: Centers For Biological Evaluation and Research
CBER:生物评价与研究中心

CDER: Centers for Drug Evaluation and Research
CDER: 药物评价与研究中心

CFU: Colony Forming Unit
CFU:菌落形成单位

CGMPs: Current Good Manufacturing Practices
CGMPs:现行药品生产质量管理规范

CIP: Clean-In-Place
CIP:在线清洁

COP: Clean Out-of-Place
COP:离线清洁

CPP: Critical Process Parameters
CPP:关键工艺参数

CQA: Critical Quality Attributes
CQA:关键质量属性

CZE: Capillary Zone Electrophoresis
CZE: 毛细管区带电泳法

DOE: Design of Experiments
DOE:实验设计

ELISA: Enzyme Linked Immunosorbant Assay
ELISA:酶联免疫吸附测定法

EPDM: Ethylene Propylene Diene Monomer Rubber
EPDM:三元乙丙橡胶

EU: Endotoxin Units
EU:内毒素单位

U.S. FDA: Food and Drug Administration
U.S. FDA： 美国食品药品监督管理局

FMEA: Failure Mode and Effects Analysis
FMEA:失效模式与效果分析

FTIR: Fourier Transform InfraRed
FTIR:傅立叶变换红外光谱

HPLC: High Performance Liquid Chromatography
HPLC:高效液相色谱法

ICH: International Conference on Harmonisation
ICH:国际协调会议

ICP: Inductively Coupled Plasma
ICP:电感耦合等离子体

IMS: Ion Mobility Spectrometry
IMS:离子迁移光谱

LOD: Limit of Detection
LOD:检测限

LOQ: Limit of Quantitation
LOQ:定量限

MAC (or MACO): Maximum Allowable Carryover
MAC (or MACO):最大允许残留量

NOEL: No Observable Effect Level
NOEL:无可见作用水平

NOAEL: No Observable Adverse Effect Level
NOAEL:无可见损害作用水平

NIR: Near Infrared
NIR:近红外

LD_{50}: LethalDose 50 Percent
LD_{50}:半数致死量

PAI: Pre-Approval Inspection
PAI:批准前的检查

PAT: Process Analytical Technology
PAT:过程分析技术

PIC/S: Pharmaceutical Inspection Cooperation Scheme
PIC/S:国际药品检查合作组织

PLC: Programmable Logic Controller
PLC:可编程逻辑控制器

PPQ: Process Performance Qualification
PPQ:工艺性能确认

PTFE: PolyTetraFluoroEthylene
PTFE:聚四氟乙烯

PW: Purified water
PW:纯化水

QA: Quality Assurance
QA:质量保证

QbD: Quality by Design
QbD:质量源于设计

QC: Quality Control
QC:质量控制

OIT: Operator Interface Terminal
OIT:操作员界面终端

RSD: Relative Standard Deviation
RSD:相对标准偏差

SAL: Surface Acceptance Limit
SAL:单位表面积限度

SEM: Scanning Electron Microscopy
SEM:扫描电子显微镜

SIP: Steam-In-Place (or Sterilization-In-Place)
SIP:在线蒸汽灭菌（或在线灭菌）

SPC: Statistical Process Control
SPC:统计过程控制

SOP: Standard Operating Procedure
SOP:标准操作程序

SUPAC: Scale Up and Post Approval Changes
SUPAC:放大和批准后变更

TACT: Time, Action, Concentration and Temperature
TACT:时间、作用、浓度和温度

TLC: Thin Layer Chromatography
TLC:薄层色谱法

TNTC: Too Numerous To Count
TNTC：不可计数

TOC: Total Organic Carbon
TOC:总有机碳

TTC: Threshold of Toxicological Concern
TTC:毒理学关注阈值

UPLC: UltraPerformance Liquid Chromatography
UPLC: 超高效液相色谱

UV/Vis: Ultraviolet/visible Spectrophotometry
UV/Vis:紫外/可见分光光度计

WFI: Water for Injection
WFI:注射用水

WHO: World Health Organization
WHO:世界卫生组织

3.0 Cleaning Process Design and Development

清洁工艺设计和开发

This section describes the application of operational parameters and measurements, design of laboratory scale experiments, selection of appropriate test soils, and scale-up for the cleaning of the manufacturing equipment. Additionally, the concept of "Design Space," a Quality by Design approach to the development of pharmaceutical processes, is discussed and applied to the development of cleaning processes.
本节介绍了运行参数和测量的应用、实验室规模的实验设计、选择合适的测试污物，制造设备的清洁工艺放大。此外，还讨论了“设计空间”概念、制药工艺开发的“质量源于设计方法”，并应用于清洁工艺开发。

The cleaning process requires design and development *prior to* implementation in a manufacturing plant to ensure the cleaning process and equipment are acceptable for use.
制造厂在执行清洁工艺之前需要进行设计和开发，以确保清洁工艺和设备符合使用要求。

The operational parameters that describe the cleaning process include:
描述清洁工艺的运行参数包括：

- Cleaning agent
  清洁剂
- Concentration
  浓度
- Contact time
  接触时间
- Temperature
  温度

Factors which affect the cleaning process include:
影响清洁工艺的因素包括：

- Product characteristics
  产品性质
- Product condition
  产品状态

Relevant specifics about the cleaning equipment include:
清洁设备相关特性包括：

- Automated cleaning pathways
  自动化的清洗方法
- The sequence of manual or automated cleaning steps
  各手工或自动化清洁步骤的顺序
- Flow rates during each step
  每一步骤时的流速

These operational parameters should be determined prior to implementation.

这些运行参数应在执行前确定。

Generally, establishment of acceptable cleaning processes (or confirmation of acceptable processes for new soils being introduced to the manufacturing plant) follows a standard progression of activities, beginning with identification of control variables, cleaning measurements, and performance criteria. Laboratory (scale-down) experimentation, analogous to laboratory experimentation for process characterization, along with specific equipment requirements may provide data to establish cleaning parameter control ranges.
一般来说，建立可接受的清洁工艺（或确认可接受工艺是否适用于新引入生产中的污物）活动遵循一个标准过程，始于控制变量的识别，到清洗效果测量，最后与标准进行比较。类似于实验室的工艺表征实验，实验室（工艺缩小）的实验，连同特定设备需求可以提供确定清洁参数控制范围的数据。

3.1 Cleaning Process Design
3.1 清洁工艺设计

Design starts with a consideration of the Critical Process Parameters (CPPs) and Critical Quality At tributes (CQAs) of the cleaning system. **Table 3.1-1** lists representativeCPPs and CQAs that might be applicable to a cleaning process.
设计始于对清洁系统关键工艺参数（CPPs）和关键质量属性（CQAs）的考虑。表 3.1-1 列举了适用于清洁工艺的有代表性的 CPPs 和 CQAs。

Table 3.1-1CPP and CQA Considerations that have Potential Risk Impact to a Cleaning Process ***(2)***
表 3.1-1 对清洁工艺有潜在风险影响的 CPPs 和 CQAs

Critical Process Parameters 关键工艺参数	Critical Quality Attributes 关键质量属性
• Process temperature 工艺温度 • Process pressure 工艺压力 • Process flow 工艺流量 • Process time 工艺时间 • Cleaning agent concentration 清洁剂浓度 • Dirty hold time (soil condition) 生产后保持时间（脏污状态） • Clean hold conditions 清洁后保持时间	• Visual detection or limits 目视检测或限度 • Cleaning agent residues 清洁剂残留 • Product residues 产品残留 • Microbiological residue limits 微生物残留限度 • Drainability/drying 排水能力/干燥 • Conductivity/resistivity 电导率/电阻率

Table 3.1-2 describes the factors in the cleaning spectrum. For each factor, there is a range of possible operating differences utilized within the industry. The development of a specific process should consider the number and complexity of issues surrounding the cleaning process and the variety of facilities, products and equipment in use.
表 3.1-2 描述了清洁谱所包含的因素。对于每个因素，行业内使用的范围存在着可能的操作差异。

具体工艺的开发应考虑清洁工艺相关问题的多少和复杂程度，以及使用的各种设施、产品、设备。

The cleaning spectrum helps manufacturers to establish the factors which are critical for individual processes, thereby enabling them to set priorities, develop grouping philosophies and establish the ‘‘scientific rationales’’that will govern the cleaning program. The cleaning spectrum can be used during the initial phases of defining a cleaning validation program or during a new product cleaning process development.

清洁谱帮助厂商建立每个清洁工艺的关键因素，从而使他们设置优先级，开发分组的基本原理和建立“科学依据”，并形成清洁计划。清洁谱可用于确定清洁验证计划的初始阶段或用于新产品清洁工艺开发过程中。

The cleaning spectrum includes cleaning program criteria, equipment characteristics, quality attributes of equipment design, formulation/product attributes, and manufacturing/process attributes. All of the factors in the cleaning spectrum directly affect the ability to clean; however, their relative importance and criticality may be different in different situations.

清洁谱包括清洁标准、设备特性、设备设计的质量属性，制剂产品属性，以及制造工艺属性。清洁谱中的所有因素直接影响清洁能力。但是，它们的相对重要性和关键性在不同的情况下可能会有所不同。

Table 3.1-2 TheCleaning Spectrum

表 3.1-2 清洁谱

Automated Cleaning 自动化清洁	Manual Cleaning 手动清洁
In-place Cleaning 在线清洁	Out-of-Place Cleaning 离线清洁
Dedicated Equipment 专用设备	Non-Dedicated Equipment 非专用设备
Indirect Product Contact Surfaces 间接的产品接触表面	Product Contact Surfaces 产品接触表面
Low Risk Site 低风险区域	High Risk Site 高风险区域
Minor Equipment 次要设备	Major Equipment 重要设备
Low Risk Drugs 低风险药物	High Risk Drugs 高风险药物
Highly Characterized 高度表征	Poorly Characterized 不充分表征
Liquid Formulations 液体制剂	Solid Formulations 固体制剂
Easy to Clean Product 易清洁产品	Difficult to Clean Product 难清洁产品
Materials with a Smooth, Non-porous Surface 表面光滑、无孔材料	Porous Materials 多孔材料

Single Product Facility 单一产品厂房	Multiple Product Facility 多产品共用厂房
Non-Campaigned Production 非阶段性生产	Campaigned Production 阶段性生产

3.2 Cleaning Process Overview
3.2 清洁工艺概况

Cleaning processes generally contain multiple steps. Each step in the process has a function and a set of parameters that are controlled within defined ranges to ensure effective soil (and cleaning agent) removal. Steps in a typical cleaning cycle for a cleaning process are outlined below in **Table 3.2-1**. Details of the cleaning processes may vary from site-to-site and for different types of process equipment. Differences may include the use and type of detergents and/or solvent, presence of an acid cleaning step, concentration of cleaning agents, contact time of cleaning agents on equipment, feed pressure or flow rate, cleaning temperature, and required length or volume, length and/or number of rinse steps.

清洗过程中通常含有多个步骤。在这个过程中每一步都有一种功能和一组参数，这些参数控制在限定范围内以确保污物（和清洁剂）的有效去除。在清洁工艺中一个典型的清洁行程包含的步骤见下表 3.2-1。清洁过程的细节可能随不同工厂和不同工艺设备类型而发生变化。差异可能包括洗涤剂和/或溶剂的使用及类型、是否有酸洗步骤、清洁剂的浓度，清洁剂和设备的接触时间，进料压力和流速、清洗温度和所需的长度或体积，冲洗步骤所需时间/冲洗液体积，和/或所需时间/冲洗次数。

Table 3.2-1 Cleaning Process Steps (Examples)
表 3.2-1 清洁工艺步骤（示例）

Step 步骤	Function 功能	Comments 注解
Vacuum or PreRinse 真空或预冲洗	Removal of readily soluble and/or non-adhering residues 去除易溶性和/或非粘附的残留物。	Reduction of soil load prior to washing step. 洗涤步骤之前减少污物负载。
Washwith Cleaning Solution 清洁溶剂洗涤	Removal of soluble and dried residues, solubilization of soils by degradation, heat, and/or wetting with detergents 去除可溶且干燥的残留物，通过降解、加热和/或用洗涤剂润湿来溶解污物。	Primary step for soil and bioburden removal. Often performed at elevated temperatures. 污物和生物负荷除去的第一步；经常在较高温度下进行； May includealkalinedetergentsor alkali hydroxides, acid detergents or acids, combinations of the two, or may be a solvent or solvent mixture. 可包括碱性洗涤剂或碱金属氢氧化物、酸性洗涤剂或酸、两者的组合，或者可以是一种溶剂或溶剂的混合物。
Rinse **冲洗**	Removalof suspendedor solubilized soils and, if applicable, of cleaning solution 去除悬浮或溶解的污物，如果适用，除去清洗液。	May includea seriesof pulse rinses, and may include final rinse with higher grade of rinse solvent. 可能包括一系列的喷淋冲洗，并可包括用更高级别冲洗溶剂的最终冲洗。

Dry **干燥**	Removal of water and other solvents 除去水和其它溶剂。	Maybe done by air or nitrogen flow or by heat. Water removal may be assisted by an organic solvent final rinse. 可以通过空气或氮气吹干，或通过加热完成。除去水分时可辅以有机溶剂的最后冲洗。

3.2.1 Physical-chemical Aspects

3.2.1 物理-化学方面

There are four principal cleaning input parameters that can be varied for each step in the cleaning process. These four parameters are typically referred to as TACT (**T**ime, **A**ction, **C**oncentration, and **T**emperature). These four variables are interrelated and have a direct relationship on the success of each phase in the cleaning cycle. For example, cleaning agents may be heated to increase their effectiveness. The effect of each of these variables on soil removal should be determined and acceptable ranges established as part of the cleaning development effort. (Soil type and condition is an additional input that is discussed in **Section 3.3.3.)**

在清洗过程中有四种主要的清洗输入参数，这些参数在每个步骤中是可以变化的。这四个参数通常被称为 TACT（时间、作用、浓度和温度）。这四个变量是相互关联的，与清洁行程每个阶段的成功有直接的关系。例如，可加热清洁剂以增加其有效性。作为清洁开发活动的一部分，应该确定每个变量对污物去除的影响，并建立可接受范围。（污物类型和状态作为额外的输入参数，将在 3.3.3 节中讨论。）

Time is defined as the length of time for the cycle step. There are two typical ways, direct and indirect, of defining and measuring contact time during a cycle step. Using the direct method, a cycle step counter is used to measure the cycle step time. Time also may be measured indirectly. For example, for a rinse step, volume is sometimes tracked instead of time because the volume and flow rate define a time. For final water rinse, it is also common to add more requirements, such as achieving a specified conductivity level.

时间被定义为清洗步骤的时间长度。在一个清洗步骤中有两种典型的定义和测量接触时间的方式：直接的和间接的。直接法中采用计时器来测量清洗步骤的所需时间。也可采用间接法测量时间。例如，对于冲洗步骤，有时记录体积而不是时间，因为通过体积和流速可以得出所需时间。对于最终淋洗水冲洗，通常有更多要求，如达到指定的电导率水平。

Action is the mechanism used to deliver the cleaning agent. This mechanism may be characterized as soak, scrubbing, impingement or turbulent flow. Agitation often enhances the chemical actions of the cleaning agents and helps to increase the effectiveness of the cleaning process, such as by shortening the required contact time. Manual cleaning typically includes soaking or scrubbing as the action to achieve cleaning. Automated cycles typically employ impingement and/or turbulence as a cleaning action. The mechanisms of action should be understood for each cleaning process step. If critical, the flow rate of the cleaning and rinse fluids traveling through the equipment should be specified and verified in the cleaning process. Spray devices have minimum and maximum flow rate requirements, and piping should be flushed at a velocity sufficient to assure adequate coverage and turbulence.

作用是指用于提供清洁剂的机制，可表现为浸泡、洗涤、冲击或者湍流。搅拌通常会增强清洁剂的化学作用，并有助于提高清洁工艺的有效性，如此缩短所需的接触时间。手动清洁通常包括浸泡或擦洗来达到清洗效果。自动清洁行程通常采用冲击和/或湍流作为清洁措施。应理解清洗工艺中的每

个步骤的作用机制。如果清洁剂和冲洗液流速是关键的，则应规定清洁剂和冲洗液的流速，并得到确认。喷淋装置具有最小和最大流速的要求，冲洗管道时应有足够的流速以保证足够的覆盖率，并保持湍流状态。

Cleaning agent *concentrations* directly affect the performance of the cleaning process. Selection of the cleaning agent should consider various aspects including soil type, ease of removal, and need for chelating agents. Cleaning chemicals are available in concentrated forms that are diluted and used in cleaning cycles. Effectiveness of the cleaners may be related to their concentration. Too low of a concentration may result in failure to remove the soil from equipment; too high of a concentration may result in difficulty in removal of cleaning agent residues and may require excessive rinsing. Chemicals may be costly, both in their purchase and disposal, and thus determining the correct concentration of cleaning agent required to ensure cleanability should be considered. The automated dilution and addition of the cleaning agent to the cleaning equipment system must be designed for reproducibility. Regardless of the method of addition, confirmation or verification of the cleaning agent concentration helps verify consistency. For automated cleaning processes, the easiest means to verify cleaning agent concentration for highly alkaline or acidic aqueous cleaning agents is by conductivity. Other considerations in the use of cleaning agents include a toxicity/safety evaluation and the possible need for surfactants, chelants and other functional aids in formulated detergents.
清洁剂的浓度直接影响清洗工艺中的性能。清洁剂的选择应考虑的各个方面，包括污物类型、易于去除和需要的螯合剂。清洁化学品可以是浓缩型，稀释后用于清洁。清洁剂的效果可能与它们的浓度有关。过低的浓度可能会导致无法从设备中除去污物；浓度太高，可能会导致难以去除清洁剂的残留并可能需要大量冲洗。无论是购买还是处置，化学品可能是昂贵的，因此应考虑确定所需的清洁剂浓度以确保可清洁性。清洁剂自动稀释和加入至清洁设备系统的设计，必须使其具有可重复性。无论添加方法如何，确认清洁剂的浓度有助于证实该方法的一致性。对自动清洁工艺，最简单的确认强碱性或酸性水溶液清洁剂浓度的方法是测量其电导率。在使用清洁剂需考虑的其他因素包括毒性/安全性评价和可能需要的表面活性剂、螯合剂和配方洗涤剂中的其他功能助剂。

A process should be in place to detect anomalies in detergent concentration based on the mechanism by which chemical make-up is performed. For example, some systems control chemical addition by volume and use conductivity as a confirmation. An alarm would be triggered if the conductivity is outside a preset range. The allowable range should be supported by cleaning development data.
一个工艺应基于化学组成的机制及时发现洗涤剂浓度的异常。例如，某些系统通过体积控制化学品添加，使用导电率作为确认方法。如果导电率在预先设定的范围之外，将触发一个警报。允许的范围应有清洁开发数据的支持。

The optimal *temperature* rangeswill vary for the different steps of the cleaning process. Initial solvent rinses are typically performed at ambient temperatures to minimize any denaturation or degradation effects and to maximize the dilution effects. Cleaning solutions may be heated to increase their effectiveness. Final rinse solvent steps may be performed at high temperatures to increase the solubility of cleaning process residues and to increase the drying rate of rinse solvents.
最适温度范围：对清洁工艺中的不同步骤会有所不同。首次溶剂冲洗通常在常温下进行，以尽量减少任何变性或降解的影响，并获得最大的稀释效果。清洁剂可以被加热以增加其有效性。最后溶剂冲洗的步骤可以在高温下进行，以增加残留物的溶解度，并提高冲洗溶剂的干燥速率。

3.3 Design Considerations
3.3 设计考虑

3.3.1 Location of Cleaning
3.3.1 清洁位置

Equipment may be cleaned at its installed location, or it may be disassembled and moved to a central location for cleaning.
设备可以在其安装的位置清洁，也可以被拆卸并移动到一个清洗间进行清洁。

3.3.1.1 In-Place Cleaning
3.3.1.1 在线清洁

The cleaning of large pieces of equipment may be performed in the equipment's permanent location, generally in a configuration very similar to that in which it is utilized for production. In this document, in-place cleaning can be either for automated or manual cleaning processes.
大型设备的清洁可以在设备的安装位置进行，一般与其用于生产时的布局非常相似。在本文档中，在线清洁可以是自动或手动清洁工艺。

3.3.1.1.1 Clean-in-Place (CIP) Systems
3.3.1.1.1 在线清洁（CIP）系统

The term ''Clean-in-Place'' usually refers to an automated system that consists of a system which uses various tanks and piping to deliver a cleaning solution through the equipment to be cleaned. There may be a pre-rinse tank and a final rinse tank. The CIP system utilizes spraying devices to provide coverage and physical impingement of the cleaning solution on the process equipment surfaces. The spray- balls may be stationary or moving (e.g., rotating, oscillating). These systems are commonly used to clean large pieces of equipment, such as manufacturing tanks, blenders, fluid bed dryers, reactors and fermentation tanks. The CIP system may be a recirculation system or it may be a single-pass system.
术语“在线清洁”通常是指一个自动化的系统，该系统使用各种罐和管道输送清洁液至待清洁的设备。也许还有一个预淋洗罐和一个最终淋洗罐。该 CIP 系统利用喷洒装置将清洁液覆盖工艺设备表面并通过物理冲击除去污物。喷淋球可以是静止的或运动的（例如，旋转、摆动）。这些系统通常被用来清洗大件的设备，如制造罐，混料机，流化床干燥机，反应器和发酵罐。该 CIP 系统可能是一个再循环系统，或者它可以是一单程系统。

Centralized CIP systems can provide a single location for handling cleaning agents and reduce the plant requirements for cleaning-related equipment (pumps, tanks) and instrumentation. However, centralized systems often require interconnected piping designs and may complicate desires to segregate parts of the process. Some process equipment may require special cleaning agents that are different than those used for the rest of the process equipment. For these situations, dedicated CIP systems that are integrated into the process skids may be desirable.
中央 CIP 系统：可以提供一个单独位置处理清洁剂，并降低企业对清洁有关的设备（泵，罐）和仪器仪表的需求。然而，集中式的系统往往需要相互连接的管道设计和复杂的工艺分隔。某些工艺设备可能需要不同于其他工艺设备的特殊清洁剂。对于这些情况，建议采用集成到工艺设备模块中的专用 CIP 系统。

Design of centralized CIP systems should consider the potential for carryover of product residuesbetween

process steps; between products being manufactured concurrently in multiproduct facilities;and between different products after a product changeover. To address the potential for product carryover,central CIP systems are often dedicated to one part of the manufacturing plant. Non-recirculatingsystems also reduce the potential for product carryover via the CIP equipment itself.
中央 CIP 系统的设计应考虑产品残留转移的潜在可能性，例如：在不同工艺步骤之间、多产品车间中同时生产的产品之间、在产品切换后不同产品之间。为了应对产品残留转移的潜在可能性，中央 CIP 系统通常专用于生产厂的某一部份。非循环 CIP 系统亦能减低产品残留经 CIP 系统转移的可能性。

Piping of the equipment being cleaned and of the CIP skid should be sloped continuously to a physicallow point to ensure acceptable draining of the lines. If supply and/or return loop headers are used,the loop must be designed such that liquid flows in both parts of the loop at adequate speeds. If this isnot achieved, one part of the loop may become a functional deadleg. The pressure drop in the pipingalso needs to be considered. The CIP skids are often located remotely from the process area, and thelength of the distribution piping results in a total pressure drop that can be significant. The greatestchallenge is sizing the distribution piping when the supply flow rates in the system have high variability.This has been addressed in some facilities by installing pumps in distribution piping before majorequipment to control flow rates. For CIP systems, diameters of drains should be adequate to ensureadequate drainage without a buildup of cleaning or rinse solution in the vessel.
需要清洁的设备管道和 CIP 模块应具有一定坡度，以确保管路可以排空。如果使用了供给和/或回流回路总管，回路的设计应确保两个回路的具有足够的流速。如果流速不够，回路中的部份管路可能会变成死角。也需要关注管道中水压的下跌，CIP 模块通常远离生产区，分配管道长度所造成的总压降会很大。当系统供水流速变化很大时，则很难制订分配管路流速限度。有些工厂会在主要设备前的分配管路中加入泵，以控制流速。对于 CIP 系统，应有足够的排水管的内径，确保充分排水，避免清洁溶剂或冲洗液积聚集在容器内。

3.3.1.1.2 Solvent Reflux Cleaning
溶剂回流清洁法
For small-molecule API manufacture by organic synthesis, cleaning may involve boiling a volatile solvent(such as methanol) in the reactor vessel. This is a type of in-place process (but not a CIP systemas defined in **3.3.1.1.1).** The solvent vapors rise to other portions of the equipment, and condense onthose cooler surfaces. The condensed solvent may dissolve residues on those other surfaces, and carrythe dissolved residue back to the boiling solvent in the bottom of the reactor vessel. Such a process iscalled solvent reflux cleaning. Key issues in solvent reflux cleaning are to make sure that the residuesare soluble in the chosen solvent, and the solvent vapors contact and condense on all intended surfaces.The cleaning should also provide an effective rinse of the reactor vessel that held the boiling solvent.
对于一些经有机合成制造的小分子 API，可以在反应罐中煮沸一些挥发性溶剂（例如甲醇）。这是一种在线操作的过程（但不是在 3.3.1.1.1 中定义的在线清洁系统），当溶剂的蒸汽上升到设备的其他部份，并在设备上较冷的表面凝结，这些凝结的溶剂可以溶解这些表面上的残留物，把残留物带回反应罐底部的溶剂中。这种操作过程称为溶剂回流清洁法。使用这种方法的关键是：确保选用的溶剂能溶解相关残留物，溶剂的蒸汽能接触并凝结于所有目标表面。该清洁方法还应对装有煮沸溶剂的反应罐进行有效冲洗。

3.3.1.1.3 Placebo Batches as a Cleaning Method

安慰剂清洁法

Placebo cleaning is another type of in-place cleaning. For certain highly viscous ointments or products,it may be feasible to use a placebo run as a method of cleaning equipment. This approach requiresthe use of a placebo that has no detrimental quality impact on the next product manufactured in theequipment. The principle of using a placebo batch for cleaning is that the action of the placebo runningthrough the equipment would clean the equipment of drug residues or process residuals fromthe previous batch. The advantage for this type of cleaning is that the placebo is processed throughthe equipment in the same fashion as the manufactured product. Therefore, the material would touchthe same surfaces and in the same manner as the next product batch. Disadvantages of this methodinclude the cost of cleaning and the difficulty of demonstration of the effectiveness of the process.

安慰剂清洁法是另一种在线清洁方法。对于一些黏性非常高的软膏或其他产品，可以采用安慰剂批次作为清洁设备的一种方法。这种方法需要选用一种不会对设备的下批产品质量造成不利影响的安慰剂。这种方法的原理是当安慰剂在设备中流动时，会将上批产品的药物残留或工艺残留物清除。这种方法的好处是安慰剂在设备中加工过程与实际生产的产品一样，因此，安慰剂与下批产品以同样的接触方式接触相同的表面。这种方法缺点是成本高，而且难以该清洁工艺的有效性。

3.3.1.2 Out-of-Place Cleaning

离线清洁

Smaller equipment items and portable process equipment that are difficult to clean as installed areoften disassembled and transported to a designated cleaning or wash area where the cleaning procedureis performed, either manually or automated. The additional activities involved with transport ofequipment to and from the wash room, component identification, and the elimination of the potentialfor cross-contamination during transfer, reassembly, and storage prior to use makes the validation ofthese procedures somewhat more complex than the comparable in-place activity. Care should be exercisedfor routes and means of soiled equipment entering a washing area and routes and means of cleanequipment exiting the washing area, as well as storage of cleaned equipment in the washing area. Careshould also be used to assure contact and/or flow of the cleaning agent through all parts of the equipment,such as for lumens or hoses. The need for manual manipulation is an integral part of out-of-placeprocedures, and generally requires both more detail in the procedures and appropriate training. Themanual manipulation makes these concerns similar to those of manual in-place cleaning.

对于安装后较难清洗的设备小部件及便携式工艺设备，通常拆卸后转移到一个指定清洗间进行自动或手动清洁。这种清洁方法还涉及以下操作：将设备运送往返清洗间，设备组件的标识，并确保在运送过程中不会造成交叉污染，重新组装设备，使用前储存。因为离线清洁涉及这些操作，使得离线清洁验证比在线清洁更为复杂。需要特别注意未清洁设备进入清洗间的路径和方法、已清洁设备离开清洗间的路径和方法以及已清洗设备的储存。同时亦要确保清洁剂能充分接触/冲洗到设备的所有部位，例如内腔和软管。手工操作是离线清洁中不可或缺的一环，一般需要在文件中进行详细描述，并进行适当培训。这种手工操作的注意事项与在线清洁中手工操作的注意事项类似。

3.3.1.2.1 Clean-Out-of-Place Systems

离线清洗系统

Clean-out-of-place (COP) equipment includes items such as wash tanks used to clean small parts orparts removed from large equipment. Examples include a recirculating bath used for cleaning smallparts, pump components, gaskets and other parts removed from larger equipment. COP systemsmay also include dishwasher type cabinets where small manufacturing vessels, drums, filter housingsor hoppers can be

loaded inside the cabinet and cleaned. The placement of the parts, disassembly ofequipment and loading patterns are critical to the success of cleaning when using COP systems. Theuse of these systems significantly reduces the differences between CIP cleaning and COP cleaning, althoughissues related to disassembly and transport of equipment to the parts washer are still present.

离线清洁(COP) 设备包括用来清洗小部件／从大型设备拆卸下来的部件的清洗槽。例如以循环水浴来清洗细小部件、泵组件、垫圈、其他拆卸自大型设备的部件。COP 系统亦包括类似洗碗机的清洗柜，可以将小容器、桶、过滤器外壳、料斗等组件放到柜中清洗。在使用 COP 系统时，部件的摆放位置、设备的拆卸、装载方式会直接影响清洗的效果。即使使用 COP 系统仍需要拆卸设备和运送设备，但已能大大减低 CIP 和 COP 清洁的差异。

3.3.2 Automated vs. Manual Systems

自动 / 手动系统

Three broad definitions of cleaning processes follow, although it should be recognized that they representpoints on a continuum. The distinctions between these processes are important to the establishmentof an appropriate cleaning process.

对清洁工艺有以下 3 种广泛定义，虽然这 3 种清洁方式其实代表一个连续体中的不同点（译按:意指这 3 种方式并不是完全独立分开的）。这些清洁方式的差异对于建立适当清洁工艺是很重要的。

3.3.2.1 Manual Processes

手动清洁

Manual cleaning is typically defined as the direct cleaning of equipment by a trained equipment operatorusing a variety of hand tools and cleaning agents. Although some process parameters maybe monitored by gauges, the regulation and control of these parameters is the responsibility of thecleaning personnel.

由经培训的操作员直接用手动操作的工具和清洁剂清洗设备。虽然有些清洁参数是可以用仪表测量的，但对这些参数的实际控制还是由操作员负责。

Important cleaning parameters for manual cleaning may include:

重要的手动清洁参数包括：

- Volume of cleaning agents
  清洁剂的体积
- Volume of rinse water
  淋洗水体积
- Temperature of wash and rinse solutions
  清洗和淋洗溶液的温度
- Sequence and duration (contact time) of soaking, wash and rinse steps
  浸泡、清洗、淋洗的次序和时间（接触时间）
- Scrubbing action
  擦洗动作
- Pressure of solutions
  水压
- Detergent concentration
  洗涤剂的浓度

It is important to specify in writing the extent of the equipment disassembly to ensure the reproducibilityof the cleaning process. Consistency of manual cleaning over time is accomplished by operatortraining, adequate supervision, and a well-defined, documented cleaning procedure.
为了确保清洁程序的重现性，需要建立文件规定设备的拆卸程度。操作员的培训、充分的监控、清晰的书面清洁程序有助于确保手动清洁的一致性。

3.3.2.2 Semi-Automated Processes
半自动清洁
As opposed to manual cleaning, semi-automated cleaning includes various levels of automatic control.At one extreme, this could consist of simply manually removing gaskets/fittings for manualcleaning prior to the automated CIP of a tank, or disassembly of a pump or filter housing prior tocleaning in an automated COP system. At the other extreme, the operator may use a high pressurespray device to clean a surface or may simply open and close valves supplying spray balls inside a vessel.This type of cleaning is intermediate between fully automated and fully manual cleaning.
相对于手动清洁，半自动清洁涉及不同程度的自动化控制。以一个极端例子来说，这包括在对罐子进行 CIP 自动清洗前，进行一些简单的垫圈/配件拆除，进行手动清洁；或是放入自动 COP 系统进行清洁前，将泵或过滤器外壳拆下。再以另一个极端例子来说，操作员在使用高压喷淋装置对一表面进行清洁或仅仅是开关容器内喷淋球供水阀门。半自动清洁就是全自动和全手动中间的一种清洁方式。

3.3.2.3 Automated Processes
自动清洁
Automated cleaning typically does not involve personnel intervention (except perhaps to select a cycleand the start/stop of the operation). The system is usually programmable for the various cleaningcycles. Use of automation provides consistent and robust control and monitoring of the automatedcycles and parameters (such as time, flow rate or pressure, cleaning agent concentration, and temperature).
自动清洁通常不涉及人员介入（除了选择清洁程序/开始或结束运行时）。清洗系统通常可对不同清洗行程进行编程。采用自动清洁方式可对自动清洗行程和参数（如时间、流速、压力、清洁剂浓度、温度）进行一致、稳健地监控。

Important cleaning parameters for automated cleaning may include the volume of cleaning agents,volume of rinse water, flow rates and temperature of wash and rinse solutions, duration of washand rinse cycles, pressure of solution, operating ranges and detergent concentration. Disassembly ofequipment may still be necessary to allow for complete cleaning or to allow for the separate cleaningof delicate parts.
使用自动清洁时重要的清洁参数包括：清洁剂体积、淋洗水体积、清洗和淋洗溶液的流速和温度、清洗和淋洗的时间、溶液压力、操作范围、清洁剂浓度。自动清洗可能仍需要进行部件拆卸，以达到完全清洗的目的，或将专用部件分开清洗。

In an automated cleaning system, the cleaning may be controlled through relay logic, a computer orprogrammable logic controller (PLC). The control system is an integral and critical part of the overallcleaning process. The control system regulates the cleaning cycles, addition of cleaning agents, temperature,time and other critical cleaning parameters.
在自动清洁系统，清洗程序可以由继电器逻辑控制器、计算机或可编程控制器(PLC)来控制。这些控制系统是整个清洁工艺中的关键部份。它们控制了清洗行程、清洁剂的加入、温度、时间和其他

关键的清洁参数。

There may also be a control interface or operator interface terminal (OIT) to start the process, stopthe process, monitorvarious stages of the process and change the process sequence. Given the increasedcomplexity of the newer PLC and computer interfaces, training and validation are importantissues that impact the ability of the system to provide consistent cleaning. The validation of controlsystems is critical to the success of automated cleaning processes.
可通过控制界面、操作者终端界面(OIT) 来启动/结束程序、监视不同清洁阶段、改变程序次序。基于现在的 PLC 和计算机界面比以往复杂，培训和验证对清洁的一致性是很重要的。控制系统的验证是自动清洁程序成功的关键。

3.3.3 Soil Evaluation and Categorization
污物评价与分类
3.3.3.1 Soil Categories
污物分类
There are a large variety of substances that contact process equipment surfaces during the manufactureof pharmaceutical products. They include manufactured products, degradation products, processaids, solvents, and cleaning agents. Cleaning processes and cleaning validation should be designedand tested to address this wide variety of potential process soils. These tasks may be simplified bycreating categories of soils and selecting representative soils for testing and tracking during the developmentand validation of cleaning processes.
生产药品时接触工艺设备表面的物料有很多，它们包括生产物、降解物、工艺助剂、溶剂、清洁剂。设计清洁过程和进行清洁验证时需要考虑这些不同的潜在污物。在清洁工艺开发和验证过程中，可通过将污物分类并选择有代表性的污物进行测试和追溯，以简化工作。

The final selection of a representative soil within a process stream should be based on the similarity ofthe physiochemical properties of the soils. In many circumstances, categories may be combined andthe number of representative soils used for development activities further reduced.
在生产线中选择具代表性的污物需要基于污物的理化性质类似性。多数情况下，可将分组合并，进一步降低工艺开发使用的代表性污物数量。

3.3.3.2 Soil Removal
污物的去除
Soils may be removed by physical and/or chemical means. Physical removal may be accomplishedby putting energy into the cleaning process through use of high pressure spray, high velocity flow,manual scrubbing, or vacuuming in order to remove soils from the equipment. Physical removal maybe dependent on solubility, soil amount and its degree of adhesion to the equipment surface.
残留物可由物理和/或化学方法移除。物理方法可采用高压喷淋，高流速的水流、手动擦洗、真空吸尘等将污物从设备上去除。使用物理方法时需考虑污物的溶解性、数量、及其在设备表面的粘附程度。

Chemical cleaning mechanisms include solubility, emulsification, wetting, chelation, dispersion, hydrolysisand oxidation. Cleaning agents are generally chosen for their ability to remove process soilsby one or more of these mechanisms. In some cases, multiple cleaning steps may be used in orderto take

advantage of different chemical cleaning mechanisms. For instance, alkaline detergent forsolubilization and emulsification may be followed by a sodium hypochlorite solution for oxidationof protein soils. It should always be kept in mind that the more aggressive the cleaning solutions are(e.g., solutions with high concentrations of sodium hypochlorite), the more corrosion may occur.The right choice of materials for cleaning purposes is part of the development phase.
化学清洗机制包括溶解、乳化、湿润、螯合、分散、水解、氧化作用。可根据清洁剂去除工艺污物能力选择清洁剂，清洁剂可通过一种或多种清洗机制发挥作用。在某些情况下，为了利用不同的化学清洗机制，可使用多种清洗步骤。例如，在使用碱性溶液来进行溶解和乳化后，可使用次氯酸钠溶液来氧化蛋白质污物。可。必须记住，使用愈强烈的清洁剂（如高浓度次氯酸钠溶液），对设备的侵蚀可能愈严重。在清洁工艺开发时，便应该选择正确的清洁剂。

Factors affecting “cleanability” also include the surface geometry, the surface type, the soil type, andthe soil level. The ease with which a soil is released from the equipment surface by one of the mechanismsdescribed above determines its cleanability. Soil response to a particular cleaning mechanismmay influence the choice of cleaning agent and cleaning conditions. Attachment to surfaces can beby a combination of van der Waals forces, electrostatic effects, and other forces. The time that thesoil resides on the equipment can also influence the difficulty of soil removal. Fresh soils are generallyeasier to remove than soils that have been allowed to dry on the surface. The time between soiling andcleaning must be considered when designing the cleaning studies to simulate the dirty hold time, if applicable.In some cases, difficulty of cleaning does not change with increased dirty hold time. If this isthe case and *any* dirty hold time can be used in a protocol, it must be clearly justified and documented.
可清洁性亦会受以下因素影响：设备表面几何结构、污物类型和污染程度。当使用以上其中一种清洁机制清洗残留物时，将残留物带离设备表面的难易度，决定了该污物的可清洁性。选择清洁剂和清洁条件时，应考虑污物对特定清洁机制的反应。表面的污物可以通过范德华引力、静电作用、或其他力组合而成。污物附着在设备表面的时间同样会影响清洗的难易度。新鲜的污物通常会比干了的污物更易清洗。在设计清洁程序模拟“生产后保持时间”时，必须考虑将设备弄脏至清洁设备的间隔时间，在某些情况下，间隔时间的增加对清洗的难易度没有影响，如果情况的确如此，方案中可采用任何“生产后保持时间”，但必须有书面理由。

High soil amounts can complicate removal by saturating the cleaning solvent or depleting surfactantsor other components of the cleaner (such as oxidizers or emulsifiers). This may impact the minimumcleaning solution volumes and should be considered in the cleaning cycle design when high soilamounts are anticipated.
大量污物可能会使清洁变得困难，它们可能会使清洁剂饱和，或者耗尽表面活性剂或清洁剂的其他组分（如氧化剂或乳化剂）。这可能影响最低清洁溶液体积，因此当预料有大量污物时，在开发清洁程序时便应予以考虑。

3.3.4 Equipment Considerations
设备相关考虑

Equipment usage during production is another important aspect to consider in designing a cleaningprocess. It is important to understand the role that the equipment plays in the production train.Equipment design characteristics, as established during product development, are often driven byequipment functionality and the requirements of the process. With the current emphasis on cleaningvalidation, it makes sense that “cleanability” be an important criterion in the design of equipment.Equipment should be free-draining and

have limited intricate or complex parts. Sanitary designs employingprinciples such as appropriately finished surfaces, lack of crevices, absence of dead legs andsuitable construction materials are recommended.
在开发清洁程序时亦应考虑生产过程中设备的用法。了解设备在生产线中的作用是很重要的。在开发产品时建立的设备设计特性，通常取决于它的功能和工艺要求。鉴于目前对于清洁验证的重视程度，设备的“可清洁性”应作为设计生产设备时重要标准之一。设备应为自排水式、尽量减少复杂部件。建议采用卫生设计原则，例如应有适当的表面加工、无裂缝、死角，具有合适的材质。

Cleaning equipment should be designed to ensure adequate coverage of all process equipment surfacesto be cleaned, and to not contribute possible contamination. In tankage and enclosed piping systems,the volume of cleaning solution available must be sufficient to clean all interior surfaces of thepipe. For spray ball or nozzle spray apparatus, all equipment surfaces should be available for contactwith the spray. The concern here is that areas can be ‘‘shadowed’’ by the presence of dip tubes andmixer baffles, blades, and shafts. Spray patterns may be originally designed by computer simulation,but should be confirmed by a spray coverage test, such as one using a dilute solution of riboflavin.
清洁用设备的设计应确保充分清洗所有生产设备待清洁表面，并且不会带来潜在污染。在水槽和密闭管系统中，清洁溶液必须足够用于清洗管路的所有内表面。使用喷淋装置时，应确保设备表面与喷洒液接触。应关注有些位置可能会被导管、混合挡板、搅拌桨叶、搅拌轴。可通过计算机模拟进行喷淋模型的设计，但应使用稀释的核黄素溶液进行喷淋覆盖测试。

3.3.4.1 Dedicated – Nondedicated Manufacturing Equipment
专用 / 非专用生产设备

Dedicated equipment is used solely for the production of a single product, or in some cases, of asingle product line (e.g., containing the same active ingredient). Concerns over cross-contaminationwith other products are markedly reduced. However, consideration must be given to residues ofcleaning agents, degradants, bioburden, and endotoxin.
专用设备仅用于生产一个产品，或单一产品线（即拥有相同 API 的产品）。对于这些设备，对产品间交叉污染的忧虑显著地减少。但是，必须要考虑清洁剂残留、降解物、微生物负载、内毒素。

Where the same piece of equipment is utilized for different product formulations (i.e., nondedicatedequipment), the prevention of carryover of active ingredients between products becomes a major focusof the cleaning process. For nondedicated equipment, a design consideration is whether a uniquecleaning process will be developed for each manufactured product, or whether one cleaning processwill be designed to address all (or a group) of manufactured products.
当一个设备用于生产不同处方的产品（即非专用设备），清洁工艺的重点是避免 API 在产品间转移。对于非专用设备，在开发清洁程序时，应考虑是否对于每种产品使用不同的清洁程序，还是对所有产品（或一组类别的产品）使用一种清洁程序。

Certain products (such as beta-lactams) may require segregated production areas. A risk-based analysisshould be performed on other products which may be highly hazardous (e.g., mutagenic active ingredients)in order to determine whether dedicated facilities should be used. For other products, dedicationof equipment may be made not on a patient risk basis, but rather as a practical business decision.
有些产品（例如 β-内酰胺类药物）可能需要独立生产区域。对其他可能高危险性的产品（例如致突变的活性成分），应进行风险分析来决定是否需要独立的厂房。对于有些产品，设备的专用不一定

基于患者风险，而是基于业务考虑。

3.3.4.2 Nonproduct Contact – Product Contact Surfaces
非产品接触部位 / 产品接触部位

Validation of cleaning has focused on product contact surfaces. However, indirect product contactsurfaces (“nonproduct contact” surfaces with close proximity to open product) may be included in acleaning validation program. An example of an indirect product contact surface for which cleaningvalidation is commonly done is a lyophilizer shelf used in lyophilization of vials. Nonproduct contactsurfaces such as floors and walls typically have cleaning processes, but those cleaning processes arelower risk, are controlled consistent with GMPs, and are outside the scope of a cleaning validationprogram. However, cleaning of floors and walls may be addressed as part of an overall cross-contaminationprogram, particularly for highly hazardous drug active ingredients.

清洁验证集中于产品直接接触的部位。但是，清洁验证计划中也可以包括非产品接触部位（邻近产品暴露的非产品接触表面）。其中一个非产品接触的例子是清洁验证通常包括用于冻干机搁板。其他非产品接触部位包括地面和墙身，它们也有清洁程序，但一般风险较低，而且按照 GMP 要求进行控制，亦不在清洁验证计划的范围内。但是，地面和墙身的清洁可以作为整个交叉污染控制计划的一部分，尤其是对于一些高危险性活性成分来说。

3.3.4.3 Low-Risk Sites – High-Risk Sites
低风险-高风险区域

Risk is a function of the identification of hazard, the ability to detect that hazard, and the potentialexposure of the hazard on product quality and patient safety. Those locations where there is the dangerof a residue affecting a single dose with a high level of contamination are high-risk sites. Examplesof such sites are a filling needle and a tablet punch. Sites which are difficult to clean are also high-risksites. Those difficult-to-clean sites may include ports, drains, baffles, and the undersides of agitatorblades. These high-risk sites may require special disassembly, cleaning, and/or inspection emphasis.Other sites which are easier to clean and uniformly transfer residue to the next product are generallyconsidered lower risk.

风险是由危害的识别、危害的可检测性以及危害对产品质量和患者安全的影响所决定的。有些位置可能会使单剂量药物受到残留严重污染的，例如灌装针头和压片机冲头，都属于高风险区域。一些难清洗的位置的风险也较高，例如接口、排水口、挡板、搅拌叶的底部等。这些高风险位置可能需要特别拆卸和清洗，和或重点检查。对于其他较易清洗，并将残留物均匀地带到下批产品的位置，一般认为其风险较低。

The distinction between “major”and“minor”equipment is not a definitive one. The Good ManufacturingPractices (GMP) ***(6)*** make mention of “major”equipment, but are silent on the subject of “minor”equipment except with regard to items described as utensils. Major and minor designationsdo not generally reflect the challenge of cleaning, nor define whether the equipment surfaces are alower or higher risk for cleaning processes. Both major and minor product contact equipment itemsrequire cleaning verification or validation for multiproduct equipment.

“主要”和“次要”设备的区分不是决定性的。GMP（6）提及了“主要”设备，除了定义为器具的设备，GMP 没有涉及到“次要”设备。主要和次要的称谓一般不反映清洁方面的挑战，也没有确定清洁过程中设备表面具有低风险还是高风险。对于多产品共用设备，与产品直接接触的主要和次要设备均需进行清洁效果确认或验证。

3.3.4.4 Materials of Construction

材质

Factors affecting “cleanability” include the surface type and the surface finish. The most commonsurface types encountered are stainless steel and glass, but surface types may include other metals anda variety of plastics and elastomers. Surface finish also affects the removal of soils. Rough surfacesprovide more area for soil contact and may contain cracks and crevices that are difficult for the cleaningagent to penetrate. The interior surfaces of stainless steel process equipment may be modifiedto smooth and/or polish rough surfaces. The materials of construction of the equipment should beconsidered carefully when designing a cleaning validation program.

影响“可清洁性”的因素包括表面的类别和表面处理。最常见的表面为玻璃和不锈钢，但有些表面可能含有其他金属和一些塑料、橡胶。表面处理同样会影响污物的去除。粗糙的表面为污物提供了更大接触表面，同时亦可能有裂缝和裂纹，使得清洁剂难易渗入。工艺设备的不锈钢内部表面应调整为光滑的和/或对粗糙表面进行抛光。在设计清洁验证计划时应仔细考虑到设备材质。

Porous materials may require special cleaning processes. Items such as filter bags and filter membranesare typically dedicated to a given product.

多孔性物质可能需要特别的清洁程序。如过滤器待和膜过滤器等物品通常为一特定产品专用。

3.3.5 Operational Considerations

操作相关考虑

Operational issues such as the use of campaigns, the utilization of equipment, and the complexity ofthe equipment impact the design of the cleaning validation program.

阶段性生产、设备的使用和设备的复杂程度等操作问题将影响清洁验证计划的设计。

A campaign is a series of batches of the same product manufactured one after the other. Considerationshould be given to the need to clean, and the extent of cleaning, between batches in a campaign.Depending on the product, there may be no cleaning between batches or some level of cleaning isdone between batches. If the cleaning between batches is simply a vacuuming (for solid products)or a solvent or water rinse (for liquid products), such cleaning is sometimes called “minor” cleaningor “in-process” cleaning. Such minor or in-process cleaning steps do not require separate validation.However, consideration should be given to the effect of such minor or in-process cleaning steps onthe efficiency of the “full” cleaning process done at the end of a campaign for changeover to a newproduct or campaign.

阶段性生产是指连续地生产多批同一产品。应考虑批间是否需要清洁，以及清洁的程度。根据产品要求，批间可能不需要清洁，或是只需要一定程度的清洁。如果批间的清洁是简单地用吸尘机（对于固体产品）或用溶剂/水来冲洗（对于液体制剂），这种清洁一般称为“小清洁”或“中间过程清洁”。这种清洁程序是不需要单独验证的。可是，要考虑这种“小清洁”或“中间过程清洁”是否会影响其后“大清洁”（在阶段性生产结束进行的清洁，用于切换生产另一产品或连续生产另一产品）的效果。

If only the cleaning process at the end of the campaign is to be validated, consideration should also begiven to the number of batches and/or the total elapsed time for a campaign. For example, elapsedtime might be critical if the active ingredient left on equipment surfaces degrades over time due toexposure to heat or light. Furthermore, the repetitive production of a single product without validatedcleaning between

batches might also result in the penetration of materials into a location wheresingle lot production might not present a problem.
如果只对“大清洁”进行验证，还应考虑可连续生产的批数 / 可连续生产的时间。例如，有些残留在设备表面的有效成份可能会因为遇热和光照而随着时间降解，这时制定可连续生产的时间便变得很关键。再者，重复地生产同一种产品，而没有使用经验证的方法进行批间清洁，可能会使物料渗入某些部位，而这对于仅生产一批产品则不是问题。

3.3.6 Cleaning Agent Selection
清洁剂的选择

Cleaning agent selection should be based on a scientific rationale. Cleaning agents should be selectedfor their suitability to remove the product residues; their compatibility with equipment; their ease ofcleaning agent removal; and low toxicity. Solvents, formulated detergents, and commodity chemicalsshould be acceptable for the process and for use with pharmaceutical products. Water alone or organicsolvent alone may be used as the cleaning agent, particularly for readily soluble soils.
清洁剂应根据科学原理来选择。选择时应根据它们去除产品残留的能力、与设备的兼容性、清洁剂本身是否容易移除、低毒性。溶剂、配方洗涤剂和日用化学品应可用于清洁工艺和药品。水或有机溶剂可以单独作为清洁剂，尤其对易溶解的污物。

At the time of design of the cleaning process, it is important to review and document informationabout any cleaning agents to be used. The established cleaning agents should be reviewed against thevendor’s current specification sheets and descriptions, including material safety data sheets. Thosedocuments should be available as a minimum requirement for use of those cleaning agents beforeevaluating the cleaning process. When selecting a new cleaning agent or utilizing an established cleaningagent for a new process, it is important to know all of the ingredients, as well as the percentageeach constituent comprises, that are in the cleaning agent. This allows for the establishment of theconsistency of cleaning agent formulation over time, as well as for selecting a possible marker componentfor analysis of cleaning agent residues.
在设计清洁工艺时，应重点审核并记录所有使用到的清洁剂的相关信息。对于已确定使用的清洁剂，应对照供货商所提供产品规格书和使用说明，包括物料安全数据表，进行检查。在评估清洁工艺之前，至少应获得这些清洁剂的相关文件。当使用新的清洁剂或将清洁剂用于新的工艺时，必须了解清洁剂中所有成份，包括每个成份的含量百分比。这使得清洁剂的配方可以保持一致性，同时有利于在进行清洁剂残留检测时选取指标组分。

Cleaning agents and their vendors should be qualified in much the same way as a raw material andraw material vendor is qualified. Change control of the cleaning agent formulation, as well as notificationof significant changes, should be required of the cleaning agent vendor.
清洁剂和清洁剂供货商应经过确认，正如对原材料和原材料供货商进行确认一样。清洁剂供应商应有变更控制系统管理清洁剂处方变更，并应将重大变更告知用户。

During the development of the cleaning cycle, quantities of cleaning agents, their concentration andtheir addition mode should be studied. Methods of storage, expiration dating, inventory control, andchange control of the cleaning agents will help establish and maintain a reproducible process.
在开发清洗程序时，应研究清洁剂的用量、浓度、加入的方式。清洁剂储存的方式、有效期、存量控制和变更控制，均有助于建立并维持一个可重现的工艺。

Water used to prepare cleaning agents and for equipment rinse should be of suitable quality ***(7)***. Generally,water used for final rinse should be the same grade as used for the manufactured product, e.g.,parenteral products should utilize WFI and oral products should employ purified water.
用于制备清洁剂和淋洗设备的水应符合适当标准（7）。一般来说，最终淋洗水应与工艺用水级别一致，例如注射剂要使用注射用水(WFI)，口服制剂则使用纯化水。

3.3.7 Product Considerations
产品相关考虑
Chemical and physical attributes of the product should be taken into account when establishing a cycledevelopment program for a specific product. Characteristics such as the solubility, concentration,physical properties of the active ingredients and excipients, possible degradation products and theeffect of the cleaning agent are important factors in establishing that the cleaning method is appropriate.The interaction of the product with all surfaces with which it will come into contact is critical.
在建立特定产品的清洁程序时应考虑产品的物理和化学性质。一些特性例如活性成分和辅料的溶解度、浓度、物理性质，可能出现的降解物、清洁剂效果都是建立合适清洁方法的重要因素。产品与其接触表面之间的相互作用也是很关键的。

3.3.7.1 Product Risk Considerations
产品风险的考虑
The cleaning of equipment is closely tied to the type of materials being removed from the surface.The product formulation (including the active ingredients and excipients and formulation aids), includingthe nature of the product at various intermediate steps of manufacture, should be considered.
设备的清洁与从表面待去除的物料类型是紧密相关。产品配方（包括原料药、辅料、配方助剂）、不同阶段中间产品的性质，都应予以考虑。

Because limits for highly hazardous drug active ingredients (e.g., those with serious allergenic, cytotoxicand mutagenic properties) are generally more stringent, more robust cleaning processes mayhave to be designed. Such highly hazardous drug active ingredients may be manufactured on nondedicatedequipment provided an appropriate risk analysis and cleaning validation is performed. Somefirms may choose to use dedicated facilities and/or equipment for such highly hazardous drug activeingredients even though that might not be a regulatory requirement. Another approach for suchhighly hazardous drug active ingredients is to include in the cleaning process a deactivation or degradationstep such that residues from the active ingredient do not have those properties that make theactive ingredient highly hazardous. In addition, any unusual hazards of degradation products (eitherunintended or intended degradation products) should be considered.
对于高危险性活性成分（例如高致敏感、细胞毒素、致突变性的药物），残留的限度更严格，因此需要设计一个可靠的清洁程序。如果经过适当风险分析和清洁验证，这些高危险性药品可以在非专用的设备上生产。有些药厂会直接使用专用厂房和/或设备生产这些高危险性产品，纵使法规没有如此要求。对于这种高危险性药品，另一种方法是可以在清洁过程中加入一个去活性或降解的工序，使残留物不再具有高危险性。另外，降解物的任何异常危害（不论是预期或非预期的降解产物）都应该加以考虑。

The route of administration of a product may affect the acceptable residue limits, and may thereforeaffect the nature of the cleaning process. Generally speaking, injectable products, intra-ocular formulations,and

some inhalants which provide direct access to the systemic circulation systems of patientsare a much greater concern if cross-contamination occurs.
产品的给药途径也会影响残留的可接受限度、并因此影响清洁工艺的特性。一般来说，注射剂、眼用剂、部分吸入剂这种会直接进入患者循环系统的药物，如果发生交叉污染将会更需要关注。

Another risk factor to consider is the amount or extent of information available on the product tobe cleaned. For example, the amount of information available for a marketed product may be muchmore extensive than information on a new drug active ingredient being manufactured for humanclinical trials. In addition, in such early clinical manufacturing, a cleaning verification approach maybe utilized. With such an approach, the cleaning process may be significantly overdesigned so thatafter the cleaning process, residue levels are well within acceptance limits.
另一个需要考虑的风险因素是对待清洁产品信息的数量和程度，举例来说，一个已在市场上销售的产品，应该会比仍然处于临床试验阶段的产品，有更多相关信息。对于一些早期临床生产阶段的产品，可采用清洁效果确认的方法。采用该方法，清洁工艺的设计更有保障，使清洁后的残留水平远低于可接受限度。

3.4 Cleaning Development Laboratory Experiments
清洁开发实验
Laboratory testing often includes screening a combination of soils and relevant process surfaces.Screening experiments are designed to test soil removal capability using representative soils and couponsof relevant surface materials. Cleaning conditions can be selected based on the soil-surface combinationencountered in the production equipment.
实验室测试通常包括对污物和相关工艺表面组合进行筛选，采用代表性污物和相关表面的材质试样测试残留的可清洁程度。清洁条件可根据实际生产中的污物-表面组合选定。

Laboratory evaluation of the interaction between product and surfaces can be performed using testcoupons made of the surface of interest under simulated cleaning conditions. Based on the processdetails, appropriate materials of construction with the appropriate surface finish characteristics shouldbe selected for use in lab-scale cleaning experiments. To minimize the number of experiments, it maybe sufficient to include only those surfaces that are expected to be the most difficult to clean (based onprior knowledge and risk assessment tools). Stainless steel coupons are the most common choice asthey often represent a majority of equipment surfaces in a production facility. Non-electro-polishedstainless steel coupons with a representative or worse surface finish compared to equipment surfacesmay be preferred for lab evaluations.
采用相关表面材质试样模拟实际清洗状况，可以评估产品与表面间的相互作用。根据工艺具体情况，应选择经适当表面处理的材料进行实验室规模的清洁试验。为了减低需要进行实验的次数，可只选取预计最难清洗的表面来进行实验（根据经验知识和风险评估工具来预测）。不锈钢试样是最常见的选择，因为它已经可以代表大部份生产设备的表面。在实验中建议使用非电抛光的不锈钢试样进行实验室评估，试样表面应具有代表性或表面处理比实际设备差。

3.4.1 Soil Selection
污物选择
Care should be taken in the choice of soils and soil conditions used for selection of cleaning agentsduring laboratory evaluation. The soils should be representative of the soils on equipment in themanufacturing

plant, including the chemical and physical (dried, baked) nature of the soils.
进行实验室评估选择清洁剂时，应小心选择污物和污物的状态。使用的污物应能代表生产中设备上的污物，包括污物的化学和物理（例如：干燥的 / 经烤干）性质。

Solutions or suspensions of soils selected for experimentation are generally coated on coupons representingthe process contact surfaces and dried to simulate the soil condition on the process equipmentprior to testing for removal with cleaning agents. The number of representative soils will vary with anorganization’s experience and history, as knowledge about the content and cleanability of the variousprocess steps.
在测试清洁剂清洁能力之前，用于试验的污物溶液或混悬剂一般应覆盖在材质试样表面，并干燥以模拟工艺设备上污物状况。代表性污物的数量应根据厂家的经验、对其成份的了解、不同工艺步骤的可清洁性来决定。

Preparation of coupons typically involves use of a cleaning procedure in order to ensure that all couponsare uniformly cleaned at the start of the experiment. This also helps to ensure that any foreignmaterial deposited on the coupon surface during the fabrication process is removed to minimizeinterference with the process soils or cleaning agent. The coupons are then completely dried beforespotting them with soils. It is important that the spotting of soil onto each coupon be kept consistentto minimize experimental variability. The coupons are then dried for a fixed time to simulate thesoiled equipment surfaces at the time of cleaning, before they are subjected to the lab-scale cleaningprocess. That fixed time is generally the desired dirty hold time, or a longer time.
材质试样准备通常包括在开始实验前采用清洁程序对所有试样进行清洁，确保试样清洁程度一致。这也有助确保除去制作过程中残留在试样表面的异物，降低对工艺污物或清洁剂的干扰。涂布污物前，应先把试样完全干燥。重要的是将污物一致地涂布到每一试样上，以减低实验变动性。在进行实验室规模清洗工艺之前，应将试样干燥一定时间，以模拟清洁时污物附着在设备表面的情况。一般来说，这个固定时间会跟生产后保持时间一样，或更长。

The purpose of the experiment could be to make one or more determinations related to cleanability,including comparison of the various materials of construction for a given soil; different processstreams for a given surface; different cleaning conditions (such as concentration of cleaning agent and temperature); different products for the same process step and surface; or a combination of these.The outcome of these studies can be analyzed to create the “design space” for cleaning. In any case, it is important that the performance of the cleaning process in the laboratory represents, as much as practical, the performance in the pilot plant or larger scale process. Important operational parameters such as temperature, time, mode of action and concentration are controlled to mimic what is used in the manufacturing plant. If it is difficult to simulate the actual process conditions in the laboratory, conditions representing a worst-case scenario should be employed. The laboratory studies can also be used to challenge the cleaning process by modifying different variables of the cleaning process to further outline the design space.
试验的目的是为了测试污物的可清洁性，包括特定污物但材质不同；特定表面但工艺流程不同；不同的清洁条件（例如不同浓度的清洁剂和温度）；相同工序和表面，但产品不同；或以上因素的组合，并比较所得试验结果。这些研究的结果，经过分析后可以建立一个清洁的“设计空间”。任何情况下，在试验中的清洁效能，应尽可能地代表小试或更大规模生产的清洗情况。重要的运行参数，如温度、时间、动作、浓度应尽可能受控，以模拟实际生产情况。如果有些参数在实验室中难以模

拟，便应采用最差条件。实验室研究亦可调整清洁参数来挑战清洁工艺，进一步确定“设计空间”。

Evaluation of performance for cleaning design space studies can utilize the various analytical methods listed in **Section 7.0.**
清洁设计空间的研究评估可采用 7.0 节中列出的不同的分析方法。

3.4.2 Parameter Selection
参数选择

A variety of parameters can impact the performance of a cleaning regimen. These include: nature and strength of the interactions between the product and the surface; nature of the interaction between the cleaning agent and the soil; time (dirty hold time, time for each cleaning cycle); cleaning agent and concentration; temperature; cleaning action [flow properties (stagnant, laminar, turbulent) and pressure]; and properties of the cleaning solution (such as ionic strength, pH, components, viscosity,and density). All of these, except the cleaning action, are independent of the equipment. Selection of parameters to be examined in an experimental study should be done on a case-by-case basis. The larger the number of parameters evaluated, the more the number of experiments may be required to understand the impact of the parameters and their interactions. On the other hand, if critical parameters are not picked, the resulting conclusions in terms of identifying the important operational parameters and their ranges are likely to be erroneous, since important effects might be overlooked.
有很多参数可以影响清洁效果，包括：产品与设备表面间相互作用的性质和强度、污物与清洁剂间相互作用的性质、时间（生产后保持时间和完成每一清洁行程所需时间）、清洁剂及其浓度、温度、清洗动作［流动特性（静止、层流、湍流）和压力］、清洁溶液性质（如离子强度、pH、成份、黏度、密度）。以上各种因素，除了清洗动作，均与设备无关。应根据具体情况选择参数进行实验研究。当需要评估的参数越多时，便应进行更多实验来测试这些参数的影响及其相互作用。另一方面，如果没有挑选出关键的参数，可能得到识别重要操作参数及其范围的错误结论，因为忽视了关键参数的重要作用。

Use of a risk analysis tool, such as Failure Mode and Effects Analysis (FMEA), may assist with prioritizingthe various operational parameters for further examination. Single parameter studies that vary one parameter at a time can be designed to identify the parameters that have significant impact onthe performance. One such study conducted at the bench scale reported concentration and temperatureof the cleaning solution to be the parameters with predominant effects ***(8).*** As discussed in thefollowing section, single-parameter studies can then be followed by Design of Experiments (DOE) toinvestigate the interactions between these parameters. Alternatively, if only a few parameters need tobe examined, just performing a DOE to measure both the main effects and the interactions may bemore resource- and time-efficient.
利用一些风险评估工具，例如失效模式与影响分析(FMEA)，有助选出需要优先进行进一步试验的参数，每次只变动一个参数进行单一参数研究，有助找出对清洁效果有重大影响的参数。例如通过一个实验室规模的清洁试验，发现清洁溶液的浓度和温度是起主导作用的参数（8）。正如以下章节所述，在单一参数研究之后，可以通过实验设计方式(DOE)来调查这些参数间的相互作用。或者，如果只有几个参数需要试验，直接进行一个 DOE 来同时测量主要参数的清洁效果和相互作用可能会更省时省资源。

3.4.2.1 Parameter Interactions

参数间相互作用

The use of DOE style experiments helps to determine the effect of varying individual parameters on cleanability as well as providing an indication of their interaction. Statistical tools including regression analysis, leverage plots, response surface analysis and interaction profiles can be used to study bothmain and interaction effects. Relationships and interactions between parameters, such as temperatureof cleaning solution and the concentration of the cleaning agent, may be determined. Such DOEanalyses can be used to construct a multi-parameter design space for the cleaning process and to establish the ranges of operational parameters that provide acceptable cleaning process performance.

使用 DOE 实验有助找出不同参数对于可清洁性造成的影响，以及找出它们的相互作用。可以使一些统计工具，例如回归分析、杠杆图、响应面分析和交互作用分布来研究主要影响和相互作用影响。这样可以确定参数间的关系和相互作用，例如清洁溶液的温度和浓度。可以利用 DOE 来建立一个多参数的清洁设计空间，确定达到可接受清洁效果的操作参数范围。

3.4.3 Measurements to Determine Cleaning Effectiveness

清洁效果的测量

Cleaning effectiveness may be determined by the sampling and analytical methods described in **Sections6.0** and **7.0.** They include visual inspection, and analytical techniques for measuring any residues, such as of manufactured product, degradant, cleaning agent, bioburden and/or endotoxin.Depending on the purpose and the design/development phase, these may be online and/or offlinemeasurements of rinse or swab samples.

清洁效果可由取样及检测方法来确定（如章节 6.0 和 7.0 所述）。它们包括目视检查、分析技术来测量产品、分解物、清洁剂、生物负载和 / 或内毒素。根据实验目的和设计开发所处阶段，可以通过在线或离线检测冲洗样或擦拭样来测量清洁效果。

Using existing knowledge and a risk-based approach, cleaning experiments can be reduced or eliminated,e.g., for transfer of a manufacturing process from one facility to another.

依据现有知识和风险管理方法，可减少或取消清洁试验，如将生产工艺在工厂之间转移时。

3.5 Cleaning Process Scale-Up

清洁工艺放大

Following selection of cleaning agents and cleaning parameter ranges (such as temperature, contacttime, cleaning agent concentration, and flow stream hydrodynamics) from historical plant data (if available)and laboratory development work, the cleaning process can be implemented for use on largerscalemanufacturing equipment. Determination of soil and cleaning agent residue removal is generallyperformed prior to formal cleaning validation protocols. Adjustments to cleaning parameters may bemade during the scale-up process based on plant experience and laboratory development studies.

依据历史数据（如果有）和实验室开发结果，确定清洁剂和清洁参数（如温度、接触时间、浓度、流体力学）后，可将清洁工艺应用到更大规模的生产设备上。在制订正式的清洁验证方案前，应先确定污物和清洁剂残留可被清除。根据工厂经验和实验室开发结果，可以在清洁工艺放大时调整清洁参数。

3.5.1 Setting Process Controls

设定过程控制

It is both prudent and consistent with current Good Manufacturing Practice (CGMP) to establishcontrol

ranges for the cleaning process operational and performance parameters. As appropriate,operational parameters for cleaning processes include:
应建立清洁工艺参数的控制范围以严格、持续符合 GMP 要求。清洁工艺的操作参数如下：

• Dirty hold time for equipment (time between completion of use and initiation of cleaning)
生产后保持时间（完成生产和开始清洁之间的时间）
• Clean hold time for equipment (time between completion of cleaning and next use)
清洁保持时间（完成清洁至下次使用之间的时间）
• Flow rate and/or delivery pressure of the cleaning stream (proof of flow for any parallel flow paths)
清洁溶液的流速和压力（确认流体流型是否为平行流的证据）
• Cleaning agent concentration
清洁剂浓度
• Duration of each step in the cleaning process (by time or volume)
清洁工艺中每个步骤的持续时间（以时间或体积表示）
• Temperature of washing solutions and rinses
冲洗和淋洗液的温度
• Air flow verification during any water removal or drying steps
干燥或除水过程中，气流的确认

Instrumentation for each of these parameters should be included in the system design. Alert and/or action levels can be set for each critical cleaning process parameter in order to maintain properoperation. Parameters may be significant for business or economic reasons, as well as for patient andproduct quality reasons, as long as the parameters set for business and economic reasons are more “stringent” than for patient and product quality reasons. Alert levels may be set based on expectedvariability of the equipment and instrumentation in the cleaning system. Action levels should be setat values that permit adjustment to the equipment to avoid jeopardizing acceptable operation. Bothalert and action levels should be within the acceptable ranges for each parameter. It is also reasonableto establish check times, so that if parameters do not reach their set points (e.g., volume flow, conductivity)within that time, then an alarm or notification occurs.
在设计系统时，应考虑这些参数的检测。可为关键清洁工艺参数订立警告/行动水平来维持正确的操作。参数可能因为经济/商业考虑、患者安全、产品质量而定，只要因商业/经济考虑建立的参数比比因患者/产品质量建立的参数更严格。警告水平可根据清洁系统中设备、仪表的预期变动来设立。行动水平的设定应能够允许对设备进行调整，避免出现不符合要求的结果。警告水平和行动水平都应该在每一参数的可接受范围内。同时亦可以设定检查时间，如果参数该检查时间内未达到设定值（如流量、电导率），便发出警告或通知。

Performance parameters should also be evaluated during scale-up. As applicable, performance parametersmay include:
在清洁工艺放大时应评估清洁效果，指示清洁效果的参数可以包括：
• Final rinse solvent analysis for active ingredients/degradants
最终淋洗液有效成份/分解物的检测
• Final rinse solvent analysis for cleaning agent
最终淋洗液清洁剂检测
• Final rinse water bioburden

最终淋洗液生物负载
• Final rinse water endotoxin
最终淋洗液内毒素含量

3.6 Applying the "Design Space" Concept to CleaningProcesses
在清洁工艺中引入"设计空间"的概念

"Design Space" is the multidimensional combination and interaction of input variables and processparameters that have been demonstrated to provide assurance of quality. The Design Space conceptthas been introduced by the International Committee on Harmonization (ICH) ***(3)*** to describe an approachto the development and control of pharmaceutical manufacturing processes. An analogousapproach can be applied to cleaning processes.
"设计空间"是指多个输入变量和工艺参数的多维度组合和相互作用，用于提供质量保证。设计空间的概念由 ICH 引入，描述了一个药品生产工艺开发和控制的方法。一个类似的方法可以应用到清洁工艺上。

The cleaning design space for a manufacturing facility is defined through a risk-and science-basedapproach relying on cleaning process knowledge, product/equipment knowledge, regulations andquality practices (requirements). Similar to manufacturing process development, control, and validation,cleaning process operational parameters (inputs) can be controlled to ensure predictable andacceptable performance as evidenced by appropriate measurements (outputs). The cleaning designspace is represented by the range of each of the operational parameters that results in acceptableperformance of the cleaning process.
生产厂房的清洁设计空间是基于所获得的清洁工艺的知识、产品/设备知识、法规和质量要求，通过基于风险和科学的方法确定的。就如工艺程序开发、控制和验证一样，控制清洁参数（输入）确保清洁效果符合预期要求，并采用适当测量结果（输出）证实。清洁设计空间可用获得合格清洁效果的每个参数的范围表示。

Steps in defining the design space for a cleaning process may be slightly different from steps taken todefine design space for a manufacturing process, in that the design space for a manufacturing processis unique to a given process (e.g., a granulation process). However, many manufacturers may want todesign one cleaning process for a specific equipment train that is used regardless of the manufacturedproduct. This may be accomplished by identifying the "worst-case"soils and defining the design spacearound cleaning process performance using these soils.
界定清洁工艺设计空间的步骤可能与界定生产工艺设计空间的步骤略有不同，因为每个生产工艺的设计空间相对于每个特定工艺是唯一的（例如制粒工艺）。可是，很多生产商希望设计一个清洁工艺用于特定设备组，而不管生产什么产品。这可以通过确定最差条件污物，并用这些污物来确定清洁工艺的设计空间来完成。

Specifications are developed to support the design, installation and operation of the cleaning system.Risks are identified and assessed for impacts to safety and cleaning effectiveness (e.g., severity, probabilityof occurrence, detectability). Parameters may be categorized based on their level of criticality,with the most critical parameters monitored closely so that the cleaning operation can be correctedif parameters are not kept within their predetermined ranges. The criticality of cleaning process operationalparameters is based on laboratory studies and other data/experiences that document theinfluence of each parameter on cleaning

effectiveness.
应通过开发标准来支持清洁系统的设计、安装和操作。识别并评估影响安全和清洁效果的风险（严重性、可能性、可检测性）。可以根据参数的关键性对参数进行分类，应严密监控最关键的参数，一但参数不在预定范围内，便可以对清洁操作进行修正。清洁工艺运行参数的关键性可以根据实验室研究或其他记录每一参数对清洁效果影响的数据/经验来界定。

Cleaning effectiveness may be influenced by the following factors:
清洁效果可受以下因素影响：
• Soil type or family
污物的类型或分类
• Nature of the soil on the surface
表面上污物的性质
• Equipment and contact surface type and finish
设备表面的类型与处理
• Cleaning technology and functional specificationsfor the cleaning process.
清洁技术和清洁工艺的功能性标准

This information is used to drive the design requirements for the cleaning method. Cleaning validation requires consideration of the worst-case operating conditions. Field conditions such as the flow rate, cleaning agent concentration, contact time, process temperature, and dirty hold time are conditions that areconsidered when developing an effective cleaning process. The assumption is that any cleaning processthat is performed within the space defined by these conditions will be effective, reliable and consistent.
此数据用于确定清洁方法的设计需求。清洁验证要求考虑最差操作条件。建立有效清洁工艺时，应考虑实际操作条件如流速、清洁剂的浓度、接触时间、操作温度、生产后保持时间。在这些条件所定义的清洁设计空间内执行任何清洁过程都是有效，可靠和一致的。

3.7Standard Operating Procedures
标准操作规程

One of the outputs of the design and development of a cleaning process should be a draft Standard Operating Procedure (SOP). That draft SOP should reflect sufficient detail to ensure process consistency. For the draft SOP, the following issues should be considered:
一个清洁工艺的设计和开发的输出是 SOP 草案。该 SOP 草案应足够详细，确保清洁工艺的一致性。SOP 草案中，应该详细考虑下列问题：

- The maximum allowable hold time for a piece of equipment:
  每一个设备在下列情况下允许的最大保持时间：
- after use, but before cleaning
  使用后，清洁前
- after cleaning, but before reuse, sanitization, or sterilization.
  清洁后，再次使用、消毒或灭菌前
- The steps to be taken for disassembly of equipment. Disassembly should be such that the equipment is broken down in a manner that will allow all parts to be effectively cleaned.
  设备拆解的步骤。设备拆卸应使所有组件均能被有效清洁。
- Critical sites or difficult-to-clean areas that may require special cleaning emphasis or a specific

inspection
关键性部位或难清洁的区域，可能需要重点清洁或特定检查。

- Cleaning process parameters
  清洁工艺参数
- Assignment of responsibility for cleaning of equipment
  设备清洁操作职责的分配
- Cleaning schedules, and where appropriate, sanitizing schedules
  清洁操作的日程表，以及必要时消毒的日程表
- Removal or obliteration of previous batch identification
  清除或涂去前批的标识
- A description in sufficient detail of the methods, equipment, and materials used in cleaning
  充分详尽的描述在清洁方法，所用设备和材料
- Sampling and testing that is part of the routine cleaning process
  日常清洁所进行的取样和测试
- The steps to be taken for reassembling equipment (as necessary) for storage and subsequent use
  因存放和后续使用而重新组装设备（如必要）所采取的步骤
- Visual inspection for equipment wear, product residuals and foreign materials
  目视检查设备磨损、产品残留或异物
- Protection of clean equipment from contamination prior to use
  保护已清洁后的设备在使用前免受污染
- Batch records as appropriate for the cleaning process. For fully automated processes, the batch record information may be collected and stored as part of the control system. For fully manual processes, the level of detail to be collected for a batch record will depend on the complexity of the process.
  合适的清洁批记录。对于完全自动化工艺，批记录的信息可能被收集和储存作为控制系统的一部分，对于完全手工的工艺，批记录的详细程度将取决于清洁工艺的复杂性。

3.8Operator Training for the Cleaning Process
清洁过程操作培训

Operator training is critical. During cycle development, operators should be trained in the requirementsof the evolving or existing SOPs. Proper training consists of understanding the SOP, demonstration ofthe correct procedure by a trained operator and demonstration of the correct procedure by the trainee. Operator training for manual cleaning may also include qualification and/or requalification of thetrainee by measuring residues on equipment cleaned by the operator. Operator training should be doneon a more frequent basis for manual cleaning processes as compared to automated cleaning processes.
操作人员的培训是非常关键的。在清洁程序开发期间，应按照不断修改或既有的 SOP 要求培训操作人员。适当的培训包括理解 SOP、由接受过培训的操作人员做示范、受培训的操作人员演示正确的操作过程。手动清洁的人员培训还包括测量清洁后设备上残留对受训人员进行资质确认和/或再确认。手动清洁过程操作人员的培训应比自动清洁过程更加频繁。

Training practices will vary from one company to another, but operator training may be improved by some of the following suggestions:
虽然各公司的培训实践有所不同，但下面的一些建议可能对操作人员的培训有所帮助：

- Clearly written, understandable and detailed SOPs

明确、通俗易懂和详细的 SOP

- Use of checklists to determine that all operations arecarried out in the proper sequence and are documented
  使用检查清单去确认所有的操作是按照顺序完成并有记录
- Periodic monitoring of cleaning processes to ensure proper training of operators and continued compliance with SOPs
  定期的监控清洁操作过程以确保操作人员培训的适宜性，并能持续符合 SOP。
- Dedicated or assigned cleaning personnel
  专职或指定的清洁操作人员
- Feedback from operators to modify procedures
  根据操作人员的反馈来修改操作程序
- Use of video to demonstrate proper cleaning operations and techniques.
  使用视频来演示正确的清洁操作和技能

The operators should understand the process of cleaning and the operation of the equipment they are cleaning. In addition the operators should be aware of the cleaning process impact on the quality and safety of the next product manufactured in the same equipment.
操作人员应能理解清洁操作程序和他们所清洁的设备的操作方法。此外，操作人员应能意识到清洁程序对相同设备生产的下产品的质量和安全影响。

3.9Introduction of New Products to a Validated Cleaning System
将新产品引入到已验证的清洁系统

When new products or significantly different raw materials are introduced to the plant, a system must be in place to ensure that the cleaning process will remain effective.
当工厂引入新产品或明显不同的原料时，应有系统确保清洁程序仍然有效。

Generally, the cleaning effectiveness of the existing system for new products can be tested by performing laboratory experiments using coupons of relevant materials (see Section 3.4 on Cleaning Development Laboratory Experiments). These experiments can be designed to test both the effectivenessof the proposed cleaning regimen and the relative difficulty of cleaning the new soils compared tosoils that have already been introduced to the plant. If the new soils are easier to clean than the mostdifficult soil already being cleaned, introduction of the new material using existing cleaning procedures can be made with confidence. If the material is more difficult to clean than each of the presentsoils, some modifications to the current cleaning process may be required, and cleaning validation for the new product is an expectation. However, if the new soil is easier to clean, then based on a risk assessment, the number of confirmatory runs needed (if any) is determined.
通常，可进行相关材质试样试验测试现有清洁系统应用于新产品时的清洁效果（见 3.4 节实验室清洁工艺开发）。这些实验可以用来测试推荐的清洁方法的有效性，以及新污物和已有污物清洁的相对难度。如果新污物比原最难清洁污物更容易清洁，可采用现有清洁程序对新物质进行清洁。如果该物质比原来污物都更难清洗，则可能需要对现有清洁工艺进行调整，并对清洁工艺进行验证。如果新污物比原污物更容易清洁，可基于风险评估确定效果确认的次数（如果有）。

4.0 Qualification

确认

Qualification is a part of cleaning validation involving the traditional activities of equipment qualification and process qualification. For cleaning validation purposes, equipment qualification focuses on qualifying (or verifying) the equipment used as part of the cleaning process, such as a CIP skid and automated parts washer. For fully manual cleaning operations, such as a brushing or scrubbing, there may be no equipment qualification activities. Design qualification has also been considered as another qualification activity, which is addressed in the design and development stage.

确认是清洁验证的一部分，它包括常见的设备确认和工艺确认。在清洁验证中，为确保验证达到预期目的，设备确认主要是对清洁工艺中使用的设备进行确认（或确证），例如 CIP 模块和自动清洗机。对于刷洗、擦洗等全手工清洗操作，则不需要进行设备确认。此外，设计和开发阶段的设计确认是另一种的确认活动。

The emphasis for this section is on process qualification activities. Process qualification involves the runs performed under a protocol designed to demonstrate the consistency of the cleaning process. The traditional approach for cleaning validation has been to focus on the qualification protocols to demonstrate effectiveness and consistency. The lifecycle approach that the industry has been moving toward involves a different approach with a more comprehensive view, with qualification runs being only one of the stages of validation. The lifecycle approach also includes design/development activities and validation maintenance (ongoing controls).

本节重点是讨论工艺确认活动，工艺确认指按照设计方案完成的用以证明清洁工艺一致性的所有活动。传统的清洁验证注重证明清洁工艺的有效性和一致性。但是在制药工业领域最引入生命周期方法提出了更加全面的观点，它将确认活动视作整个验证中的一个阶段。生命周期的验证方法还包括前期设计、开发活动和验证的持续维护（持续控制）。

This section covers protocol elements and specific important issues for cleaning validation protocols, including the number of validation runs required, mock soiling for validation runs, worst-case process conditions, and the disposition of equipment/product during validation runs. It also covers grouping approaches for products and equipment as well as important considerations in clean hold time studies. It ends with a discussion of documentation for “cleaning verification”.

本节内容包括清洁验证方案要素和验证方案中关键点，包括验证次数、验证中的模拟污物、最差工艺条件和验证期间设备/产品处置。此外，还包括产品和生产设备的分组方法、清洁保持时间研究要点以及对“清洁效果确认”文件的讨论。

4.1Protocol Elements

验证方案要素

Cleaning validation protocols have many of the same elements as process validation protocols. For reasons of clarity, the format of a cleaning validation protocol usually follows the same approach (as appropriate) as used for process validation protocols for a given company. Common elements include (but are not limited to) purpose, validation design/strategy, scope, responsibilities, applicable product(s) and equipment, cleaning procedure and associated documentation, acceptance criteria, training, and a requirement for a final report. Key elements for cleaning validation protocols include residue limits (see Section 5.0),

sampling procedures (see Section 6.0) and analytical methods (see Section 7.0).
清洁验证方案要素与工艺验证方案相似。为便于表述，特定公司的清洁验证方案通常采用与工艺验证方案相同的模板（适当时），一般包括（但不限于）验证目的、验证设计/策略、验证范围、职责、适用产品和设备、清洁程序和相关文件、可接受标准、人员培训和最终验证报告的要求。清洁验证方案中关键要素包括允许残留限值（见 5.0 节）、取样程序（见 6.0 节）和分析方法（见 7.0 节）。

Two approaches are used for documentation of elements. One general approach is to reference other documents for details regarding that element. For example, specification of swab sampling sites can be in the protocol while the rationale for selection of those sites can be in another document that is referenced in the protocol. The advantage of referencing other documents is that only the detailed information required for executing the protocol is included in the protocol; supporting information is only referenced thus allowing for more “streamlined” protocols. Another approach is to include all relevant details for a given element in the protocol. The advantage of having more details in the protocol is that greater clarity is provided to those executing the protocol. The approach used should consider the knowledge management systems within a given firm.
有两种方法可用于组织和编写验证文件，常见的方法是引用其他文件相关要素的详细内容。例如，将擦拭取样布点写在验证方案中，而取样点的选择依据在另一个文件中，则可以在验证方案中引用该文件的相应内容。由于方案中只需要详细说明项目需完成的操作，相关支持信息引用即可，这种编写方法可以使方案更加流畅。另一种方法是将方案特定要素的所有相关信息全部描述清晰，验证方案执行者可直接获取明确的信息。企业应当根据自身的知识管理系统选择适当的方法。

4.2 Key Protocol Issues
验证关键点

The validation protocol is not written and approved until the cleaning process has been designed and developed (see Section 3.0). The execution of the protocol should not begin until the protocol is approved. However, execution of the protocol as an engineering or practice run can be helpful in some circumstances (e.g., for activities that are highly complicated or new to those executing the protocol). Any problems in the execution of the engineering/practice run can be corrected before actual validation runs. The time spent in such runs may lead to the higher likelihood of “right first time” protocol execution for the formal qualification runs.
清洁验证方案应在清洁工艺设计和开发（见 3.0）后起草和批准，并在获得批准后实施。在某些情况下（如操作高度复杂或方案执行者首次实施的活动），可以先模拟实施验证方案。在模拟验证中发现的任何问题均可在实际验证实施前纠正。这种模拟有助于提高正式验证的一次成功率。

Key issues for protocols (aside from limits, analytical methods and sampling procedures, which are covered elsewhere) are discussed below.
下面对验证中的关键点进行讨论（残留限值、分析方法和取样程序在其他章节讨论）

4.2.1 Number of Runs in a Protocol
验证次数

The traditional approach for cleaning validation protocols has been to require an evaluation of three consecutive runs of the cleaning processes. “Consecutive” means that no cleaning events of that same process are skipped without an appropriate rationale. For example, if the cleaning validation is for cleaning of Product A, there may be manufacture and cleaning of Product B in between manufacture of lots or

batches of Product A.
传统的清洁验证要求评价连续三次清洗活动。“连续”意味着没有充分理由，必须连续完成相同的清洁工艺，不得中断。例如产品 A 清洗验证实施过程中不可以穿插生产和清洗产品 B。

Based on lifecycle approaches to validation, as well as several regulatory documents including the 2011 U.S. FDA process validation guidance, the newer approach has been to provide a rationale, based on an understanding of the cleaning process, documentation from the design and development phase, and data from sufficiently similar cleaning processes, for a specific number of validation runs required (9,10). This might result in fewer than three runs or greater than three runs. It should be recognized that this new U.S. FDA process validation guidance does not formally cover cleaning validation. However, a number of principles in that document may be applicable to the validation of cleaning processes.
基于验证生命周期方法以及其他几个法规如 2011 年美国 FDA 颁布工艺验证指南，提出一种新的验证方法。基于对清洁工艺的充分理解、设计和开发阶段记录和足够相似清洗工艺的的数据，该方法提供了确定需要完成的验证次数的依据（9,10）。清洁验证次数可少于三次，也有可能多于三次。应该认识到，虽然 FDA 新的工艺验证指南并不涵盖清洁验证，但是指南中的一些原则可用于清洁工艺的验证。

4.2.2 Mock Soiling
模拟污染
Ordinarily a cleaning validation run is performed by cleaning on a commercial-scale batch. An alternative approach is to use what is called “mock soiling” or “artificial soiling” to simulate the nature and condition of the manufactured product on the commercial equipment at the time of initiating the cleaning process.
If mock soiling is used, a rationale must be provided for its use as well as why the mock soiling simulates a “realistic” manufacturing situation. A common reason for mock soiling has been to obtain three consecutive cleaning validation runs without being forced to make three commercial-scale batches of the cleaned product. “Mock soiling” (a process) should be distinguished from a “mock soil” (sometimes called a “surrogate soil”), which is a product which simulates the physicochemical properties of the actual soil.
通常情况下，清洁验证需要在产品商业规模生产时进行。还有种方法是在启动清洁工艺时采用“模拟污染”或者“人造污染”模拟所生产产品在商业生产设备上的特性和状态。使用这种方法时，必须提供“模拟污染”的依据，并说明它如何模拟“实际”生产状态。常见的原因是采取模拟污染的方式可以完成三次连续的清洁验证活动，而无需生产三批次商业规模产品。应将“模拟污染”（一个过程）同“模拟污物”（也称作污物替代物）区分开来，模拟污物是一个产品，用来模拟生产中真实污物的理化性质。

4.2.3 Worst-Case Process Conditions
最差工艺条件
The traditional approach for cleaning validation protocols has been to include worst-case process conditions in the three protocol runs. Rationales for worst-case conditions should be given in or referenced in the protocol. For example, worst-case process conditions may include maximum dirty hold time, maximum batches or elapsed time in a campaign, shortest allowed time for manual cleaning steps, lowest allowed temperature for manual cleaning processes, and worst-case circuits for CIP skid selection.
在设计传统的清洁验证方案时已经考虑到需在最差工艺条件下完成三次验证，评价最差工艺条件的原则应包含或引用在验证方案中。例如，最差工艺条件可包括最长的生产后保持时间、阶段性生产中最大批量或者最长运行时间、最短的手工清洗时间、最低的手工清洗用水温度和最差的 CIP 模块

循环回路。

Parameters such as temperature, cleaning agent concentration, flow rates, and process step times for automated cleaning processes are generally controlled in a narrow range such that challenging the cleaning process in the validation runs at the lower or upper end of the specification is not appropriate. If those narrowly controlled parameters are to be challenged in the extremes or outside the specified range, those challenges can be evaluated in development studies to demonstrate the robustness of the cleaning process.
由于自动清洁工艺中温度、清洁剂浓度、流速和工艺步骤运行时间等参数一般控制在一个狭窄的范围内，所以采用参数的上下限进行清洁工艺挑战验证是不合适的。清洁工艺开发研究时，可以通过挑战规定范围内极限值或者超出范围的参数来证明所建立清洁工艺的耐用性。

There may be different approaches for addressing worst-case process conditions. In one approach, a worst-case process condition is addressed in each of the required validation runs. An alternative approach is to address a specific worst-case condition in the design and development of the cleaning process such that the cleaning process is developed to address a worst-case condition. Data from such design and development studies may support the use of worst-case conditions in fewer runs.
有多种方法可用来确定最差清洁条件，一种方法是在每一清洁验证批次均采用最差清洁参数。另一种方法是在清洁工艺设计和开发过程时针对一个特定最差条件进行研究，这样开发的清洁工艺已经涵盖了最差条件。这种设计和开发研究中获取的数据有助于减少采用最差条件的验证批次。

Another example of worst-case conditions is the number of batches in a campaign where validated cleaning is only performed at the end of campaign. In such cases, there may be no cleaning between batches or there may be only “minor cleaning” (such as vacuuming for solids manufacture or a water rinse for liquids manufacture). In this case, the maximum number of batches may represent the worst case. Therefore, the validation protocol should consider the effect of the maximum number of batches in the campaign.
另一类的最差条件是在阶段性生产后进行清洁验证，批次之间不进行清洁或者仅进行“小清洁”（例如固体生产时真空吸尘或者液体生产时的水冲洗）。在这种情况下，最多连续生产批次即为最差条件，因此验证方案应考虑阶段性生产时最多批次的影响。

In such an approach, it may not be feasible to schedule three consecutive campaigns with the same maximum number of batches. One practical way to address this is to manufacture and perform cleaning validation after a specified number of batches that may represent a minimum campaign length. When a campaign involves more than the previous number of batches, a validation protocol is executed on that longer campaign. Data from the longer campaign are then compared with data from the earlier validation runs to determine whether the data are equivalent. The specifics of the results will indicate whether additional validation runs are needed to extend the validated length of the campaign.
采用这一方法，安排具有相同批次的三个连续阶段性生产并不可行。一个解决办法是在生产指定批次（可代表最小阶段性生产批次）后进行清洁验证。如连续生产批次超过该指定数量，则应对更长的连续生产批次进行清洁验证。然后对比分析前后两次验证数据是否一致，是否需要额外的验证来延长阶段性生产批次。

A third approach is to address campaign length during the design and development phase. If data or a rationale can be developed to support no change in the difficulty of cleaning regardless of the campaign

length, then the validation runs can be at any campaign length.
第三类方法在设计和开发阶段对阶段性生产批次进行研究。如果有实验数据和原理能够证明阶段性生产批次不影响清洁难易程度，清洁验证过程中就可以任意选择阶段性生产批次进行验证。

4.2.4 Disposition of Products and Equipment during Validation
验证期间产品和设备的处置

A cleaning process generally only affects the next product manufactured in the cleaned equipment. Therefore, following protocol execution the “cleaned” product may be released following company procedures for product release. That release of product is independent of the data obtained for the immediately following cleaning process. The data from that cleaning process is used for the release of the cleaned equipment.
一个清洁工艺通常只影响已清洁设备中生产的下一个产品，因此，按照验证方案执行后，可按照产品放行程序对所生产产品进行放行。产品的放行与生产后的清洁过程数据无关，清洁过程所获得数据可用于已清洁设备的放行。

There are several approaches used for disposition of the equipment following the cleaning process. One approach is to not release the equipment until acceptable data (including meeting all residue criteria) are obtained for that specific validation run. At that time, the equipment may be safely released for manufacture of the same or another product.
清洁验证中，清洁后的生产设备有多种处置方法。一种方法在确定本批次清洁验证数据符合要求（包括符合所有残留限度）前该设备不得放行使用，设备放行后方可用于该产品或其他产品的生产。

An alternative approach is to release the equipment following company procedures at risk for manufacture of the next product. However, that next product cannot be released until acceptable data (including meeting all residue criteria) are obtained for that specific validation run. If the cleaning validation run fails to meet its acceptance criteria, then the impact on that specific next manufactured product should be assessed as part of the investigation into that non-conformance. The results of the investigation will determine whether that next manufactured product can be released.
另一种方法是在符合公司风险控制程序的前提下放行设备，用于生产下一产品。但该产品需等到该批次清洁验证数据符合要求（包括符合所有残留限度）后放行。如果该批次清洁验证不符合要求，那么作为该“不符合”调查的一部分，应评估其对该产品的影响。调查的结果将决定该产品能否放行。

If there are separate validation protocols for equipment items in a train used to manufacture the product on which the validation is being performed, each equipment item can be released based on the protocol data for that validation run for that equipment item. It is not necessary to wait until validation is complete on all equipment items in the train before any item can be released for subsequent manufacture.
如果一条生产线中的不同设备需单独进行清洁验证，那么每一设备都可以基于特定批次清洁验证数据放行使用，无需等待所有设备均验证成功。

4.3 Grouping/Family Approach
分组/分类的方法

Grouping is a strategy whereby manufactured products and/or equipment are considered together, and a formal protocol is performed on a representative from the group. The representative from the group is

usually the worst case among products or equipment in a group. Grouping is also called matrixing, family approach or bracketing. The rationale for grouping is to generate optimum value from cleaning validation tasks based on a risk approach. One requirement for grouping is that product and equipment be cleaned by the same cleaning process. The use of products and equipment grouping may be used to streamline cleaning validation programs while ensuring sufficient data are available to support the validation of procedures, processes, and equipment associated with cleaning. The grouping program for a given facility or company should be specified or referenced (e.g., by pointing to a facility cleaning rationale) in a well-designed validation program/validation master plan.

分组法是综合考虑所有产品/设备后对其进行分组，选取组内代表性的产品/设备来替代整组进行验证的策略。用来作为代表的产品或者设备通常是组内最难清洗的。分组法也被称为矩阵法、分类法或交叉法，它是一种运用风险分析的方法在清洗验证中选择最合理的验证目标的方法。分组的原则是划分为一组的产品和设备必须采用同一清洗工艺。运用产品和设备分组的方法可以在简化清洁验证程序的同时又获得足够有效的数据来支持所验证的程序、工艺步骤和设备达到预期。特定工厂或企业的分组方案应当在一个精心设计的验证计划/验证主计划中予以明确或引用 (例如索引至一个关于工厂清洗验证原则的文件)。

4.3.1 Product Grouping

产品分组

Products may be grouped together if they are manufactured on the same or equivalent equipment, and cleaned by the same cleaning procedure. Products may be assessed for their relative cleanability by several methods. Relative cleanability may be affected by the nature of the active ingredients, of the excipients, and/or of degradation products. One example of assessing relative cleanability involves selecting the product with the leastsoluble active ingredient in the cleaning solution. This approach may be appropriate for small-molecule API synthesis cleaned with a solvent or for finished drug product manufacture involving water-soluble formulations. Such an approach may also be possible for solid dosage drug products provided that the excipient portion of the different drug products has the same effect on the difficulty of cleaning.

可以将在同一或者等同设备上生产，同时清洁工艺又相同的产品定义为一组。组内产品相对可清洁性有多种方法来评价。活性成分、辅料和/或降解产物的特性都会影响相对可清洁性。例如可选择 API 在清洁溶液中最难溶解的产品，进行相对可清洁性的评估。在使用溶剂清洗合成的小分子 API 或者清洗水溶性配方的制剂时，这种方法比较适用。此外，如果固体制剂产品中辅料部分（赋形剂）对清洁难易程度具有相同影响时，也可以采用这一方法。

Another approach involves determining relative difficulty of cleaning using laboratory studies. For laboratory studies, cleanability is assessed on coupons or small equipment parts using representative surfaces, with stainless steel being the most common because of its predominance in pharmaceutical equipment. For coupons, the roughness of the surface should be the same or rougher (as a worst case) than actual equipment surfaces. From the lab results, the relative cleanability of each product is defined, typically by determining under proposed cleaning parameters which product requires the longest time to clean. Bioactivity and clinical effects may also be considered for the selection of a representative product.

另一种方法是通过实验室研究确定相对可清洁性，采用材质试样或设备小部件表面，评估可清洗性，由于不锈钢设备在制药行业广泛使用，一般选择不锈钢材质的部件进行研究。材质试样的表面粗糙度应该与生产设备表面相似或者更加粗糙（作为最差条件）。根据实验室研究结果，确定每一产品的相对可清洁性，通常采用推荐的清洁工艺参数确定哪个产品清洁耗时最长。此外，产品的生物活

性和临床药理活性也应该作为代表性产品选择的依据。

One option for product grouping is to use a surrogate worst-case product. In this situation, the worst-case product is an artificially constructed product (which may not be a commercial product) designed to be more difficult to clean than products expected to be routinely manufactured. One rationale for this approach is to maintain continuity of the worst-case product (in cases where a commercial product might be discontinued). Another rationale is to minimize situations in which new worst-case products are added.
产品分组的另一个方法是引入一种最差条件产品替代物。通常，用作替代品的物质是人工创造出的（可能不是商业产品），它比组内其他产品更难清洁。这种方法的一个优点是可以保证组内最差产品的延续性（如选择上市产品，存在停产的可能），另一个优点是可以降低引入新的最差产品时重新验证的可能。

A qualification protocol on the representative (worst-case) product is performed. The acceptance criterion for that worst-case product is generally the most stringent acceptance criterion of all products in the group (that is, the lowest residue limit). Successful cleaning validation of the representative (worst-case) product means the cleaning of the other products in the group is also validated. Based on risk assessments (addressing both quality risks and business risks), one approach is to perform a single confirmatory validation run on every other product in the group. Also based on a risk assessment, another approach is to perform qualification protocols on both the most difficult to clean product and the product with the lowest limit.
采用代表性产品（最差条件产品）进行确认。最差条件产品的最低可接受残留限值可作为组内所有产品最严格的可接受标准。代表性产品（最差条件产品）清洁验证的成功同样意味着组内其他产品的清洁工艺已验证合格。但基于风险评估(包括质量风险和商业风险)，一种方法是组内的其他产品都进行一批次清洁确认；另一种方法是同时选择组内最难清洁产品和允许残留限值最低的产品进行验证。

4.3.2 Equipment Grouping
设备分组
Equipment may be grouped together if they are similar and can be cleaned by the same cleaning procedure. Grouping of equipment is an effective method for encompassing equipment from a limited population of systems undergoing cleaning validation without redundant testing. The grouping strategy is based on designating equipment as “identical” or “similar,” based on design, mode of operation, and cleanability. Such a determination usually involves evaluating the equipment qualification, with the stipulation that qualification differences that do not affect the cleaning process may allow one to conclude that two equipment items are identical for cleaning purposes. Regulatory documents such as the U.S. FDA SUPAC guidance may assist in that determination (11).
设备分组要求组内设备相似，并且清洁工艺相同。在清洁验证中，设备分组是一种将需清洁验证的设备合理分组，避免多余测试的有效方法。分组策略是以设备设计、操作模式和可清洁性的“等同”或“相似”为基础的。判定设备是否“等同”或“相似”，需要对设备确认进行评估，如果设备确认的差异不影响清洁工艺，在可判定两个设备在清洁方面是等同的。法规如美国 FDA 颁布的 SUPAC 指南（药品放大和批准后变更指南）有助于“等同性”判定（11）。

Once equipment has been placed within a designation, the designation defines the cleaning validation requirements. If it involves identical equipment, a protocol involving any combination of identical

equipment items in the group is performed.Provided an adequate rationale is given for determining the equipment items are identical, there is no need to perform validation runs on every item in the group.For similar equipment, the representative equipment is the worst case or may involve bracketing of the equipment. For example, for storage tanks that are of the same size but different complexity due to the number of baffles, the more complex equipment is chosen as the worst case. For similar equipment of different sizes, the largest and smallest (representing the extremes) may be chosen for the formal validation runs (unless one size can be determined as the worst case). If there is no worst case or bracketing involved, then any equipment items in the group of similar items may be chosen for validation runs. Confirmatory validation runs (perhaps only one run) are an option for other equipment (not a worst-case) within the group.

一旦将设备划分到指定组，就可以对这个组的验证要求进行定义。当组内设备均等同时，组内等同设备的任意组合进行验证。假如有足够的证据证明组内设备等同，就没有必要对组内每个设备进行验证。当组内设备相似时，可以选择最难清洁或者通过交叉法选择。例如大小相同，但内部隔板数量较多、结构复杂的罐子就是最难清洁设备；大小不同的设备，最大和最小两个规格（两个极端）均作为最难清洁设备（除非最大和最小中有一个可以作为最差条件）。如没有最差条件设备或者没有采用交叉法确定代表性设备，可以选择组内任一设备进行验证，组内其他设备（非最差条件）完成清洁确认即可（也许只需进行一个批次)。

A specific case of equipment grouping involves “minor” equipment, such as utensils, small parts, and smaller equipment. In the case of such minor equipment, it may be appropriate to evaluate a cleaning procedure for those parts and to validate the cleaning process using equipment grouping. The grouping of the parts may involve selection of worst-cases based on complexity, size and functionality.

容器、小部件以及较小设备等小设备分组时，也可以采用设备分组的方法评价和验证这些部件的清洁工艺。分组时可以通过对比小设备的复杂性、尺寸和功能，来选择最难清洁的部件。

4.3.3 Introduction of a New Product or Equipment into a Group

组内引入新产品或设备

The introduction of a new product into an already validated group is assessed using the same science and risk-based evaluation process (e.g., based on solubility in the cleaning solvent, a laboratory coupon study, and/or information from other process cleaning studies) to initially determine the worst-case product. It is recommended that if each new product is tested in a lab evaluation, a suitable control, such as the previous worst-case product, be included. Relative product cleanability is then used to determine validation requirements for that new product on equipment used for other products in that group. The relative cleanability of the product in relation to the preceding worst-case product, as well as any change in the lowest limit for products in the group, will dictate the validation requirements. Based on a documented risk assessment, introduction of an easier-to-clean product may just require laboratory and/or scale-up studies to confirm ease of cleaning or may require one confirmatory run. Introduction of a more difficult-to-clean product requires validation of that new worst-case product.

向已验证过的组内引入新产品，需使用与最初确定最难清洁产品时相同的科学风险评估过程进行评估，例如评估产品在清洁溶液内的溶解性、进行实验室材质试样研究和/或者其它的清洁工艺研究。假如每新增一个产品都进行实验室测试应采用适当的对照，如前最差条件产品进行研究。通过比较新产品和组内产品的相对可清洁性来确定引入新产品的验证需求。而新产品与前最差条件产品的相对可清洁性，以及组内产品最低允许残留限值的变化都决定着验证要求。基于书面的风险评估，组内新增较容易清洁品种一般只需要在实验室和/或中试放大研究时确认其容易清洁或进行一批次清

洗确认即可；组内引入更难清洁品种则需要对新最差条件品种进行清洁验证。

Based on risk considerations, introduction of new identical equipment may simply involve a determination that it is equivalent or may require an additional confirmatory run. Introduction of new similar equipment requires an evaluation if that new equipment represents a new worst case or a new bracketing extreme. If not a new worst case or new extreme, special attention should be paid to the first commercial cleaning event to confirm effectiveness. If the new equipment is a new worst case or bracketing extreme, the validation requirements for the previous worst case or bracketing extreme should be performed for the new worst-case or bracketing extreme equipment.
基于风险的考虑，组内新增等同的设备时，可确认新旧设备是等效的，或者需要额外进行一个批次清洗确认即可。当组内引入相似的生产设备，需要评价新设备是否形成最差条件或新的交叉法极端条件，如果不是，则应特别注意新设备第一次商业生产后的清洁后效果确认，确认清洗工艺有效；如果形成新的最差条件或交叉法极端条件，新设备需按照原先最差条件或交叉法极端条件设备的验证要求重新完成清洁验证。

4.4 “Cleaning Verification” Documentation
“清洁效果确认”文件
“Cleaning verification” as used in this Technical Report refers to documentation which says that a one-off cleaning event is effective for cleaning equipment so that the equipment can be used for subsequent manufacture of a product. There may be a variety of other terms for this same concept that are used by various companies. Examples of where cleaning verification might be used include cleaning after manufacture of a clinical trial product or cleaning after product manufacture where there is a deviation (e.g., the dirty hold time is exceeded) that affects a validated cleaning processes.
在本技术报告中，“清洁效果确认”是指用来证明生产设备经一次清洁操作后可以用于后续生产的文件。对于“清洁效果确认”，不同企业用语各不相同。清洁效果确认适用于如临床样品生产后的清洁，或者出现偏差（如超出了规定的生产后保持时间）影响了清洁工艺验证状态。

Documentation for cleaning verification purposes is similar to the documentation for cleaning validation, except that the verification data is specific to one cleaning event. From a compliance perspective, the data applies only to the one cleaning event (although from a scientific perspective the data may suggest similar performance if the cleaning event were repeated). Another difference is that because cleaning verification is typically performed on a unique cleaning event, there may be limited cleaning design and development before execution of that event. One approach is to utilize a cleaning SOP and a cleaning verification protocol. Alternatively, companies might use a concept that defines explicit requirements for cleaning verification in an SOP and documents the specific activities, sample positions and so on in a form which will be approved. It is generally not appropriate to consider three cleaning verification runs as constituting a “validation” especially if the element of appropriate design and development is absent.
除了清洁效果确认针对一次性清洁活动，清洁效果确认的记录与清洁验证相似。从合规的角度来看，清洁效果确认数据只用于证明一次的清洁效果符合要求（尽管从科学角度来说数据可暗示重复清洁能够得到相似效果）。另一个区别是由于清洁效果确认通常是针对一次单独的清洁活动，在进行清洁活动前可能只进行了有限的清洁设计和开发。一种方法是建立一个清洁 SOP 和一个清洁效果确认方案。另一种方法是在一个 SOP 中明确规定清洁效果确认活动的各项要求，并在批准的表格中记录所进行的活动、取样点位置等。需要指出的是，将三个批次清洁效果确认看做“清洁验证”是不合适的，尤其是在缺少适当设计和开发工作的前提下。

5.0 Residue and Limits

残留和限度

Based on the understanding of the cleaning process, potential residues remaining on equipment surfaces after cleaning can be identified. Residues may include the active drug, excipients, processing aids, cleaning agents, bioburden, endotoxin, and degradants. Those residues, if present at unacceptable levels and could potentially contaminate or adulterate the next manufactured product, should be identified. Based on a risk assessment, residues are selected that will be measured in a cleaning validation protocol, and for which limits should be established. Typically for non-sterile manufacturing, this includes the drug active, the cleaning agent and bioburden. Typically, for sterile manufacture, endotoxin should also be included. Other potential residues may be added to this list based on the risk assessment. Furthermore, based on a process understanding and risk assessment, it may be acceptable to not set limits for potential residues in this list. For example, in non-sterile manufacturing, setting limits for and measuring bioburden in a protocol may not be required if there is a final wipe or rinse of equipment surfaces with a sanitizing or disinfecting agent, such as 70% isopropanol, provided there is a scientific rationale and/or supporting laboratory studies.
根据对清洁过程的理解，可以确定清洁后设备表面可能存在的残留物。残留物可能包括活性成分、辅料、工艺助剂、清洁剂、微生物负载、内毒素和降解产物。应确定那些超出允许限度并可能使下一批产品污染或掺入杂质的残留物。根据风险评估，选择那些将在清洁验证方案中测量的残留，并建立可接受限度。对于非无菌生产过程，通常包括活性成分、清洁剂和微生物负载；对于无菌生产过程，还应包括内毒素。根据风险分析结果，也可增加其他可能存在的残留。而且，基于对工艺的理解和风险评估结果，也可以不设定这些可能存在残留的限度。例如，对于非无菌生产过程，清洁后最终用一种消毒剂如 70%异丙醇擦拭或冲洗设备表面，假如有科学依据和/或实验室研究数据支持，可不必在方案中设定限度并测量微生物负载。

The determination of cleaning limits and acceptance criteria is a crucial element of a cleaning validation program. A limit is typically an actual numerical value and is one of the acceptance criteria of a cleaning validation protocol. Limits and acceptance criteria should be:
确定清洁可接受标准是清洁验证计划中关键要素。限度通常表示为数值形式，也是清洁验证方案中可接受标准之一。限度和可接受标准应该：

- Practical 务实的
- Verifiable 可确认的
- Achievable 可达到的
- Scientifically sound 科学合理

The limits should be practical in the sense that the limit chosen should be appropriate for the actual cleaning situation to be validated. Also, the limits must be verifiable by a qualified analytical procedure. In addition, the limits must be achievable by the cleaning process for the product and by the analytical methodology available for the target residue. Finally, the company should develop a scientifically sound rationale for the limits chosen. It is very important that cleaning limits not be selected arbitrarily butrather there be a logical and scientific basis for the limits selected. The scientific rationale should be appropriately documented and should be logical, comprehensive, and readily understood.
限度应务实指得是选择的限度应适合待验证的实际清洁状况。同样，也必须能够采用已验证的分析

方法对限度进行确认。另外采用特定产品的清洁工艺进行清洁后，经现有分析方法测量，目标残留物必须能够达到预定的可接受限度。最后企业应能提供限度建立的科学合理依据。非常重要的是不能随意地选择清洁限度，而应有符合逻辑的科学依据。科学依据应有书面记录，具有逻辑性、全面，并容易理解。

5.1 Considerations for Developing Limits 限度设定要点

As used in this Technical Report, “product” may be drug product, API, intermediate, or another type of formulation. If “drug product” is intended, that terminology will be utilized.
本技术报告中的产品可以是制剂、原料药、中间体或其他类型配方。如果特意指“制剂”，应采用相应的术语。

Residues remaining on equipment may transfer to a subsequently manufactured product. Thus, it is important to have information about the potential residues as well as the product which could become contaminated. Furthermore, the nature of the cleaning process itself is also important. Once these areas have been considered, it is important to obtain a cleaning process understanding (e.g., through process mapping), and then to perform a risk assessment for the appropriate evaluation of limits.
设备上残留物可转移至后续生产的产品中。因此了解可能存在的残留以及可能被污染的产品就十分重要了。而且，清洁过程的本质也很重要。一旦已经考虑到这些方面，重要一点就是获得对清洁工艺的认识（如通过流程分析），再通过风险评估对限度进行适当评价。

Relevant information for the *subsequently manufactured* product may include, as appropriate for the nature of the product (drug product, API, or intermediates), the formulation, the product’s specifications, the dosing, the route of administration, the batch size, and the shared equipment. Product specifications may be important, e.g., for establishing bioburden limits. Relevant information on the *cleaned product* includes the formulation, the dosing, the toxicity, and the route of administration. Relevant information on the cleaning process includes the cleaning agent, cleaning method, and the various cleaning parameters (see **Section 3.0** on design and development of cleaning processes).
后续生产产品相关信息包括，产品的性质（制剂、原料药或中间体）、处方、质量标准、剂量、给药途径、批量、共用设备。产品质量标准可能是重要的，如建立生物负载限度。已清洁产品相关信息包括，处方、剂量、毒性、给药途径。清洁工艺相关信息包括，清洁剂、清洁方法、各清洁参数（见 3.0 节清洁工艺的设计和开发）。

5.2 The Basis for Quantitative Limits 定量限度的确定基础

Limits are usually based on one of the following as described in later sections:
限度通常基于以下几点建立，详见后续章节：

- The medical or pharmacological potency of the drug active 活性成分的医学或药理效力
- The toxicity of the residue 残留的毒性
- A default value 默认值

Different manufacturing and cleaning situations may require different approaches. For example, for in vitro diagnostics, the effect of the residue on the stability or performance of the subsequently manufactured product may provide a better scientific rationale for establishing limits. The following section discusses the basis of typical carryover calculations. Depending on the manufacturer, the expression of those

calculations may be different because it may combine various steps given below. However, it is critical that the units used in the equation be internally consistent; for this reason, unit conversion factors (e.g., grams to micrograms) may be utilized in these equations. In addition, companies may use different terms (or acronyms) for the same concept but still apply the same basic principles in calculations; this is to be expected in a field as diverse as cleaning validation.

不同的生产和清洁过程可能采用不同的方法。例如，对于体外诊断试剂，残留对后续生产产品稳定性或性能的影响可作为确定限度的科学依据。下节讨论了计算残留的基本要求。生产企业不同，这些计算的表述也不一样，因为这些计算包含了下述不同步骤。然而，关键是公式中采用的单位应一致，因此这些公式中可能用到单位转换因子（如将克转换为微克）。另外，对于同一个概念，不同生产企业可采用不同术语，但计算中应用的基本原则是相同的；这在清洁验证领域是常见的。

5.3 Acceptable Concentration of Residue in Next Product 下一产品中允许的残留浓度

The first determination is the acceptable level (i.e., concentration) of the target residue in the subsequently manufactured product. This may be called by different terms, but for this document that concentration will be called Acceptable Residue Level (abbreviated ARL). This is an expression of the maximum concentration of residue allowed in that next product, as determined by medical, pharmacological, safety, stability and/or performance issues. For chemical residues (such as the drug active or cleaning agent), this concentration is typically given as µg/g or µg/mL (or an equivalent expression depending on the units selected). For bioburden, this is typically given as colony forming units (CFU), CFU/g or CFU/mL.

首先要确定目标残留在后续产品中的可接受水平（即浓度）。对此可有不同术语，但本文中浓度被称作可接受残留水平（简称 ARL），它是下一产品中允许的最大残留浓度，由医学、药理、安全、稳定和/或效用因素决定的。对于化学残留（如原料药或清洁剂），该浓度通常以 µg/g 或 µg/mL 表示（或根据选择的单位采用等同表述）。对于生物负载，通常以菌落数（CFU）、CFU/g 或 CFU/mL 表示。

5.3.1 ARL Based on Drug Active Dose 基于活性成分剂量的 ARL

For drug actives in *drug product manufacture*, this is typically determined as one-one thousandth (0.001) of minimum daily dose of the drug active in a maximum daily dose of the next drug product. This approach is an alternative to the acceptable daily exposure (ADE) (see **Section 5.3.2.1)** approach for non-highly hazardous active ingredients for manufacture in nondedicated equipment.

对于制剂中的活性成分，一般定为已清洁产品活性成分最小日剂量占下一产品最大日剂量的千分之一。对于非专用设备生产的非高毒性活性成分，该方法是可接受日暴露量法（见 5.3.2.1）之外的另一种选择。

This is expressed in the following equation:

以下式表示：

[Equation 5A] 公式 5A

$$ARL = \frac{MDD \times SF}{LDD}$$

Where 其中:

ARL = the acceptable residue level in the next drug product
下一产品中可接受残留水平

MDD = the minimum daily dose of the *active* of the cleaned product
已清洁产品活性成分的最小日剂量

SF = the safety factor, which is typically 0.001
安全系数，通常为 0.001
LDD = the largest daily dose of the next *drug product* to be manufactured in the same equipment
同一设备中生产的下一制剂的最大日剂量
[Note 1: For *API manufacture*, where both the cleaned product and the next manufactured product are APIs, **Equation 5A,** as well as other applicable equations in **Section 5.3,** is modified with LDD being the largest daily dose of the next drug *active* manufactured in the same equipment**.]**
[备注 1：对于 API 生产，已清洁产品和下一产品都是 API，公式 5A，以及 5.3 节其他相关公式，LDD 调整为同一设备中生产的下一活性成分的最大日剂量**]**

[Note 2: For MDD, another approach is to use the single therapeutic dose rather than the minimum daily dose. The use of a minimum daily dose has a scientific rationale based on normalizing the dosage frequency for the cleaned product and the next product. For products administered daily, the use of a single therapeutic dose may be more stringent so it is an acceptable practice. However, if the cleaned product is administered once a week, and the next product is administered once a day then the use of a single therapeutic dose in place of the MDD will result in patients who take the next product receiving 0.001 of a single weekly dose taken on a weekly basis. Therefore, in the latter case, it is preferable to compare both products on the same basis, either weekly or daily (convert a daily dose to a weekly dose by multiplying by 7, or convert a weekly dose to a daily dose by dividing by 7)**.]**
[备注 2: 对于 MDD，另一种方法是用单次治疗剂量，而不是最低日剂量。采用最低日剂量的一个科学依据是已清洁产品和下一产品的给药频次是一样的。对于每日给药的产品，采用单次治疗剂量可能更严格，所以允许这样操作。但如果已清洁的产品每周给药一次，而下一产品每天给药一次，用单次治疗剂量替代 MDD，将导致服用下一产品的患者一周都要接受已清洁产品单周剂量千分之一的残留。因此，在后一种情况下，应在同等基础上进行两个产品的比较，每周或者每日（将日剂量乘以 7 转变为周剂量，或将周剂量除以 7 转换为日剂量）。**]**

[Note 3: Another approach is to express the safety factor (SF) as 1000 rather than 0.001. In such cases, SF will be in the denominator of **Equation 5A.]**
[备注 3: 另一方法是安全因子以 1000 而不是 0.001 表示。此时 SF 应在公式 5A 的分母中。**]**

5.3.2 ARL Based on Toxicity 基于毒性的 ARL

There are typically two types of calculations based on the toxicity of the residue for either drug product or API manufacture.
对于制剂或原料药，通常有两种基于残留毒性的计算方法。

One approach is the Risk-MaPP Acceptable Daily Exposure (ADE) approach ***(12)***, which may be applicable to residues of drug actives, intermediates, and degradants. The limit is generally based on a No Observable Adverse Effect Level (NOAEL) or other relevant toxicological data. For highly hazardous drug actives, using the ADE approach is generally required in order to justify manufacturing those active ingredients in nondedicated equipment. For non-highly hazardous drug actives, the ADE approach is an alternative to the dose-based approach (see **Section 5.3.1).**
一种方法是 Risk-MaPP 可接受日暴露量法，适用于活性成分、中间体残留和降解物。限度一般基于无可见损害作用水平（ＮＯＡＥＬ）或其他相关毒性数据。对于高毒性活性成分，应用ＡＤＥ法来证明采用非专用设备生产这些活性成分的合理性。对于非高毒性活性成分，ＡＤＥ法可作为剂量法

外的另一种选择（见 5.3.1）。

A second approach may be the use of LD50 values for limits for residues like cleaning agents which do not have a dose.
另一种方法是采用 LD50 值（半数致死量）作为残留的限度，如没有剂量的清洁剂。

5.3.2.1 ADE Determinations Based on ISPE's Risk-MaPP 基于 ISPE 的 Risk-MaPP 确定 ADE

The safe daily amount in this approach is called the ADE. The first step is to identify the NOAEL for that chemical (usually in an animal study or from relevant human data) by evaluating the response that makes the chemical hazardous. An ADE is estimated by a qualified toxicologist based on the body weight and a variety of adjustment factors as given in Equation 5B. While the ADE definition specifies safety by *any* route of exposure, use of an ADE for a specific and relevant route of exposure is also allowed; this may allow for higher ADE value provided that the potential exposure is limited to that specific route of exposure.
本方法中的安全日剂量称作可接受日暴露量（ADE）。首先通过评估化学品毒性反应来建立该化学品的无可见损害作用水平（NOAEL）（通常通过动物试验或人体数据获得）。ADE 由有资质的毒理学家按照体重和公式 5B 中不同调整因子估算。尽管 ADE 针对任何给药途径的安全性，也可用于特定给药途径；如果仅有特定给药途径可能，可允许更高的 ADE 值。

[Equation 5B] 公式 5B

$$ADE = \frac{NOAEL \times BW}{UFC \times MF \times PK}$$

Where 其中:
NOAEL = No Observable Adverse Effect Level
无可见损害作用水平
BW = body weight of patient taking next product
服用下一产品患者体重
UFC = a composite uncertainty factor determined from such factors as interspecies differences, intraspecies differences, subchronic to chronic extrapolation, LOAEL to NOAEL extrapolation, and database completeness
综合不确定度，由种间差异、种内差异、亚慢性到慢性的推断、最低可见损害作用水平到无可见损害作用水平的推断和数据库完整性等因素确定
MF = a factor based on the judgment of the toxicologist
基于毒理学家判断的因子
PK = a pharmacokinetic factor to account for different routes of exposures
与给药途径相关的药代动力学因子

The ARL for drug product manufacture is then calculated by the following equation:
制剂的 ARL 可用下式进行计算：
[Equation 5C] 公式 5C

$$ARL = \frac{ADE}{LDD}$$

Where 其中:

ARL = the acceptable residue level in the next drug product
下一制剂中可接受残留水平

ADE = Acceptable Daily Exposure of the residue
残留的可接受日暴露量

LDD = the largest daily dose of the next drug product to be manufactured in the same equipment
同一设备中生产的下一制剂的最大日剂量

[Note: For API manufacture, the LDD value is the largest daily dose of the next drug active manufactured in the same equipment**.]**

[备注: 对于 API 生产，LDD 值为同一设备生产的下一活性成分的最大日剂量。**]**

5.3.2.2 Toxicity Calculations Based on LD Data 基于半数致死剂量计算毒性

This approach is used for residues where the relevant data are short-term toxicity studies, such as a LD50 study. Examples of such residues include cleaning agents and intermediates. In this case, the NOEL isestimated from the LD50 value using the following equation:

该方法针对具有短期毒性研究（如半数致死量）数据的残留。这类残留包括清洁剂和中间体。本方法中，可用下式通过半数致死量数值估算无可见作用水平（NOEL）:

[Equation 5D] 公式 5D

$$NOEL = \frac{LD_{50} \times BW}{MF1}$$

Where 其中:

NOEL = No Observable Effect Level
无可见作用水平

LD_{50}= the 50% lethal dose of the target residue in an animal, typically in mg/kg of body weight (by the appropriate route of administration)
目标残留物在动物中的半数致死剂量，通常以mg/kg体重表示（采用适当给药途径）。

BW = body weight of patient taking next product
服用下一产品患者的体重

MF1 = modifying factor or factors, selected by the toxicologist
修正因子，由毒理学家确定

The cumulative modifying factors selected are generally no more than 1000. Once the NOEL is estimated, the SDI is determined by **Equation 5E.**

累积修正因子一般不超过 1000。一旦估算出 NOEL，可用公式 5E 计算出 SDI。

[Equation 5E] 公式 5E

$$SDI = \frac{NOEL}{MF2}$$

Where 其中:

SDI = Safe Daily Intake of the residue
残留每日安全摄入量

NOEL = No Observable Effect Level

无可见作用水平

MF2 = modifying factor or factors, selected by the toxicologist

修正因子，由毒理学家确定

The cumulative modifying factors selected are generally no more than 1000. Once the SDI is established, the ARL is determined by **Equation 5F.**

累积修正因子一般不超过 1000。一旦确定 SDI，可用公式 5F 计算出 ARL。

[Equation 5F] 公式 5F

$$\mathrm{ARL} = \frac{SDI}{LDD}$$

Where 其中:

ARL = the acceptable residue level in the next drug product 下一制剂中可接受的残留水平

LDD = the largest daily dose of the next *drug product* to be manufactured in the same equipment

同一设备中生产的下一制剂的最大日剂量。

In **Equations 5D** and **5E,** the modifying factors can be based on one of several published references***(13-15)***. An alternative approach for this series of calculations is to combine **Equations 5D, 5E** and **5F**into one equation for determining the ARL directly.

公式 5D 和 5E 中，修正因子可基于已出版的参考文件（13-15）制订。也可将公式 5D、5E 和 5F 整合在一个公式中直接计算 ARL。

5.3.3 Other ARL Determinations 确定 ARL 的其他方法

For residues which are genotoxic, one alternative approach used when the NOEL values are not available is to determine the SDI using the Threshold of Toxicological Concern principle ***(16)*** which, based on anU.S. FDA determination about safe levels in foods, is established at 1.5µg/day. While this may be appropriate for oral doses, it may not be appropriate for injectables since the U.S. FDA determination was based on safe levels in foods (which are taken orally). The ARL is expressed in the following equation:

对基因毒残留物，在没有 NOEL 数据的情况下，可用毒理学原则(16)的阈值来确定 SDI，该原则是基于 FDA 确定的在食品中安全水平，一般为 1.5 µg/天。尽管这可能适用于口服制剂，对于注射剂却不适用，因为 FDA 的这一原则是基于食品中的安全水平，而食品都是口服的。ARL 以下式表示：

[Equation 5G] 公式 5G

$$\mathrm{ARL} = \frac{SDI}{LDD}$$

Where 其中:

ARL = the acceptable residue limit in the next drug product

下一制剂中可接受残留水平

SDI = the safe daily intake of the residue

残留每日安全摄入量

LDD = the largest daily dose of the next drug product to be manufactured in the same equipment

同一设备中生产的下一制剂的最大日剂量。

For residues for which the concern is a possible deleterious effect on stability, performance or efficiency of a subsequent product or process, the ARL must be determined directly based on an understanding of the

products, the process, and the expected effect. For example, for an in vitro diagnostic, the acceptable level of residue of a previous product may be determined based on the effect on stability or performance of that next in vitro diagnostic. That level may be determined by spiking studies of residue in the in vitro diagnostic to determine effects on stability and/or performance (e.g., false positives or false negatives).
对于可能影响后续产品或过程的稳定性、产品性能、效力的残留物，必须根据对产品、工艺和预期作用直接确定 ARL。例如对于体外诊断试剂，前一产品残留物的允许水平可根据对下一体外诊断试剂稳定性或性能的影响确定。该允许水平可通过在体外诊断试剂中加入目标残留试验，考察其对稳定性和/或性能（如假阳性或假阴性）的影响来确定。

5.4 Acceptable Total Carryover 可接受的残留总量

Once the ARL is determined, the maximum allowable carryover (MAC or MACO) can be calculated. MAC is the total amount of a target residue allowed in a batch of the next manufactured product. It is calculated by multiplying the ARL by the minimum batch size of the next product. MAC, which may be expressed in mass units for chemical residues (e.g., µg or mg or g), is expressed in the following calculation:
一旦确定了 ARL，可计算出最大允许残留量（MAC 或 MACO）。MAC 是下一批产品中允许的目标残留物总量，可将 ARL 乘以下一产品的最小批量算出。对于化学残留物，MAC 可以质量单位（如 µg 、mg 或 g）表示，如下式：

[Equation 5H] 公式 5H

$$MAC = ARL \times MBS$$

Where 其中:
MAC = the Maximum Allowable Carryover 最大允许残留量
ARL = the Acceptable Residue Limit in the next product 下一产品中可接受残留水平
MBS = the Minimum Batch Size of the next product 下一产品的最小批量

Note that the minimum batch size is typically expressed in mass units if ARL is expressed as µg/g or in volume units if ARL is expressed as µg/mL. For API manufacture, where both the cleaned product and the next manufactured product are APIs, **Equation 5H** is modified with MBS being the minimum batch size of the next drug active manufactured in the same equipment
注意：如果 ARL 以 µg/g 表示，则最小批量以质量为单位；如果 ARL 以 µg/mL 表示，则最小批量以体积为单位。对于原料药生产，已清洁产品和下一产品都是活性成分时，公式 5H 应予以调整，MBS 应为同一设备中生产的下一活性成分的最小批量。

Because the MAC is the total amount allowed in the next manufactured product, it is also the total amount allowed on shared equipment surfaces (that is, shared between the cleaned product and the next manufactured product).
MAC 是下一产品中总的残留允许量，它也是共用设备（已清洁产品和下一产品共用）表面允许的残留总量。

5.5 Surface Area Limit 单位面积限度

Once the MAC is determined, the surface area limit (SAL) can be calculated by dividing the MAC by the *total* equipment shared surface area between the two products. SAL, which may be expressed for chemical

residues in mass units per surface area (e.g., µg/cm^2), is expressed in the following calculation:
一旦确定了MAC，用MAC除以两个产品的设备共用表面积计算出单位共用面积限度。对于化学残留，SAL以单位表面积的质量表示（如µg/cm^2），通过下式计算：

[Equation 5I] 公式 5I

$$SAL = \frac{MAC}{SSA}$$

Where 其中:
SAL = the Surface Area Limit (on shared equipment surfaces) 单位表面积限度（在共用设备表面上）
MAC = Maximum Allowable Carryover 最大允许残留量
SSA = Shared Surface Area 共用表面积

5.6 Limit in Protocol Samples 样品的可接受限度

Once the SAL is determined, the limit in swab or rinse samples can be calculated. Three typical cases of limits in samples are covered below.
一旦确定了 SAL，擦拭或冲洗样中残留限度即可计算得出。以下介绍了样品残留限度的 3 种典型例子。

5.6.1 Limit per Swab 擦拭样残留限度

For swab sampling, one approach is to express the limit as a mass-per-swab sample (e.g., µg of residue per swab or µg/swab). The mass-limit-per-swab is determined by multiplying the SAL by the area sampled (typical swab sampling areas are 25 cm2 and 100 cm2) ***(17)***. This is expressed in the following calculation:
对于擦拭取样，可用残留限度（以质量表示）/每一擦拭样（如µg/每个棉签）表示限度，将SAL乘以取样面积（棉签取样面积通常为 25 cm^{2}和 100 cm^2）（17）即得。以下式表示：

[Equation 5J] 公式 5J

Limit per swab = SAL × swabbed area
Where 其中:
SAL = the Surface Area Limit (on shared equipment surfaces) 单位表面积限度（在共用设备表面上）

5.6.2 Concentration Limit in Extracted Swab Solvent 擦拭样提取液中残留浓度限度

For swab sampling, another approach is to express the limit as a concentration of the residue in a fixed amount of solvent (aqueous or organic) used for extracting the swab. The concentration limit is typically expressed in units such as µg/g, µg/mL or ppm. This concentration limit is determined by multiplying the SAL by the area sampled, and then dividing the result by the amount of solvent used for extracting the swab (in g or mL). This is expressed in the following calculation:
对于擦拭取样，另一种限度表示方法为固定量提取溶剂（水溶液或有机溶液）中残留浓度。该限度通常表示为 µg/g、 µg/mL 或 ppm。将 SAL 乘以取样表面积，再除以所用提取溶剂量（以 g 或 mL 表示）即得。可通过下式进行计算：

[Equation 5K] 公式 5K

$$Concentration\ Limit = \frac{SAL \times swabbed\ area}{SEA}$$

Where 其中:
SAL = Surface Area Limit (on shared equipment surfaces) 单位表面积限度（在共用设备表面上）
SEA = Solvent Extraction Amount 提取用溶剂量

5.6.3 Concentration Limit in Rinse Sampling Solution 冲洗样中浓度限度

For rinse sampling, most companies express the limit as a concentration of the residue in a fixed amount of the rinse sampling solution. This concentration limit is typically express in units such as µg/g, µg/mL or ppm. This concentration limit is determined by multiplying the SAL by the area sampled by rinse sampling and then dividing the result by the amount of rinse solution used for the sampling rinse (in g or mL). This is expressed in the following calculation:
对于冲洗样，限度多表示为固定冲洗液中残留的浓度。该限度一般表示为 µg/g、µg/mL 或 ppm。将 SAL 乘以冲洗法取样面积，再除以所用冲洗液量（以 g 或 mL）为单位。

[Equation 5L] 公式 5L

$$Concentration\ Limit = \frac{SAL \times Area\ Sample\ by\ Rinse\ Sampling}{\text{Rinse Sampling Volume}}$$

Where 其中:
SAL = the Surface Area Limit 单位表面积限度（在共用设备表面上）

If the entire equipment train is rinsed with one rinse solution, then the SSA and the “Area Sampled by Rinse Sampling” are identical. Therefore, a simplified expression for the concentration limit in the rinse sample (avoiding the need to determine the SSA) is:
如果整个设备组是用一种冲洗液冲洗的，则 SSA（共用表面积）和冲洗法取样面积是等同的。那么冲洗样中残留浓度限度简化（无需计算 SSA）为：

[Equation 5M] 公式 5M

$$Concentration\ Limit = \frac{MAC}{Rinse\ Sampling\ Volume}$$

5.7 Consolidated Expressions 计算公式整合

While the calculations in **Sections 5.3** to **5.6** are presented to explicitly show the steps in quantitative calculations for limits, it is common for companies, based on an understanding of their cleaning validation practices, to combine several equations together to simplify calculations. For example, companies that set limit for a drug active primarily on a fraction of the therapeutic dose may address all the factors in **Equation 5A**and **5H** with an overall equation for MAC as follows:
5.3 节至 5.6 节详细说明了限度定量计算方法，也可以基于对清洁验证操作的理解，将几个公式整合在一起，以简化计算。例如，根据治疗剂量确定活性成分限度时可以用一个全面的公式计算 MAC，并涵盖公式 5A 和 5H 中所有因子：

[Equation 5N] 公式 5N

$$MAC = \frac{MDD \times SF \times MBS}{LDD}$$

Where 其中:
MAC = Maximum Allowable Carryover 最大允许残留量
MDD = the minimum daily dose of the active of the cleaned product 已清洁产品最低日剂量
SF = the safety factor, which is typically 0.001 安全因子，通常为 0.001
MBS = the Minimum Batch Size of the next product 下一产品的最小批量
LDD = the largest daily dose of the next drug product to be manufactured in the same equipment 同一设备生产的下一产品的最大日剂量

Other companies that set limits for drug active primarily on a fraction of the therapeutic dose may address all the factors in **Equations 5A, 5H, 5I,** and **5K** with an overall equation for the concentration limit in an extracted swab sample as follows:根据治疗剂量确定活性成分限度时也可用一个公式计算出擦拭提取样中浓度限度，并涵盖公式 5A、5H、5I 和 5K 的所有因子：

[Equation 5O] 公式 5O

$$Concentration\ Limit = \frac{MDD \times SF \times MBS \times swabbed\ area}{LDD \times SSA \times SEA}$$

Where 其中:
MDD = the minimum daily dose of the active of the cleaned product 已清洁产品的最低日剂量
SF = the safety factor, which is typically 0.001 安全因子，通常为 0.001
MBS = the Minimum Batch Size of the next product 下一产品的最小批量
LDD = the largest daily dose of the next drug product to be manufactured in the same equipment 共用设备生产的下一产品最大日剂量
SSA = Shared Surface Area 共用表面积
SEA = Solvent Extraction Amount 提取溶剂量

5.8 Example Calculations 实例演示

As an example of an overall calculation of a MAC limit based on a fraction of a therapeutic dose, we use the case of the cleaned drug product having a daily therapeutic dose of 100 mg of the active. If the next drug product to be manufactured in the same equipment has a batch size of 10 kg, and a largest daily dose of 800 mg, then using a safety factor (SF) of 0.001, the calculation (using **Equation 5N)** would be:
因为 MAC 计算是基于治疗剂量，本例中已清洁产品的日剂量为 100mg。如果共用设备生产的下一产品的批量为 10kg，且最大日剂量为 800mg，安全因子为 0.001，计算如下（采用公式 5N）：

$$MAC = \frac{MDD \times SF \times MBS}{LDD}$$

$$= \frac{100\text{mg} \times 0.001 \times 10,000,000mg}{800\text{mg}} = 1250mg$$

This is the total limit for all residues of the specified active on all shared equipment between the two

products.
这是两个产品所有共用设备上特定活性成分残留的总限度。

Below is a second example of an overall calculation of a concentration limit in an extracted swab sample, again using the case of the cleaned drug product having a daily therapeutic dose of 100 mg of the active. The next drug product to be manufactured in the same equipment has a batch size of 10 kg and a largest daily dose of 800 mg, and a safety factor of 0.001. If the shared surface area is 250,000 cm2, the swabbed area 100 cm2, and the amount of solvent used for extraction of the swab is 5 mL, then the calculation (using **Equation 5O)** would be:
以下为擦拭提取液中残留浓度限度的计算，同样已清洁制剂的日剂量为 100mg。同一设备中生产的下一产品的批量为 10kg，最大日剂量为 800mg，安全因子为 0.001。如果共用面积为 250,000 cm2，擦拭提取用溶剂量为 5mL ，计算（采用公式 5O）如下：

$$Concentration\ Limit = \frac{MDD \times SF \times MBS \times swabbed\ area}{LDD \times SSA \times SEA}$$

$$= \frac{100mg \times 0.001 \times 10{,}000{,}000mg \times 100}{800mg \times 250{,}000 \times 5}$$

=0.1mg/mL(或 100μg/mL)

5.9 Other Considerations
其他需考虑因素

The items discussed below are issues that may be considered as part of any evaluation in establishing limit.
以下是设定限度时，可能需要考虑的问题

5.9.1 Multiple Next Products
后续生产产品的多样性

In many pharmaceutical manufacturing situations, there is not just one product that could possiblybe manufactured after a given product for which limits are being established. If flexibility is desired tomanufacture products in any order, calculations should be considered for all “subsequently manufactured products”, and the resulting lowest limit (typically the lowest limit per surface area) should beestablished for the cleaned product. As discussed previously, relevant factors to consider for the nextproduct are dosing, batch size and shared surface area. In this manner, any of the products consideredmay be safely manufactured after cleaning of the first product. In such evaluations, the combinationof the specific relevant factors for each next product should be considered. However, it is also acceptableas a worst-case to consider only the most stringent of each of the three relevant factors.
在制药行业中，很多时候在一个指定产品（其残留限度已确定）生产结束后，后续生产的可能不只是一个产品。如果希望可以灵活生产任何产品，计算已清洁产品残留最低限度（通常是每单位表面积的最低限度）时应考虑所有“后续生产产品”。如之前讨论，需要考虑的后续生产产品的相关因素包括剂量、批量以及共用表面积。这样，第一个产品清洁之后，可以安全地生产任何其他产品。评估时应该综合考虑每一种后续生产产品的相关因素组合。当然，采用最严格的三个相关因素组合作为最差条件也是可以接受的。

Another option is to restrict the order of manufacturing based, for example, on a specific subsequentlymanufactured product causing a limit to be very low. In such cases, procedures should be in placeto assure that the restricted order of manufacture is consistently followed.
另一种方式是限定生产顺序，例如，基于后续生产产品建立的残留限度非常低。这种情况下，要有相应的规程以确保严格执行限定的生产顺序。

A third option is to operate in cleaning verification mode where the acceptability of each specificcleaning event is determining based on a limit for the immediately following next product. In this way,the limit for cleaning a given product may vary depending on subsequently manufactured product.In this verification mode, residues are measured after each cleaning event and compared to the acceptancelimit calculated based on the product immediately following.
第三种方式是按照清洁效果确认的模式来执行，基于后续生产的第一个产品建立的残留限度，确定每一清洁活动是否符合要求。这样的话，指定产品的清洁限度可能会根据后续生产产品的不同而不同。在这种清洁效果确认模式中，每次清洁后都要测量残留，并同基于后续生产产品计算出的残留可接受限度进行比较。

5.9.2 Next Product in Verification Approach
清洁效果确认方法中的后续产品

In a cleaning verification protocol, only the actual *immediately following* product is required for establishinglimits. Particularly in development or clinical manufacturing, where a verification approach iscommonly used, the next product may not be known *at the time of the cleaning verification evaluation*.In such cases, one approach is to measure residues following cleaning, and then not to release theequipment until the next product is determined. At that time, a carryover evaluation is performed todetermine whether the residues measured are acceptable. If the measured residues are not acceptable,the equipment may be recleaned and cleaning verification performed again. A second approachis to establish, based on the types of products manufactured, some worst-case values for the relevantfactors for the next product. These worst-case values are used for establishing limits, and the equipmentis cleaned to meet those values. When the next product is determined, it is appropriate to verifythat the relevant parameters of the next product are within the worst-case values.
清洁效果确认方案中，只需要根据紧接着生产的产品确定残留限度。尤其是在研发批或临床批的生产中，经常使用清洁效果确认的方法，在清洁效果确认的评估时可能不知道后续产品会是什么。这种情况下，一种方式是清洁后检测残留，直到确定了后续生产产品后才允许设备的使用。进行残留评估，决定检测出来的残留是否可接受。如果检测出来的残留无法接受，应重新清洁设备并再次进行清洁效果确认。第二种方式是基于生产的产品类型，为后续产品建立一些最差条件。这些”最差条件”数值被用于设定限度，同时设备清洁后需要符合这些数值。当确定了后续生产产品时，合适的做法是确认该后续产品的相关参数没有超出最条件数值范围。

5.9.3 Default Limits
默认限度

As used in this document, default limits are one of two types. One type is a default limit which is utilizedif the default value is more stringent than what is established by the medically safe calculation (asgiven in **Sections 5.3** through **5.8).** A second type is a default limit where a medically safe limit cannotbe established, such as for intermediates in API manufacture. In the latter case, the default limit maybe established on criteria that are specific to the individual situation, based on process understandingand a risk

assessment.
本文件有两种类型默认限度，。第一种默认限度是默认值比通过医学安全计算（如 5.3 至 5.8 中所描述）建立的限度更严格。第二种默认限度是医学安全限度无法建立时，如 API 生产过程中的中间体。在后一种情况中，默认限度可根据对工艺的理解以及风险评估，建立针对特定情况的限度标准。

One example of the first type of default limit is a default limit used *for the ARL*. For drug products,the most common default limit for the ARL (the limit in the next product) is 10 ppm; however, othervalues may be used. If the ARL calculation **(Equation 5A, 5D** or **5F)** results in a value above 10 ppm,then 10 ppm is used as the ARL. If the ARL calculation results in a value below 10 ppm, then thatlower calculated value is used as the ARL. For API manufacture, more common default limits for theARL are 50 ppm or 100 ppm ***(18)***, although other values may be selected and used if they are morestringent than what is established by the medically safe calculation.
第一种情况可以 ARL 使用的默认限度为例。对于制剂来说，ARL（下一产品中残留可接受标准限度）最常用的默认限度为 10ppm。当然，也可以采用其他数值。如果 ARL 计算结果（公式 5A, 5D 或 5F）大于 10ppm, 则选用 10ppm 作为 ARL。如果 ARL 的计算结果小于 10ppm，则选择计算得来的较小的数值作为 ARL。在 API 生产中，ARL 更常用的默认限度是 50ppm 或 100ppm **(18)**，当然如果其他数值比医学安全计算得来的数值更严格，则也可能被选用。

A second example of this type of default limit is a default limit for the SAL. For either drug productor API manufacture, the most typical default value for the SAL used is 4μg/cm^2. This level is commonlycited as the upper limit for what is considered visually clean. If the SAL calculation **(Equation5I)** results in a value above 4μg/cm2, then 4μg/cm2 is used as the SAL. If the SAL calculation resultsin a value below 4μg/cm2, then that lower calculated value is used as the SAL.
这一情况的第二个例子是SAL的默认限度。无论是对于制剂还是API生产，最广泛使用的SAL默认限度是 4μg/cm^2。这一水平常被作为上限，也就是目检洁净。如果SAL计算结果（**Equation5I**）大于 4 μg/cm^2，则选用 4 μg/cm^{2}作为SAL。如果SAL计算结果（**Equation5I**）小于 4 μg/cm^2，则选择计算得来的较小数值作为SAL。

It should be understood that in these two examples, the logic is that any value below the *medically safe*value may be used as it represents a more stringent criterion.
需要理解的是，这两个示例的逻辑是可采用任何低于医学安全数值的值作为限度，因为它代表了一个更严格的标准。

5.9.4 Use of Different Safety Factors
不同安全系数的使用

The safety factor applied to a minimum daily dose is typically 0.001 (one one-thousandth), regardlessof the route of administration. Based on a risk assessment, a more stringent or less stringent safetyfactor may be applied as appropriate for a specific situation. For example, for clinical trial materialswhere the dose is not fully established, a more stringent safety factor may be considered. Since thesafety factor of 0.001 was originally established for drug product administered chronically, it may beacceptable (again based on a risk assessment) to use a less stringent factor for drug products administeredfor a short time (such as cold tablets, which may be administered for only 10 days).
无论什么类型的给药途径，每日最小有效剂量的安全系数通常是 0.001。基于风险评估，在特定的情况，可以适当使用一个更严格或不那么严格的安全系数。例如，对于用于临床试验的药品，其剂

量尚未完全确定，则可以考虑使用一个更严格的安全系数。因为安全系数 0.001 本是为长期给药的制剂而设定的，那么基于风险评估，对于短期给药的制剂（如治疗感冒的片剂，服药时间可能只有 10 天），则可以使用一个不那么严格的安全系数。

5.9.5 Different Routes of Administration
不同的给药途径

If the cleaned product and the next product are administered by different routes(such as the firstproductbeing an oral dose and the second product being an injectable), a risk assessment should beconsidered. This risk assessment might include an evaluation of hazards of the oral drug if administeredas an injectable, or it might include a review of data for the extent of systemic availability of theoral drug if given orally.

如果已清洁产品和接下来要生产的产品使用不同的给药途径（比如第一的产品是口服给药，第二个产品用于注射），则需进行风险评估。风险评估可能包括对口服给药的产品如果被用于注射的危害评估，或者可能包括口服制剂口服给药后的生物利用度的数据回顾。

5.9.6 Different Doses for Adults and Children
成人和儿童剂量差异

For two products where both products have different doses for adults and for children, it is appropriateto determine the ARL based on both products with the adult dose, and then for both productsusing the child's dose. The lower ARL of the two values should be used for subsequent limit calculations.In cases where one product may be dosed only for adults and the next product only dosed forchildren, then a risk assessment should be considered.

如果两个产品对于成人和儿童都分别有不同的剂量，比较合适的做法是先基于两个产品的成人剂量计算 ARL，再基于两个产品的儿童剂量计算 ARL。较小的 ARL 将被采纳用于后续限度计算。如果一个产品只有成人剂量，后续产品只有儿童剂量，则需要进行风险评估。

5.9.7 Human and Veterinary Products Manufactured on the Same Equipment
同一设备用于生产人用产品和兽用产品

For this situation, a risk assessment should be considered to set limits appropriately. In addition to thespecies difference, the body weight difference may also be a significant factor.

在这种情况下，应进行风险评估以设定适当的限度。除了物种不同，个体重量差异也可能是个重要因素。

5.9.8 Residues of Genotoxic and Other Highly Hazardous Active Ingredients
基因毒性残留以及其他高危活性成分

One approach to genotoxic residues is covered in **Section 5.3.3,** which is to utilize the Threshold ofToxicological Concern (TTC) value of 1.5µg/day as the safe daily intake ***(16)***, and utilize conventionalcalculations to set an acceptable limit in an analytical sample. Another approach for genotoxic residues(provided the genotoxic residue is the active ingredient and not a degradant), as well as other residuesof special medical concern, is to dedicate equipment to that one product and thus avoid the issue ofthe genotoxic residue being carried over to a different product. A third approach is to perform cleaningvalidation, with limits based on a toxicological evaluation related to the genotoxic effect (or otherspecial toxicity concern) using the principles in **Section 5.3.2.2.** A fourth approach is to set the limit forthe genotoxic residue as below the limit of detection of the best available analytical technique. In

thelatter case, a medical risk assessment should be performed to determine whether residues *at that detectionlimit* are acceptable. In this latter case, it may also be possible to include in the cleaning process astep which deactivates or degrades the genotoxic material such that genotoxic properties are no longerpresent. Such a determination of deactivation or degradation is preferably performed as a laboratorystudy. These approaches may also be applicable to other active ingredients with special concerns, suchas reproductive toxicity hazards, allergenicity, cytotoxicity, and mutagenicity.

5.3.3 节涵盖了基因毒性残留限度的一个设定方法，也就是利用毒理学阈值（TTC）1.5 μg/day 作为每日安全摄入量（16），并利用传统的计算方法设定分析样品中残留的允许限度。对于基因毒性残留（假如该基因毒残留是活性成分而不是降解产物）以及其他需特殊医学关注的残留，另一个方法，是采用专用设备生产该产品以防止基因毒性残留转移到另一个产品中。第三种方法是进行清洁验证，使用 **5.3.2.2 节**的理论，根据基因毒性（或其他需要关注的特殊毒性）作用进行毒理学评估并设定限度。第四种方法是将基因毒性残留的限度设置为低于目前最好的分析技术的检测限。在最后一个方法中，需要进行医学风险评估以决定是否是可以接受位于检测限的残留水平，同时可能需要在清洁程序中增加一步，使基因毒性的物料因失活或降解而不再表现出基因毒性。基因毒物料的失活或降解方法最好作为实验室研究进行。以上方法可能也适用于其他需特殊医学关注的活性成分，如生殖毒性、致敏性、细胞毒性和致突变性。

5.9.9 Limits Based on Analytical Detection Limits
基于分析方法检测限的限度

Limits may be established based on the analytical detection limits providing residues at those analyticaldetection limits are determined to be safe. It should be recognized that this method is not normallyrecommended because with ever improving analytical methods, the limits will be driven exceedinglylow so as not be practically achievable. The issue is not whether the residue can be measured, butrather whether the residue is medically safe and does not affect subsequent product quality.

如果确定残留水平位于检测限是安全，则可以基于分析方法检测限确定残留允许限度。需注意的是，通常并不推荐采用该方法，因为检测方法的不断改进，检测限度趋于非常低，以至于实际操作中无法达到该水平。问题不在于残留是否是可以被测量的，而是从医学的角度来说残留是否是安全的，且不会对后续产品的质量产生影响。

5.9.10 Degradation of the Active Ingredient
活性成分的降解

If the active ingredient degrades during the cleaning process(or after the cleaning process during the timebefore sampling), it may not be appropriate to measure residues of that active ingredient using a specificanalytical procedure in a cleaning validation protocol. The reason is that the relevant residue to measureis the degradant. There are at least two approaches to dealing with this situation. One approach is to setlimits for the degradant, and then measure the degradant in the protocol using an appropriate analyticalmethod. This assumes that there is a specific degradant for which limits can be established (e.g., based ona toxicity calculation). Another approach is to set limits for the undegraded active based on its dose. Residuesare then measured with a nonspecific analytical method (such as TOC). The residue as measuredby that nonspecific method is converted to an equivalent amount of undegraded active ingredient andcompared to the calculated limit. This approach may be acceptable if the safety concerns from residuesof the degradant(s) are no more serious than the safety concerns of the active ingredient. There may beother acceptable approaches based on the specific of the situation and a risk assessment.

如果活性成分在清洁过程中降解，或清洁后取样前这一时间降解，则清洁验证方案中使用指定分析

方法测量该活性成分的残留是不合适的，因为应该测量的是降解产物的残留。至少有两个方案可解决这个问题。一个是为降解产物设定限度，然后在方案中用合适的分析方法测量降解产物。前提是可以设定一个特定降解产物的残留限度（如，基于毒性计算）。另一个方案是基于活性成分的剂量，为未降解的活性成分设置限度，再采用非专属的检测方法测量残留量，如 TOC。使用非专属检测方法测量出的残留被转换成相应的未降解的活性成分的含量，并同计算得来的限度进行对比。如果降解产物残留的安全危害没有活性成分的安全危害严重，则可以采用这个方法。根据特定的情况和风险评估，也可采用其他方法。

5.9.11 Limits Not Measureable
无法测量的限度

If calculations for the limit of the active ingredient in the analytical sample result in values that are notmeasurable by available analytical methods, there are several options. One option is to dedicate the equipmentto that one product, thereby reducing the need to measure the active ingredient except by a visuallyclean criterion. A second option is to modify the parameters of the next manufactured product such thatthe limit is higher. For example, raising the minimum batch size of the next product will increase the limit.It may also be possible to restrict the order of manufacture such that certain products, which drive thelimit lower, are not manufactured after the cleaned product with the low limit. In such cases, appropriatemeasures should be put in place to insure that only those approved products are manufactured as the nextproduct. A third option is to modify the sampling parameters. For example, for swab sampling, samplinga larger area (100 cm2 rather than 25 cm2) or extracting the swab with a smaller amount of solvent willresult in an increased limit in the analytical sample. A fourth option is lower the rinse volume for rinsesampling. A fifth option is to concentrate the rinse sample by a technique such as vacuum evaporation.

如果计算得来的被检测样品中活性成分限度无法采用现有的检测方法进行测量，可有多种选择。一种是该设备专用于一个产品，因此减少了测量该有效成分的需要，仅需符合目检清洁标准。第二个选择是调整后续生产产品的相关参数以提高残留限度。例如，增大后续产品的最小批量会提高限度。也可能限制生产顺序，如果已清洁的产品残留限度较低，则下一生产产品不能为限度更低的部分产品。这样的话，需要用适当措施来保证只有被批准的产品才能作为下一生产产品。第三个选择是更改取样参数。例如，擦拭取样中，通过增大取样面积（从 25cm^{2}增加到 100cm^2）或者减少拭子萃取的溶剂量来提高被检测样品的残留限度。第四个选择是冲洗取样过程中减少冲洗量。第五是通过技术，如真空蒸发，对冲洗样品进行浓缩。

5.9.12 Limits for Organic Solvents
有机溶剂限度

For organic solvents that are typically used for cleaning in small molecule API synthesis, limits maybe established based on toxicity calculations. Another approach is to use the values in ICH Q3C (R5),which establishes acceptable levels for solvents in API’s and in drug products ***(19)***. It should be recognizedthat Q3C technically applies to solvents used in the *manufacture* of API’s. While cleaningprocesses are sometimes considered manufacturing steps, they are often considered part of the supporting“equipment and facilities”. Therefore this approach should be carefully evaluated before use.Another approach is not to set limits for volatile organic solvents. One situation where this may applyis if there is an adequate determination (based on process understanding and appropriate studies) thatthere are adequate conditions for the volatile solvent to evaporate. Note that this latter considerationalso applies to use of isopropanol or ethanol used as final rinse or wipe for drug product manufacture.

对小分子原料药合成的清洁时使用的有机溶剂，可根据毒性计算来设定残留限度。另一种方式是使用 ICH Q3C (R5)中的数值，建立原料药和制剂中的溶剂的可接受标准。需要注意的是，从技术角度来说，Q3C 适用于生产 API 过程中使用的溶剂。虽然有时候清洁过程也会被认为是生产步骤，更多的是将其作为对设备、设施的支持程序。因此这个方法在使用前需要仔细评估。另一种方法是不对挥发性有机溶剂设定限度，当有充分理由（基于对工艺的理解以及适当的研究）确定可有充分的条件允许该挥发性有机溶剂挥发时，可以采用该方法。注意这一要求同样适用于制剂生产中使用异丙醇或乙醇进行最终的冲洗或擦拭。

Another situation where limits may not be required is where the same solvent is used for the finalrinse as for manufacture of the next product.
另一种不需要设定限度的情况是下一产品生产中使用相同的溶剂进行最终冲洗。

5.9.13 Dedicated Equipment
专用设备

For equipment trains dedicated to manufacture of only one product, the concern about carryoverof the active ingredient from one batch to the next is minimized. As stated in the U.S. FDA guidancedocument, visually clean may be appropriate to address such a concern ***(20)***. However, cleaning validationmay still be required because of concerns about other residues, such as degradants, cleaningagent and bioburden, carrying over to the next batch of the same product.
对于只用于生产一个产品的专用设备组，则较少担心将活性成分转移至下一批产品中。如美国 FDA 指南文件所述，目视洁净即可。但是，考虑到其他残留可能仍需进行清洁验证，如降解产物，清洁剂和生物负载，这些残留可能转移到相同产品的下一批次中。

If only parts of an equipment train are dedicated to one product, then that dedicated part is not consideredas part of the shared surface area for calculating limits for an active ingredient. However, the surfacearea of that part may be relevant for calculating other limits, such as the limit for the cleaning agent.
如果设备组中只有一部分是专用于一个产品，那么在计算活性成分残留限度时，这一部分不视为共用表面积。但是，在计算其他限度时，这一部分表面积可能是相关的，比如清洁剂的限度。

Another approach is to set limits for the active ingredient and measure residues of the active ingredientin a cleaning validation protocol for dedicated equipment for other reasons, such as concerns aboutbatch integrity or certain equipment surfaces may not be easily evaluated by visual examination.
考虑到批的完整性，或有些特定的设备表面可能不容易通过目检来评估，另一种方法是设定活性成分的残留限度，并在专用设定的清洁验证方案中对活性成分残留进行测量。

5.9.14 Dividing a Limit among Various Pieces of Equipment
区分不同设备的限度

In order to evaluate a processing operation composed of several unit operations, it is important toconsider the accumulated residue from each piece of process equipment. The MAC is the sum of alltarget residues that could be present on the various pieces of relevant shared equipment surfaces. Acommon practice is to require the same SAL for each and every surface in an equipment train. Analternative is to apportion the total amount (the MAC) differently among the different equipmentitems, such that the total amount present still reflects the MAC amount. For example, for an equipmenttrain comprising three separate vessels each of the same surface area, the SAL limit might be1.0 μg/cm^2 if the MAC is distributed evenly over all

surface areas. In contrast, the MAC might beapportioned such that the SAL was 0.5 µg/cm2 for Equipment A, 1.0 µg/cm2 for Equipment B, and1.5 µg/cm2 for Equipment C, provided the total carryover limit was still at the calculated MAC value.

为了评估一个由多个操作单元组成的操作步骤，重要的是计算每一操作设备中的累积残留。MAC是可能存在于不同设备的共用面积上所有目标残留的总和。通常一个设备组中每一共用表面都采用相同的SAL。另一种选择是将MAC的总量不平均地分配给不同的设备，其总量依然可以有效反应出MAC。例如，如果一个设备组包含三个独立容器，三个容器具有相同的表面积，如果将MAC按照总表面积平均分配，则SAL限度可能为 1.0 µg/cm^2，相反，可以不平均地分配MAC，使设备A的SAL为 0.5 µg/cm^2，设备B是 1.0 µg/cm^2，设备C是 1.5 µg/cm^2，残留限度总和仍然等同计算出的MAC值。

5.9.15 Limits for Preferential Transfer to a First Portion of the Next Product
向下一个产品前一部分优先转移的残留限度

An equipment train should be delineated to separate those portions in which the residue would beevenly (homogeneously) distributed in the next product (e.g., blender, granulator) from those inwhich the residue could be transferred to an individual dosage unit of the next product (e.g., tabletpress, vial filler). To address the situation of preferential (non-homogeneous) transfer, the carryovercalculations can be adjusted based on the surface area subject to preferential transfer and the portionof the next batch subject to being potentially contaminated with the transferred residue. This willresult in using a different, more stringent limit to the equipment surfaces which can preferentiallytransfer to the next product, thus restricting potential carryover to an initially manufactured singleproduct dose of the next product. In addition, this preferential transfer can be addressed based onproduction techniques if an adequate first portion of the next manufactured product (e.g., filled vials,tablets) is discarded. Another option is to utilize equipment parts dedicated to one product where thispreferential transfer may occur.

设备组中有些设备上的残留会平均的（均匀的）分布在下一产品（如，混合机，制粒机）中，有些设备的残留会转移至下一产品单个剂量单元（如压片、装瓶）中，应将这两类设备区分开来。对优先转移（不均匀）的情况，可以根据优先转移的设备表面积以及下一批次中可能受到残留污染的产品的多少对残留计算结果进行调整。这将导致对存在优先转移设备表面采用不同的、更严格的残留限度，以控制下一产品中最初生产单个剂量单元中残留量。另外，如果下一产品最初生产的部分（如已灌装的瓶子、片子）有足够数量作报废处理，则可通过生产技术控制解决该优先转移的问题。另一方法是当存在优先转移的可能时，就采取产品专用的设备部件。

5.9.16 Limits for Biotechnology Manufacture
残留限度-生物技术制造

More information on limits for biotechnology manufacture is given in PDA Technical Report No. 49,“Points to Consider for Biotechnology Cleaning Validation” ***(2)***.

关于生物技术制造中的残留限度的更多信息，见 PDA T49 号技术报告“生物技术清洁验证要点”(2)。

5.9.17 Products with More Than One Active Ingredient
有不止一种活性成分的产品

In drug product manufacture, there may be more than one active ingredient in the drug product. Insuch cases, there are at least two options. One option is to set limits for all active ingredients and measureeach active ingredient in a cleaning validation protocol. Another option is to determine a “worstcase” among the different active ingredients, and to only set limits for that worst-case active ingredientbased on the lowest limit of any active ingredient in the group. Considerations for determiningthe worst-case active ingredient

include difficulty of cleaning, solubility in the cleaning solution, andconcentration of the active.
制剂中可能存在不止一种活性成分。这种情况下，至少有两种选择。其一是对所有的活性成分都设定限度并在清洁验证方案中测量每个活性成分残留。另一种在不同的活性成分中确定“最差条件”，并基于这一组活性成分中最低的残留限度，只对“最差条件”的活性成分设定限度。判断“最差条件”活性成分，需要考虑清洁难易程度，在清洁溶剂中的溶解能力以及活性成分的浓度。

5.10 Bioburden Limits

生物负载限度

In considering bioburden limits following cleaning, it is not expected that the cleaning process itselfresults in sterile equipment. If limits are established for bioburden in a cleaning validation protocol,those limits can be established using carryover calculations using the principles in **Sections 5.3**through **5.6.** For non-sterile manufacture, the starting point is an ARL in CFU/g or CFU/mL of thenext manufactured product. The starting point for that ARL value is the bioburden specification ofthat next product. However, since there are sources of bioburden other than the cleaned equipment(e.g., from the raw materials of the next product), an adjustment factor is usually applied to theproduct specification to lower the bioburden ARL. These carryover calculations typically result inSAL values significantly above 10 CFU/cm2 or a rinse sampling solution limit significantly above 100CFU/mL. A risk assessment should be done to determine the acceptability of such values, includingthe nature of the next product (low water activity, which will not allow proliferation in the productvs. high water activity which, without preservatives, will allow proliferation in the next product). Theacceptable bioburden level should also take into consideration effects on bioburden proliferation duringthe clean hold time. For this reason, many companies will establish very conservative bioburdenlimits, such as 1-2 CFU/cm2 for surface sampling methods and the typical purified water limit of 100CFU/mL for rinse samples.
考虑清洁之后的生物负载限度时，不能期望仅依靠清洁过程本身就使设备达到无菌状态。如果在清洁验证方案中需设定生物负载限度，则可根据 **5.3** 到 **5.6** 节中的理论，采用残留物计算方法确定生物负载限度。对于非无菌生产，首先是确定下一产品的ARL，以CFU/g或CFU/ml为单位。该ARL值是下一产品的生物负载标准。当然，由于除了已清洁设备，生物负载还有其他来源（如，来自下一产品的原料），常采用调整因子对产品标准进行调整，以降低生物负载ARL。这些残留物计算通常导致SAL的值远高于 10CFU/cm^2，或冲洗样品溶液限度远高于 100CFU/ml。需要进行风险评估以确认这些数值是否可接受，包括下一产品的特性（低水分活度：这不利于产品中的微生物的繁殖；高水分活度：没有防腐剂的情况下，微生物将在下一产品中的繁殖）。允许的生物负载水平还应考虑在清洁有效期内对生物负载的增殖有影响的因素，因此许多公司都采用非常保守的生物负载限度，如对于表面取样法采用 1-2CFU/m^2，对冲洗样品，则通常采用 100CFU/mL纯化水限度。

However, even if the process equipment is steamed in place or autoclaved prior to manufacture ofthe next product, or even if the next product is sterile-filtered, it is typically the practice to evaluatebioburden to establish that the subsequent process is not overly challenged. Achievement of typicalbioburden limits for non-sterile manufacturing (1-2 CFU/cm^2) is considered more than adequate forsurface sampling. For rinse sampling that is performed with WFI, one approach is to utilize typicalWFI values (10 CFU/100 mL), while another approach is to utilize a value of either 100 CFU/100 mLor 1,000 CFU/100 mL. The rationale for the higher limit is that the equipment will be subsequentlysteamed. Furthermore the WFI value is the value for the WFI in the recirculating loop; once it isremoved from that loop and passed through clean equipment, there is not *necessarily* an expectationthat it will still meet the WFI value.
然而，即使 在生产下一产品前对工艺设备进行在线或高压灭菌，或者即使下一产品是除菌过滤过的，

通常会评估生物负载来确定后续工艺没有被过度挑战。非无菌生产的典型的生物负载限度（1-2CFU/cm^2）被认为足以用于表面取样。对于采用WFI冲洗取样时，一种方法是使用典型的WFI的值（10CFU/100ml），另一方法是使用 100 CFU/100 mL或 1,000 CFU/100 mL其中的一个。使用更高限度的基本原理是该设备将会被蒸汽灭菌。而且，该WFI的值是WFI在循环回路中的允许限值，一旦WFI从回路中移出，并转移到清洁设备中，没有必要期待它仍然符合WFI的限值。

An additional consideration for bioburden evaluation is the determination of objectionable organisms.Objectionable organisms are not necessarily limited to the USP specified organisms, but includeorganisms selected based on an understanding of the product and manufacturing situation. Whatmakes an organism objectionable is not just the species, but also the number. The degree of identificationmay be identification down to the species level, or it may just include methods to excludeobjectionable organisms. Furthermore, one approach is to identify all colonies that are found, whileanother approach is to only identify colonies if the number is above a certain threshold (e.g., 50% ofthe acceptance limit).
对于生物负载，另一个需要考虑的是有害微生物的鉴定。有害微生物没有必要局限于 USP 中列出的微生物，而是应该结合产品和生产情况确定有害微生物。而判断微生物是否是有害的也不应以种属作为唯一标准，也要考虑数量。可以是鉴定到“种”（备注：界(Kingdom)、门(phylum)、纲 (Class)、目 (Order)、科(Family)、属(Genus)、种 (Species)）的级别，也可能只是排除有害微生物的方法。另外，一种方法是鉴别出所有发现的菌落，另一种是只对数量超出一阈值的菌落（如可接受限度的50%）进行鉴别。

5.11 Endotoxin Limits
内毒素限度

Endotoxin carryover to the final product is a concern for any product with endotoxin specifications.In this situation, it is common practice to measure endotoxin in the final rinse water, with limits typicallyset at the WFI limit of 0.25 EU/mL. If the equipment is depyrogenated by heat, endotoxin willbe deactivated and measurement of endotoxin for cleaned equipment may not be required.
对于任何有内毒素限度要求的产品，都需要关注转移至成品的内毒素残留。通常测量最终冲洗水中的内毒素，限度通常和 WFI 标准（0.25 EU/mL）相同。如果通过加热除去设备上的热原，内毒素将失去活性，则不需要测量已清洁设备的内毒素残留。

5.12 Visually Clean Criterion
目视清洁标准

Visual appearance of production surfaces is a direct measurement that verifies removal of residuals.The most common use of a visually clean criterion is to supplement swab and/or rinse testing forresidues for cleaning validation protocols. In such cases, it is common practice *not* to establish a quantitativevisual limit.
对生产表面的目检是确认残留去除的直观方法。通常，目检在清洁验证方案中作为擦拭法或冲洗水法检测残留的一种补充。此时，通常不需量化目检限度。

If visual examination is used *without* swab and rinse sampling, it is *required* to establish a *quantitativevisual limit* for a residue on a specified surface under specified viewing conditions. If visual examinationsupplements swab and/or rinse sampling, such a visual limit determination *may* be done to furtherrefine and/or limit what visually clean means. A discussion of that methodology for establishinga

visual limit is given in **Section 7.7.3.** Provided the quantitative visual limit is *more stringent* than aSAL carryover limit (see **Section 5.5)**and provided that the equipment surfaces can be viewed in thecleaning validation protocol under conditions that are the same or more stringent than the viewingconditions established for the quantitative limit, then this visually clean criterion may be used withoutswab or rinse sampling. If this approach is used, a second-person verification in protocol executionshould be utilized. Typical visual limits reported in the literature are 1-4 μg/cm^2. However, it shouldbe recognized that this limit depends on factors or conditions such as the nature of the residue, thenature of the surface, the lighting, the distance of viewing, the angle of viewing, and the visual acuityof the operator.

如果没有擦拭取样或冲洗水取样，仅使用目视检查，则需要量化指定表面上残留的目检限度，并说明具体观察条件。如果目检作为擦拭或冲洗水取样的补充，则确定目检限度可以明确和/或限制目视清洁的具体含义。关于设定目检限度方法的讨论详见 **7.7.3** 节。假如量化的目捡限度比SAL限度（见 5.5 节）更严格，同时假如清洁验证方案中设备表面的目检条件同建立量化限度时的目检条件相同或更苛刻，则可采用该目视清洁标准而无需进行擦拭或冲洗取样。如果采用该方法，在方案执行时需要另一个人进行目检的确认。通常文献中的目捡限度是 1-4 μg/cm^2。当然，该限度受许多因素或条件影响，如残留特性，表面特性，灯光，观测的距离，观测角度以及观测人员的视力情况。

The requirement for “visual cleanness” usually applies to equipment surfaces. It is not necessarily arequirement that swabs be visually clean after a surface is swabbed, due to the fact that residue whichis not visible on a larger surface may become “visible” when concentrated on the smaller area of theswab head.

“目视洁净”的要求通常应用于设备表面。没有必要要求设备表面擦拭后拭子本身也是“目视清洁”的，因为在更大的表面上看不到的残留，可能由于聚集在拭子头部而变得“可见”了。

6.0 Sampling

取样

In order to evaluate cleaning effectiveness, it is necessary to sample the surfaces of the equipment to establish the level of residuals present. It is essential for a cleaning validation program that the appropriatesampling methods are utilized. This section discusses issues that might be addressed in determining the appropriateness of types of sampling methods, sampling recovery validation studies,and training and qualification of samplers。

为了评估清洁效果，有必要对设备的产品接触表面进行取样并确定存在的残留量。适当的取样方法是一个清洁验证计划的基本要素。本章将探讨如何选择适当的取样方法，取样回收率验证，培训以及取样人资格确认问题。

6.1 Sampling Method Selection

取样方法的选择

Selection of a sampling method depends on the nature of the equipment, the nature of the residue being measured, the residue limit, and the desired analytical method.Sampling methods discussed here are:

取样方法的选择取决于设备、待检测残留物的性质，残留物限度以及所需的分析方法。这里讨论的取样方法包括：

- Direct surface sampling
  直接表面取样
- Rinse sampling
  冲洗取样
- Swabbing
  擦拭法
- Placebo sampling.
  安慰剂取样法

It should be noted that while regulatory documents refer to swabbing as “direct” sampling and to rinse sampling as “indirect” sampling, it is operationally more descriptive to refer to those sampling methods as “swab sampling” and “rinse sampling,” and reserve the term “direct sampling” for techniques such as visual inspection.

需要注意的是，虽然相关规范性文件将擦拭法称为“直接”取样方法，冲洗法称为“间接”取样方法，但更具有可操作性的描述是将这些取样方法称为“擦拭取样”以及“冲洗取样”，而对于目检等技术则保留了“直接取样”的术语。

Swab/wipe sampling, rinse sampling, and visual examination are listed as acceptable sampling techniques in most regulatory documents ***(20, 21, 22)***. Each method has its advantages and limitations. In a given protocol, multiple sampling methods may be used, such as “both rinse sampling and visual examination” or “rinse sampling, swab sampling, and visual examination,” as required to adequately determine that the equipment is acceptably clean.

在大多数法规文件（20,21,22）中，擦拭法，冲洗法以及目检都是可以接受的取样方法。这些方法有其它们自身的优点与局限。在一个给定的验证方案中，为了充分确认设备清洁是可接受的，可以采用多种取样方法，例如“冲洗取样与目检结合”或者“冲洗取样，擦拭取样以及目检相结合”。

6.1.1 Direct Sampling Methods
直接取样法

Direct sampling methods (*as used in this document*) include both instrumental methods and visual inspection. It should be recognized that direct surface sampling incorporates elements of both sampling and analytical methods.
直接取样法包括仪器法以及目检法。应注意直接表面取样法包括了取样以及分析方法。

6.1.1.1 Visual Inspection
目检

It is a well-accepted practice that a cleaning process should remove visible residues from the production equipment surfaces. The visual inspection of equipment has limitations in that some equipment surfaces (e.g., piping) are usually not accessible for viewing. The use of optical equipment like mirrors or endoscopes, as well as the use of additional lighting, can help to facilitate visual inspection. Ordinarily surfaces that are visually examined should be dry, as this represents a worst-case condition for visual inspection.
一个清洁过程应从生产设备表面去除可见残留物。目检存在局限性，如一些设备的表面（如管路）无法直接观察。一些光学设备如镜子或者内窥镜，连同辅助照明一起有助于进行目检。一般来说，需要目检的表面应干燥，因为这代表着目检的最差条件。

Remote inspection techniques (e.g., with fiber-optic probes and a viewing screen) are utilized when visual inspection by a trained inspector is difficult to perform. Things that might make visual inspection difficult include issues related to tank entry, the hazards of a potential residue, or inaccessibility of critical equipment surfaces. Additionally, one might use remote inspection techniques to supplement an “unaided” visual inspection procedure.
当一个训练有素的检查员也难以进行目检时，可以采用远程检测技术（例如使用光纤探针和可视屏幕）。罐的入口、潜在残留物的危害，或者难以接近关键设备表面等问题，都会使目检变得困难。此外，可采用远程检测技术作为“裸眼”目检程序的补充。

Borescopes, Fiberscopes, and Videoscopes allow visual inspection of hard-to-reach areas. Borescopes have been used to view the interior of piping and tank welds. A benefit of these scopes is that they typically can fit into confined spaces not accessible to operators. They are typically very maneuverable, have additional lighting attached, and may come with optional magnification and/or zooming capabilities. The major drawbacks of these scopes are the difficulty of use, controlling lighting/brightness, and that the operator still has to make the determination if the area viewed is visually clean.
管道镜，纤维内窥镜以及光纤视镜可以检查到视线难以抵达的区域。管道镜可以用来检测管路内部以及罐体焊缝。这些视镜的一个优点是它们可以适用于操作人员无法进入的限制性空间。它们通常易于操作，带有额外的照明，以及可能带有的放大和/或缩小功能。这些视镜的主要缺点是很难使用、控制灯光/亮度，以及仍然需要操作人员要判断观察区域是否目视洁净。

A Remote Visual Camera allows operators to view remote areas on a screen. The camera has most of the same strengths and weaknesses as the scopes, but the added benefit that operators can typically also record video or take pictures. Multiple operators can, at the same time, view what is on the screen. The potential to record video and allow multiple operators to view the screen may help support a site’s visual inspection

training program. Pictures printed from the camera may distort theactual amount of residue present since operators will typically zoom in on a particular area when taking a picture.
操作人员可通过一个可视远程相机在屏幕上进行远程监测。相机的优、缺点同视镜相似，但额外的优点是操作人员可以录制视频或拍照。多个操作人员可以同时观察屏幕。能够录制视频以及允许多名操作人员观察屏幕有助于实施目检培训计划。由于操作人员在拍照时通常放大特定区域，因此相机打印出来的照片可能无法真实反映残留物的实际数量。

It should be noted that the basic regulatory expectation is that the equipment be visually clean by viewing with the *unaided* eye. Use of aids to magnify or otherwise improve visibility of residues should be seen as a more stringent use of visual examination.
需要注意的是，法规要求应通过肉眼观察确认设备是否清洁。可以认为使用辅助工具来放大或提高残留物的能见度比裸眼目检更加严格。

6.1.1.2 Instrumental Methods
仪器法

Instrumental methods typically involve a surface probe connected to an analytical instrument by afiber-optic cable. For example, this may involve an attenuated total reflection probe connected toan FTIR instrument by a fiber-optic cable. The advantage of this type of sampling is that it is notnecessary (as in swab and rinse sampling) to remove the residue from the surface for analysis. It alsotherefore does not require a separate sampling recovery study. The main disadvantages of this techniqueare limited length of the fiber-optic probe and the requirement that surfaces be relatively flat(therefore, many worst-case locations may not be sampled by this technique).
仪器法通常采用一个通过光纤电缆连接至分析仪器的表面探针。例如，可能是一个通过光纤电缆连接至傅立叶变换红外光谱仪的衰减全反射探针。这种取样法的优势是不需要像擦拭法和冲洗法那样从表面取残留物进行分析（如擦拭以及冲洗取样）。因此也不需要单独的取样回收率研究。这种方法的主要缺点是光纤探头的长度有限以及被取样表面需相对平坦（因此，很多最差条件的位置不能采用这种方法取样）。

6.1.2 Rinse Sampling
冲洗法取样

Rinse sampling involves sampling the equipment by flowing solvent (which may be water, an aqueoussolution, an organic solvent, or a water/organic solvent mixture) over all relevant equipment surfacesto remove residues, which are then measured in the rinse solvent. Collection of rinse samples shouldconsider solubility, location, timing and volume. One type of rinse sampling technique is to take a“grab” sample from the final portion of the rinse solvent during the final rinse of the cleaning process.A “grab” sample is a single sample collected from a rinse solution that represents the composition ofthe rinse solution at that time. As used in this document, a grab sample generally refers to a singlesample withdrawn from the final portion of a CIP rinse.
冲洗法取样是指在相关设备表面采用流动的溶剂（水，含水溶液，有机溶剂或者水/有机溶剂混合物）去除残留物，然后再检测冲洗液中残留量。冲洗样本的采集应考虑溶解度，位置，冲洗时间以及冲洗体积。冲洗取样的一种方法是在最终冲洗过程中“抓取”冲洗溶液的最后一部分作为样品。一个“抓取”样本是从冲洗液中收集单一样本，能够代表此时冲洗液的组成。本指南中，一个“抓取”样本一般指从在线清洁的最终冲洗部分取出的单一样本。

A second type of rinse sampling is to utilize a separate sampling rinse after completion of the processrinse.This separate sampling rinse may involve filling the equipment to an appropriate level with solventand agitating that solvent to make the composition of the residue in the sampling rinse is homogeneous.Then a sample of that solvent is taken and analysed. This separate sampling rinse may alternatively bea separate CIP sampling rinse, which may involve a once-through sampling rinse or a recirculating samplingrinse. For a once-through separate sampling rinse, it is necessary to collect the entire volume of theseparate sampling rinse, agitate it until it is homogeneous, and analyze a sample from the homogenousrinse. For a recirculating separate rinse, homogeneity is generally achieved by recirculation.
第二种冲洗取样方法是在冲洗过程结束后，单独进行冲洗取样。这个单独的取样包括向设备中加入一定体积的溶剂，搅拌使冲洗液中残留物分布均匀。然后取出冲洗溶液样品进行分析。这个单独的冲洗取样可以是一个单独的 CIP 冲洗取样，这涉及了一个单程冲洗取样或循环冲洗取样。对于一个单程的独立冲洗取样，必须收集全部体积的冲洗溶液，搅拌至均匀，然后进行分析。对于循环的独立冲洗取样，冲洗样均匀性通常可以通过循环过程实现。

Advantages and disadvantages of both methods for rinse sampling are shown in Table 6.1.2-1.
两种冲洗取样方法的优缺点如表 6.1.2-1 所示

Table 6.1.2-1 Comparison of Grab Sampling versus Separate Sampling Rinse
表 6.1.2-1 “抓取”取样与独立冲洗取样的比较

	“Grab”SamplingfromFinalProcessRinse 最终冲洗过程“抓取”样本	SeparateSamplingRinse 独立冲洗取样
Advantages优点	• Representsthenormalcleaningprocess 代表通常的清洁过程 • Requiresnoadditionalamountsofrinsesolvent 不需要额外的冲洗溶剂 • Equipmentcanbeusedforfurtherprocessing withoutadditionalsteps 不需要额外操作，设备即可进一步使用	• Resultscaneasilybeusedforcarryovercalculations 结果容易用来计算残留量 • Representswhatisleftonsurfacesaftercompletionof cleaningprocess 体现清洁结束后残留在表面的污染物 • MorelikelytoresultinanacceptableresultifdoneCorrectly 如果操作正确，更更容易获得合格的结果 • Recirculatingrinselikelytoprovidehigherrecovery 循环冲洗回收率更高 • Allowsuseofasamplingsolutionotherthantheprocessrinse 可以采用其他样品溶液，而不是清洁工艺冲洗溶液

Disadvantages缺点	• Samplerepresentsaworstcasecarryovertothe nextbatchinthatitreflectsresidueinthefinal rinse,notresidueonsurfacesaftercompletionofthe finalrinse(butcandemonstraterobustnessof cleaningprocess) 样品代表了可能转移至下批产品的残留的最差条件，因为它反应了最终冲洗液中的残留量，而不是最终冲洗后的表面残留（但是可以证明清洁工艺的耐用性） • Needtomakeassumptionsaboutsamplingfor carryovercalculations 残留量计算需用到“假设”	• Utilizesanadditionalstep 需要额外的步骤 • Requireadditionalamountofrinsesolvent 需要额外的冲洗溶剂 • Possiblecontaminationduetomethodofrinsesolventaddition 冲洗剂加入方式可能带来污染

Advantages and disadvantages of rinse sampling are given in Table 6.1.2-2.
冲洗法取样的优缺点如表 6.1.2-2 所示

Table 6.1.2-2 Advantages and Limitations of Rinse Sampling
表 6.1.2-2 冲洗法取样的优点及局限性

Advantages优点	Limitations局限性
• Duringrinsing,theentireproductcontainingsurfaceiswetted. Oneanalysisresultrepresentsthesum of all removed residues for the flow path. 冲洗过程中，所有产品接触的表面是湿润的。一个分析结果可以代表冲洗液中所有被移除的残留物的总和 • Thesamplingproceduremaynotcontaminatetheequipmentif Processsolventisused. 如果使用工艺溶剂，取样过程不会污染设备 • Re-cleaningmaynotberequiredaftersampling. 取样后无需重新清洗 • Thismethodallowsforconclusionsonthecleanlinessofareas Thatarenotaccessibleforswabbing. 适用于无法采用擦拭取样的区域 • Adaptabletoon-lineanalysis. 适合在线分析 • Lesstechniquedependent. 更少的技术支持 • Applicableforactives,cleaningagents,andbio-burden. 适用于活性成分、清洁剂、生物负载 • Allowssampling ofunique (e.g., porous) surfaces suchas Membranesandresins. 可对独特（如多孔的）表面，膜和树脂进行取样 • Usefulforcleaningprocessdesign/development. 有助于清洁工艺的设计/开发	• Onlyresiduessolubleinrinsesolventcanbedetected. 只能检测到溶于冲洗溶剂的残留物 • Mustassurethatrinsesamplingsolutioncontactsallsurfacesto Adequatelymeasureresidues. 必须确保冲洗液接触到所有表面以充分检测残留物 • Doesnotdealwithresiduesthatpreferentially transferfromone Partoftheequipmenttothenextproduct. 无法检测从设备的某一部位优先转移到下一个产品中的残留物 • Maydiluteouttheresiduetobeundetectablebytheanalytical method. 样品稀释，可能无法检出 • Limitedinformationaboutlocationofareasthatcontributedto residues. 残留的分布位置信息有限 • Knowingtherinsevolumeiscriticaltoensureaccurate Interpretationofresults. 冲洗量对于获得准确结果非常关键 • Usually limited to rinsingan entire piece of equipment,such as a vessel (except for extractionsampling). 通常仅限于冲洗整个设备，比如一个容器（除了提取取样法） • Accessibilityorpresenceofsamplingportsforlegacy Equipmentmay beproblematic.

	对旧设备而言，是否有设备取样口或者取样口飞否容易接近可能存在问题

Rationales for the use of rinse sampling include the following:
使用冲洗法取样的理由如下：
• Equipment not accessible for other types of sampling
无法采用其他取样方法（设备表面不易接近）
• The residue is volatile, so measuring it on dried surfaces is not appropriate
残留物易挥发，因此不适合在干燥表面取样检测
• Rinse sampling adequately measures residues on surfaces.
冲洗取样能够充分检测到表面的残留物

6.1.2.1 Extraction Rinse Sampling for Small Parts
小部件提取冲洗取样法

One special case of rinse sampling is sampling of small parts. Those parts may be sampled by swabbingbut there are two options for rinse sampling. One type of rinse sampling is extraction from smallparts. In an extraction procedure, the extraction solvent is placed in a clean vessel large enough tohold the sampled part. The small part is then placed in the extraction solution and agitated or sonicatedfor a fixed time. The sampling solution is then analyzed for potential residues. A second type ofrinse sampling for small parts is typically used for items with an orifice, such as filling needles. In thisprocedure, a fixed volume of sampling solution is passed through the lumen and collected in a cleancollection vessel. The sampling solution is agitated for uniformity, and then analyzed for the potentialresidues. Because the surface area

and sampling volume are precisely known, limits can be accuratelycalculated for such situations.
小部件取样是冲洗取样的一个特殊情况。这些部件可以通过擦拭取样也可以采用冲洗取样。冲洗取样的一种类型是从小部件上提取残留。在提取过程中，将提取溶剂放置在一个干净的容器中，该容器足够容纳被取样部件。将小部件置入提取溶液中，搅拌或超声处理一定时间。然后分析样品溶液中的残留量。另一种类型的小部件冲洗取样通常适用于有小孔的部件，如灌装针头。在取样过程中，一定体积的冲洗液流经腔体后被收集到一个干净的容器中。搅拌样品溶液至均匀，分析其中的残留物。由于可以精确得到表面积和取样体积，因此可以准确地计算出残留的限度。

6.1.2.2 Solvent Reflux Sampling
溶剂回流取样法

A second special case of rinse sampling is organic solvent reflux sampling. In this process, volatileorganic solvent is added to the reactor of a manufacturing vessel. The solvent is heated to vaporize it.The solvent vapors condense on various upper parts of the manufacturing equipment, dissolve anysoluble residues and carry it back to the reactor. While the technique for distribution of the solvent tothe surfaces for sampling is different, the principles of rinse sampling are still present.
第二种特殊的冲洗取样方法是有机溶剂回流取样。在这个过程中，将易挥发有机溶剂加入到反应器中。加热至溶剂蒸发。溶剂蒸气凝结在生产设备的上部不同部位，溶解所有可溶性残留物后将其带回反应器中。尽管溶剂分配到设备表面进行取样的技术不同，冲洗取样的基本原理依然适用。

6.1.3 Swab and Wipe Sampling
擦拭取样法

Both swab sampling and wipe sampling involve wiping a surface with a fibrous material (most commonly).During the wiping procedure, the residue on the surface may be transferred to the fibrousmaterial. The fibrous material is then placed in a solvent to transfer the residue to the solvent. Thesolvent is then analyzed for the residue by an appropriate and validated analytical method. For swabs,the fibrous material is some kind of textile (knitted, woven or nonwoven) attached to a plastic handle.Wipes are fibrous materials, usually woven or non-woven textiles, which are applied to the sampledsurface by hand. A special case of swabs is the use of cotton balls or pads, which are moved across asurface with forceps. The selection of swab or wipes to be used requires an evaluation of the swabproperties, such as extractables and shedding properties. Recovery of residues from surfaces also dependson the size and shape of the swab head or wipe, as well as the properties (such as flexibility andlength) of the swab handle.
拭子以及擦拭取样都采用纤维材料（最常用）擦拭表面。擦拭过程中，表面的残留物会被转移到纤维材料上。然后再将纤维材料置于溶剂中，将残留物转移到溶剂中去。然后用经过验证的合适方法分析溶剂中的残留物。拭子的纤维材料是一种带有塑料把手的纺织物（针织、机织或无纺布）。擦拭巾是机织或无纺布类的纤维材料，用来手工对表面进行取样。用钳子钳住进行表面擦拭的棉球或棉垫是一种特殊类型的拭子。选择拭子或擦拭巾前需要评估拭子性质，如析出物和脱落物。表面残留物的回收率还取决于拭子头部或擦拭巾的大小和形状以及把手的性质（例如弹性和长度）。

In most cases, the swabs and wipes are wetted with a solvent prior to sampling the surface. Thesolvent selected should be able to assist in dissolving the residue and also be compatible with theanalytical method. For example, for HPLC analysis, the solvent could be mobile phase. For TOC andconductivity, the solvent is almost always water. For sampling the same site, companies may choose to sample the same surface area with multiple swabs or wipes in order to provide a higher percentrecovery of residue from the surface. In

such cases, the additional swab(s) or wipe(s) utilized may beeither dry or wetted with the same solvent.
大多数情况下，表面取样前要用溶剂润湿拭子以及擦拭巾。选择的的溶剂应有助于溶解残留物并同分析方法兼容。例如，对于高效液相色谱分析，溶剂应当选择流动相。对于有机碳和电导率分析，溶剂一般选择水。为了得到更高的表面残留物回收率，公司一般选择采用多个拭子或擦拭巾对同一表面进行取样。在这种情况下，其他的拭子或擦拭巾可以是干燥的或用同一溶剂润湿。

Wipes are typically larger pieces of textile material, and may be used to sample larger equipment areas.
擦拭巾通常是大块的纺织材料，适用于设备较大表面的取样。

The swab or wipe that has been applied to the surface is then extracted with a suitable solvent to remove the analyte from the swab into the extraction solvent for analysis (see **Table 6.1.3-1** for advantagesand limitations). The extraction solvent may be the same or different solvent as that used forwetting the swab.
用合适的溶剂萃取表面取样后的拭子和擦拭巾，将被测物从拭子转移至提取溶液中进行检测（参见表 6.1.3-1 优点和局限性）。提取溶剂可以和润湿拭子的溶剂相同或不同。

Table 6.1.3-1 Advantages and Limitations of Swab/Wipe Sampling
表 6.1.3-1 擦拭取样的优点和局限性

Advantages优点	Limitations局限性
• Enables the analysis of residues found on the specific surfaces. 适用于特定表面残留物的分析 • Allows for sampling of areas that are more difficult to clean (i.e., worst cases). 可对较难清洁区域（即最差条件）的取样 • Allows both dissolution and physical removal of residues. 可溶解和物理性去除残留物 • Adaptable to a wide variety of surface 适用于各种表面 • Economical and widely available. 经济、应用广泛 • Allows sampling of a defined area. 可对指定区进行取样 • Applicable to active, microbial, and cleaning agent residues. 适用于活性成分，微生物和清洁剂残留 • Small extraction volumes may provide for greater detectability. 较少的提取溶剂可以获得较大的检出能力	• Only discrete sampling areas can be analysed to represent the entire equipment – sampling must include worst case locations. 仅对部分表面取样分析，并代表整个设备的状况-取样必须包括最差条件的位置 • The sampling itself can potentially contaminate (from fibers or solvent) the equipment. Re-cleaning may be required after sampling. 取样操作本身可能对设备带来污染（纤维或溶剂）。取样后需要重新清洁 • Some areas are not accessible for swabbing (e.g., piping systems). 某些区域不容易进行擦拭取样（如管道系统） • Results may be technique dependent (such as surface area sampled). 结果可能取决于取样方法（例如被取样的表面积） • Results may be location dependent (such as difficult to access surfaces) 结果可能取决于取样位置（例如难以接触的表面） • Swab material and design may inhibit recovery and specificity of the method 拭子材料和设计可能影响方法的回收率和专属性。

6.2 Placebo Sampling
安慰剂取样法

Placebo sampling can be used to detect residues on equipment through the processing of a placebobatch subsequent to the cleaning process. Placebo sampling is used primarily to demonstrate the lackof carryover to the next product. The placebo should mimic product attributes. The equipment characteristicsalso impact the choice of the placebo batch size. Placebo sampling may present analyticalchallenges for measuring

residues in a true placebo. Placebo sampling may also be called “mock runs”or “blank runs”, which in biotechnology generally involves processing only with water. This latterconcept is different from rinse sampling, in that the water is processed through the equipment muchas the product would be processed.
安慰剂取样法是在清洁后，进行安慰剂批的加工，以检测残留量。安慰剂取样法主要用于证明未将残留携带到下一产品。选用的安慰剂应模拟产品性质。设备特点也影响安慰批量的大小。对于安慰剂取样，可能难以测量安慰剂中的残留量。安慰剂取样也被称为“模拟生产”或“空白生产”，在生物技术中一般只采用水进行加工。后一概念不同于冲洗取样，安慰剂取样中水在设备中的加工与产品的加工几乎一样。

In this sampling process, the equipment is first cleaned. Following cleaning, a manufacturing processis performed (to the extent feasible) using only a placebo product. Following processing, the placeboproduct is evaluated for residues as for any other cleaning validation sample as measures of possiblecontamination of a manufactured product with those residues. Placebo runs can be performed todemonstrate *actual* carryover to the processed material, but if done, are typically done to complementswab/wipe and/or rinse sampling.
在取样过程中，首先要清洁设备。清洁完成后，执行安慰剂产品的生产过程（尽可能同生产工艺一致），同其他清洁验证样品一样，对安慰剂产品中残留物进行评估，检测下一产品中可能存在的残留物污染。安慰剂取样法可以展示下一产品中的真实残留量，通常作为擦拭或冲洗取样的一种补充。

6.3 Sampling for Microbial and Endotoxin Analysis
微生物以及内毒素分析取样

Sampling for bioburden may involve rinse-water sampling and/or swabbing, but may also involvecontact plates. Consideration should be given to the sampling solution for swabbing and rinsing. Forswabbing, a sterile solution, such as phosphate-buffered saline, should be used. For rinse sampling, itis generally not practical to sample large equipment items with sterile water; however, for extractionof small parts, the use of sterile water or a sterile solution is preferred. For large equipment, rinsesampling is generally done with purified water or WFI, and results may be compared to a blank takenfrom the same use point. Rinse-water sampling for bioburden should involve use of sterile samplecontainers. “Aseptic” sampling technique, much like is used for cleanroom bioburden sampling, isrequired for any microbial method to avoid external contamination of the sample.
生物负载取样可采用冲洗和/或擦拭法，也可包括接触碟法。应关注擦拭法以及冲洗法中的样品溶液。对于擦拭法，应采用无菌溶液，如磷酸盐缓冲液。对于冲洗法，用无菌水对大型设备进行取样一般是不现实的。然而，对于小部件的提取取样，首选使用无菌水或无菌溶液。对于大型设备，一般选用纯化水或注射用水进行冲洗取样，结果需与同一用水点所取空白对照进行比较。生物负载的冲洗水取样应使用无菌取样容器。为了避免对样品的污染，同洁净室生物负载取样相同，任何微生物取样都需要采用无菌技术。

Sampling for endotoxin is almost always a rinse water sample, preferably with low endotoxin water.
内毒素取样几乎就是冲洗水样，最好采用内毒素含量低的水。

6.4 Additional Considerations
其他注意事项

It is preferred to have a separate sampling SOP (apart from any special instructions in a cleaning validationprotocol). This helps prevent “procedure drift”, which might occur if the swabbing proceduretext

is just repeated in every protocol. It also helps insure that the same sampling procedure is used inrecovery studies as in protocol execution, and thus simplifies training. The rinse sampling proceduremay be the same procedure that is used for sampling water systems, appropriately modified to coversampling of process equipment.
最好有一个单独取样的 SOP（不同与清洁验证方案中任何特殊说明）。这样可以避免“程序漂移”，如果在每个方案中重复擦拭取样程序的文字内容，则可能出现“程序飘移”。这也有助于确保回收率研究采用与验证方案相同的取样程序，从而简化培训。冲洗取样程序可同水系统取样程序相同，并适当修改以包含工艺设备的取样程序。

In selecting sampling techniques, considerations should be given to the compatibility of the samplingmaterials (such as vials, swabs, sampling solutions) with each other, with the nature of the residue,and the nature of the analytical method. Furthermore, any requirement for cleaning or removingsampling materials from the sampled surface in a cleaning validation protocol should be addressed inthe design/selection of sampling methods, materials, and parameters.
选择取样方法时，需要考虑取样材料（如瓶子，拭子，取样溶液）之间、取样材料与残留物特性以及分析方法之间的兼容性。此外，在设计/选择取样方法，材料以及工艺参数时，应在清洁验证方案中涵盖从被取样表面清洁或去除取样材料的任何要求。

Finally, in taking samples in a protocol, consideration should be given to the impact of a given sampleon subsequent samples. This includes the order in which samples are taken. This “order” includesconsideration of the type of sampling method (e.g., visual, rinse, swab) as well as the type of residue(e.g., active, cleaning agent, bioburden, endotoxin).
最后，清洁验证方案中应当考虑既定取样对后续取样的影响。这包括取样顺序。这个“顺序”需要考虑取样方法（例如目检，冲洗法，擦拭法）以及残留物（例如活性成分，清洁剂，生物负载，内毒素）的类型。

6.5 Sampling Recovery Studies
取样回收率研究

Sampling recovery studies are generally required to adequately demonstrate that a residue, if presenton equipment surfaces, can be adequately measured or quantified by the combination of theanalytical method and the sampling procedure. These studies provide a scientific basis for utilizingthose sampling and analytical methods to measure residues. The objective should be to establish areproducible level of recovery from the equipment surfaces. Three types of sampling recoveries arediscussed below: swab sampling recovery, rinse sampling recovery and “visual examination” recovery.For swab and rinse sampling, recovery studies may be performed as part of the analytical method validationor they may be performed as separate studies once it is determined that the analytical methodcan appropriately measure residues in solutions. Sampling recovery studies arelaboratory studies involvingcoupons of sampled equipment of different materials of construction (such as stainless steel,glass, PTFE, and EPDM) spiked with residues to be measured.
取样回收率研究通常需要证明采用适当的分析方法和取样程序，可充分测量或量化设备表面的残留物。这些研究为残留物测量的取样以及分析方法建立提供了科学依据。它的目的是建立一个可重现的设备表面回收率。以下探讨三种类型的取样回收率：擦拭取样回收率，冲洗取样回收率以及“目检”回收率。对于擦拭以及冲洗取样而言，回收率研究可以作为分析方法验证的一部分，或者一旦确定分析方法能够检测溶液中残留物，可单独进行研究。取样回收率研究是实验室研究，需要不同

被取样设备材质（如不锈钢、玻璃、PTFE 以及 EPDM）试样，并在上面涂布待检测残留物。

6.5.1 General Considerations

一般注意事项

Recovery studies *may* not be required for certain residues that are known to be readily soluble (e.g., asdefined in the USP or Merck Index) and used well below the solubility limit (such as sodium hydroxideor phosphoric acid used as cleaning agents), provided the residues are not reactive with or absorbedinto the surface.

对于一些可溶的残留物（例如，USP 或默克索引里定义的）且用量远低于溶解度极限的残留物（如作为清洁剂的氢氧化钠或磷酸），可不进行回收率研究，假如这些残留物不会与表面发生反应或被表面吸收。

In performing recovery studies for swabbing and rinse sampling, the amount of material spiked ontocoupons should represent an amount equal to what could be present at the residue limit. If additionallevels are spiked, levels should represent levels of actual values present in cleaning validationprotocols. It should be recognized that spiked levels at extremely low levels may give lower recoverypercentages due to the inherent variability of the analytical method at those low levels.

在擦拭以及冲洗取样的回收率研究中，在材质试样上涂布的残留物量，应与残留限度一致。如果涂布更多的残留，那么涂布量应与清洁验证方案一致。需要注意的是极低的涂布量将导致更低的回收率，这是由于在低残留水平时分析方法的固有变动性导致。

Thespiked residue should represent the same residue present at the end of the cleaning process. Inactual fact, the residues at the end of cleaning may include a combination of active ingredient,cleaning agent, excipient, and/or degradation products. It is common practice, however, to only spikethe active ingredient when doing recovery studies for the active ingredient, and to only spike withcleaning agent when doing recovery studies for cleaning agent. Spiking of the active ingredient in its finalformulation may be considered when spiking of the active ingredient alone is not practical. Finally,drying and/or holding times of spiked coupons should be appropriate for the nature of the residue.

加入的残留物应该代表清洁过程结束时设备表面存在的同一残留物。事实上，清洁结束后的残留物可能包含活性成分、清洁剂、辅料 以及/或降解产物。通常的做法是，在做活性成分的回收率研究时，仅仅加入活性成分，做清洁剂的回收率研究时，仅仅加入清洗剂。当无法单独加入活性成分时，也可考虑以最终配方的形式加入活性成分。最后，材质试样的干燥以及/或保持时间应该适用于残留物的性质。

If the active degrades during the cleaning process, it is common practice to perform recovery studiesby spiking with the active ingredient itself, unless there is information that indicates the degradationproducts may have a significantly different recovery level from the active ingredient itself. Furthermore,if the degradation product has unusual safety or solubility concerns, recovery studies by spikingdirectly with that degradant should be considered. Because of possible concerns aboutdegradationof the active ingredient after completion of the cleaning process, but before sampling, that maximumtime interval between spiking and sampling should be considered in performing recovery studies.

如果清洁过程中活性成分降解，通常通过加入活性成分本身来进行回收率研究，除非有资料表明降解产物同活性成分本身回收率水平显著不同。此外，如果降解产物有异常的安全或溶解性问题，必须考虑直接加入降解产物进行回收率研究。由于担心清洁过程完成后，但在取样前活性成分可能会

发生降解，进行回收率研究时，应该考虑残留物涂布和取样之间的最大时间间隔。

Recovery values should be established for all surfaces sampled. For swab and rinse sampling, one approachfor this is to perform recovery studies on all surfaces. An alternative is to perform one residuestudy on a surface which through documented evidence is equivalent (in terms of percent recovery)to other surfaces for which a formal recovery study is not performed. This is essentially a grouping orfamilyapproach for recovery studies. Equivalence for establishing the group or family may be establishedbased on published studies or in-house data. Another approach is to exclude formal recoverystudies for sampled surfaces constituting less than a small percentage (such as 1% or 2%) of the totalequipment surface area; in such cases, the recovery value used for that excluded surface is the lowestrecovery of any other surface type for which a formal sampling recovery study was performed, or theminimum acceptable recovery percentage required by the company's procedures.

应建立所有被取样表面的回收率值。对于擦拭和冲洗取样，一个方法是在所有表面上进行回收率研究。另一种是在其中一个表面上进行的残留物回收试验，但应有文件证明这个表面等同于（就回收率百分比而言）其他未进行回收率研究的表面。本质上是分组或分类的回收率研究方法。分组或分类的依据是已发表的研究或内部数据。另一种方法对于占设备总表面面积比例很小（如低于 1%或2%）的被取样表面，不进行正式的回收率研究。在这种情况下，未进行回收率研究的表面的回收率值应为其他任何正式进行回收率研究的被取样表面中的最低值，或者是公司程序中要求的最低回收率百分比。

6.5.2 Swab/Wipe Recovery

擦拭法回收率

For this section, the term swab or swabbing is used; however, descriptions for swab recovery studies alsoapply to wipe sampling, except as noted. For swab recovery studies, coupons are spiked in a controlledmanner with solutions of the sampled residue, allowed to dry, and sampled with the swabbing procedureto be utilized in the cleaning validation protocol.The swab is extracted in a suitable solvent and theamount of residue measured in that solvent sample. The amount recovered is compared to the amountspiked on the coupon and the result is expressed as percentrecovery. Because swabbing is a manual procedure,typically each person performs a recovery study with three replicates. It is preferable to have atleast two people perform swabbing recovery studies for each combination of residue and surface type.The recovery percentage established by the study may be defined in different ways,but typically is definedas the lowest average recovery of any one swab operator. An acceptable swab recovery depends on howthat swab recovery is being used.If the recovery is performed to qualify the sampling method *withoutcorrection* of either a limit or an analytical result then a recovery percentage such as 70% or more istypicallyrequired. If the recovery percentage is *used to correct* a residue limit *or* an analytical result then arecovery of 50% or more is typically required.An upper limit for percent recovery should be establishedto deal with studies where the measured recovery is greater than 100%. Recoveries of less than 50% typicallyrequire a written rationale of why that percentage is appropriate.

本部分采用了“拭子”或“擦拭”的术语，但是除非另有注明，拭子回收率研究的描述同样适用于擦拭取样。拭子回收率研究中，将已知浓度的残留物溶液以受控的方式涂布在材质试样上，自然晾干，采用清洁验证方案中的相同的擦拭方法进行取样。选用合适的溶剂提取拭子上的残留，然后检测提取液中残留物的数量。回收量与材质试样上的加入量之比就是取样百分回收率。由于擦拭属于人工操作，通常每人需要重复三次回收率研究。每个残留物和表面类型的组合至少需要两个人进行擦拭回收率研究。研究建立的回收率可以通过不同的方式定义，但通常定义为任意一个擦拭取样人

员的最低平均回收率。一个可接受的拭子回收率取决于如何进行拭子回收率试验。如果在进行回收率研究确认取样方法时，没有对残留限度或分析结果进行修正，回收率通常要求 70%或更高。如果回收率用于修正残留物限度或分析结果，回收率一般要达到 50%或以上。应建立回收率上限，用于处理实测回收率高于 100%的研究。回收率低于 50%通常需要书面解释为什么这个残留百分比是合适的。

As part of the swab method development, spiking of residue directly onto the swab head to determinerecovery (release) from the swab head material may be done. Such a study should also be consideredif recovery levels from spiking of surfaces is unacceptable, and it is desired to find the causeof the low recovery.
作为拭子法开发的一部分，可直接将残留物加入到拭子头部来确定回收率（释放度）。如果加入法获得的表面残留物回收水平不符合要求时，并需要找出回收率低的原因时，应当考虑这样的研究。

At a minimum, recovery values are generally performed at the residue limit on the surface (e.g., inμg/cm^2). While it is possible to perform recoveries at different spiked levels, in general there is littlevalue to such additional spiked levels because of the variability of the sampling procedure. It is preferableto perform additional replicates at the one residue limit rather than studies at additional levels.Acceptable variation for recovery results at one spiked level is typically on the order of 15-30% RSD.If recovery studies are done by more than one swab operator, it is also appropriate to have a criterionfor determining acceptable variation between operators. Examples of criteria used include variationof no more than a maximum amount between average percentage values, or variation of no morethan a maximum relative percentage between average percentage values. Use of statistical tests forsignificance is generally not necessary for such determinations.
回收率试验至少应在表面残留物限度的水平进行（例如，以μg/cm^{2}表示））。尽管可以在不同涂布量下进行回收率试验，由于取样程序的变动性，通常这些额外涂布量试验价值不大。最好是在同一残留物限度水平重复回收率试验而不是对不同涂布水平进行研究。同一涂布水平的回收率结果的允许误差通常是RSD 15-30%。如果 由多个操作人员进行回收率研究，通常应有一个不同操作者试验结果允许误差的标准，例如不超过平均值之间最大差值，或者不超过平均值之间的最大相对偏差。通常不需要为此进行显著性统计学检验。

Swab recovery studies are typically performed on a nominal coupon surface area using the same area as is swabbed during sampling for protocol execution. This area is typically either 25 cm^2 or 100 cm^{2}while wiping studies are done on larger areas. In sampling manufacturing equipment for a protocol,it is not always possible to swab a 10 cm×10 cm area (it might be necessary to swab a 5 cm × 20 cmarea). Furthermore, it might not be practical to swab exactly 100 cm^2 (an area of 60 cm^2 or 128 cm^{2}may be required because of the specific equipment geometry).In such cases, the recovery percentagebased on sampling 10 cm × 10 cm may be applied to each of those cases. If such an approach is used,a range of acceptable surface area (such 25% to 150% of the nominal sampled area) should be established.However, if the sampled area for equipment surfaces in a protocol varies from the nominalvalue, the residue limit for that sample should be adjusted based on the actual surface area swabbed.
通常在一个标准的材质试样表面上进行回收率研究，并采用验证方案实施取样相同的表面积。在较大面积进行回收试验时，通常可取 25 cm^{2}或 100 cm^2。方案中对生产设备擦拭取样时，面积不可能都是 10 cm × 10 cm（也可能是 5 cm× 20 cm）。此外，恰好擦拭 100 cm^{2}面积是不现实的（某些特殊几何形状的设备可能需要擦拭 60 cm^{2}或 128 cm^2）。基于 10 cm×10 cm取样面积的回收率可能适用于

这些情况。如果采用这种方法，应当确定可接受的表面积范围（标准取样面积的 25%到 150%）。然而，如果方案中设备表面取样面积与标准值不同，样品中残留物限度应当根据实际的擦拭面积进行调整。

6.5.3 Rinse Recovery
冲淋法回收率

Rinse recovery studies address the validity of rinse sampling for that residue. They demonstrate that ifthe residue were on a surface, that residue would be effectively removed and could be analyzed in therinse solution. Rinse recovery studies address the U.S. FDA's "dirty pot" and "baby/bath water" analogies***(20)***. Rinse recovery studies, like swab recovery studies, can be performed on coupons that havebeen spiked with solutions of the target residue and then allowed to dry. For swab recoveries, it is necessaryto perform the exact swabbing procedure to be used in the cleaning validation protocol. For rinsesampling, in contrast, the exact rinsing procedure (except for the special case of extraction sampling)cannot be *duplicated* in the laboratory. However, it is possible to *simulate* the rinsing procedure in thelaboratory. Where possible, the conditions of the simulated rinse should be the same as the equipmentrinsing situation. This includes selection of rinsing solvent as well as the temperature of the rinsing solvent.In other cases, the rinsing conditions should be selected as the same or a worst case as comparedto the equipment rinsing situation. For example, the ratio of solvent to sampled surface area should bethe same or lower in the recovery study as compared to the equipment rinsing situation.
冲洗法回收率研究证明了残留物冲洗取样的有效性。它证明如果表面存在残留物，残留物能被移除并在冲洗液中得到检测。冲洗法回收率研究解决了美国 FDA 的"脏罐子"以及"婴儿/洗澡水"的问题（20）。冲洗法回收率研究同拭子回收率相似，将目标残留物溶液涂布在材质试样上，自然晾干。对于拭子取样的回收率，必须严格执行清洁验证方案中采用的擦拭步骤。与之相反，对于冲洗取样，无法在实验室中准确地重复冲洗步骤（除了提取取样的特殊情况）。然而，在实验室中模拟冲洗程序是可行的。在可能的情况下，模拟冲洗的条件应该同实际的设备冲洗条件相同。包括冲洗溶剂以及冲洗溶剂温度的选择。其他情况下，应该选择与设备冲洗相同或最差的冲洗条件。例如，回收率研究中溶剂量与被取样表面积之比应该同设备冲洗时相同或更低。

One method of simulating the rinse process is to suspend a spiked coupon above a clean collectionvessel, and cascade rinse solution across the surface into the collection vessel. Another method is tospike the bottom of a beaker of the appropriate material of construction, allow the residue to dry,add rinse solution to the beaker and apply gentle agitation for a time which approximates the time ofthe final rinse. The rinse solution is either pipetted or decanted from the beaker and analyzed. A thirdoption, used in cases where a beaker of suitable material of construction is not available, is to placea spiked coupon in the bottom of a beaker and perform a simulated rinse as in the second method.
模拟冲洗过程的一个方法是在干净的收集容器上方悬挂一个已涂布的材质试样，然后将冲洗液从表面冲过，并收集在收集容器中。另一个方法是在合适材料的烧杯底部涂布残留物，让残留自然晾干，向烧杯中加入冲洗液并轻轻搅拌，搅拌时间同最终冲洗相同。采用移液管移出或从烧杯中倒出冲洗液并分析。第三种方法适用于没有合适材质烧杯的情况，在烧杯底部放置一个材质试样然后同第二种方法一样模拟冲洗。

Since laboratory rinse sampling studies are generally not operator dependent, three replicates by oneoperator may be adequate to determine the percent recovery. Acceptable percent recoveries are typicallyestablished at the same levels and conditions as for swab recovery studies.

因为实验室冲洗取样研究一般并不取决于操作人员，一个操作人员重复三次足以确定百分回收率。合格的回收率通常可以在同拭子取样回收率研究相同的水平和条件下建立。

6.5.4 “Recovery” in Visual Inspection

目检回收率

This process is actually the determination of a quantitative “visual detection limit”. If visual examinationis used to supplement swab or rinse sampling, such determination of a visual detection limitmay be done but is not required. A visual detection limit under specified viewing conditions can bedetermined by spiking coupons of the equipment surface materials with solutions of the residue atdifferent levels (in µg/cm^2), and having a panel of trained observers determine the lowest level atwhich residues are clearly visible across the spiked surface. The significance of such a visual detectionlimit is that if equipment surfaces are determined to be visually clean under the same (or more stringent)viewing conditions in a cleaning validation protocolthe level of the residue is below the visualdetection limit. Appropriate viewing conditions include distance, lighting and angle. The visual limitdepends on the nature of the residue as well as the nature of the surface (e.g., stainless steel vs. PTFE)and the visual acuity of the inspector. Typical values reported in the literature for a visual detectionlimit are 1-4 µg/cm2 ***(23)***.For this determination, a percent recovery is not established;the purpose isto establish a value where residues are clearly visible so that any surface observed as visually clean isclearly below that value.

这个过程实际上是确定一个定量的“目视检测限”。如果目检只是作为擦拭或冲洗取样的补充，则可以但不要求确定“目视检测限”。指定观察条件下的目视检测限可以通过在设备材质试样上涂布不同浓度（µg/cm^2）的残留物来确定。并需要一组训练有素的观察者来确定表面残留物明显可见时的最低残留水平。目视检测限的意义在于，如果在清洁验证方案中，在同样（或更严格）的观察条件下确定设备表面已目检洁净，则可认为实际残留水平低于目视检测限。适当的观察条件包括距离，光照以及观察角度。目视检测限取决于残留物性质，表面性质（例如，不锈钢对PTFE）以及观察者的视力。文献报道的典型的目视检测限是 1-4 µg/cm^2(23)。对于 目视检测限，不需要确定百分回收率；该研究的目的是确定残留物明显可见时的一个残留物水平，这样目视洁净的任何表面上残留水平都低于目视检测限。

6.5.5 Recovery for Bioburden and Endotoxin Sampling

生物负载以及内毒素取样回收率

Recovery studies to determine percentage recovery *from surfaces* are not appropriate and are not normallydone for microbiological sampling. One reason for this is the question of enumeration in microbiologicaltests – “colony forming units” are typically counted as opposed to individual organisms.A second reason for this is that vegetative organisms will die or lose viability when dried on a couponin a standard sampling recovery procedure. A third reason is that it is unclear which species should beused for a recovery study. A fourth reason is that typically the limits set for bioburden are significantlybelow what could possibly cause either product quality issues orprocess performance (e.g., SIP) issues;therefore, even though recovery may be low (<50%), product quality and/or process performanceis not impacted by not including a recovery factor

对于微生物取样，不适合进行回收率研究以确定表面百分回收率。原因之一是微生物检测的计数问题–通常以“菌落形成单位”进行计数而不是单个微生物。第二个原因是在一个标准的取样回收率研究中，当材质试样晾干时微生物会死亡或失去生存能力。第三个原因是不清楚选用哪种微生物进行回收率研究。第四个原因是通常生物负载限度已明显低于可能影响产品质量或工艺性能（如在线灭菌）的水平。因此，即使回收率低（<50%），不引入回收因子也不会影响产品质量和/或工艺性能。

Endotoxin recovery studies from surfaces using the sampling method are not ordinarily performed.One reason is related to the low levels that are typically present on cleaned surfaces. Additionally, onlystandard endotoxin from LAL test kit suppliers can be used for recovery studies and these may not beindicative regarding detection and/or removal of endogenic endotoxins present from a manufacturingprocess. Finally, the largest quantity of endotoxin present in a manufacturing vessel typically isendotoxin within a soil matrix. The cleaning process itself is very effective in physically removing thisendotoxin along with other manufacturing soils.
通常不进行取样表面内毒素的回收率研究。原因之一是洁净表面的内毒素水平通常较低。此外，只有鲎试剂供应商提供的标准内毒素才可以用于回收率研究，但这些研究无法指示生产过程的内源性内毒素的检测和/或去除情况。最后，生产容器中内毒素大多存在于污物中。清洁操作本身可以有效清除这种内毒素以及其他污物。

6.6 Training and Qualification of Samplers
取样人员的培训和资格确认

Training involves the steps taken to assist the prospective sampler in learning the technique of sampling/inspection. For purposes of this section, “sampling” and “sampler” also include “inspection”and “inspector” for visual evaluation. Qualification involves the process of “certifying” that the prospectivesampler can appropriately sample.
培训是为了帮助未来的取样者学习取样/检查技术。本章“取样”和“取样者”同样包括目视评价中的“目检”和“目检员”。资格确认包括证明未来的取样者能够正确取样的过程。

Training always precedes qualification. At a minimum, *training* involves reading of the sampling procedureand demonstrating the correct procedure by a trained sampler. During the reading and demonstration,the trained sampler provides commentary on the rationale for certain practices or aspectsof the sampling procedure. Demonstration of technique may also utilize a visual indicator on theswabbed surface which assists the trainee in seeing consequences of poor technique. The last step intraining is demonstration of the correct procedure by the prospective sampler.
培训总在资格确认之前。培训至少包括学习取样步骤以及观看培训过的取样者示范正确的取样程序。在学习和示范的过程中，训练有素的取样人需要解释取样过程中某些做法或取样程序的基本原理。在演示过程中，也可以在已擦拭表面上使用“指示剂”，协助学员观察到错误方法造成的后果。培训的最后一步是受训者演示正确的取样步骤。

Qualification processes used for sampling will depend on the type of sampling performed. Qualificationmay involve merely demonstration of correct technique (that is, the last step of the trainingprocess), or it may involve a “test” that challenges the trainee’s ability to perform the activity correctly(e.g., perform visual inspection using an array of coupons where some are soiled and others are notor perform swab sampling for a known soil residue level on coupons). Either type of qualificationmay be repeated on a regular basis or upon any retraining of a sampler. Retraining may be conductedbased on suspected operator error in a swabbing process, or it may be done because an operator hasnot performed a swabbing event over a certain time frame.
取样的资格确认程序取决于取样类型。资格确认可能只是正确方法的示范，（也就是培训的最后一步），或者是一个挑战受训者是否有能力正确取样的测试（例如，目检时采用一系列材质试样，其中有些是被污染的，有些没有被污染；或者在已知残留物水平的材质试样上进行擦拭取样）。可定

期进行资格确认，或对取样人进行再培训时重新进行资格确认。当操作者在擦拭过程可能存在错误操作时，或操作者没有在规定时间完成擦拭活动时，应进行再培训。

6.6.1 Key Issues for Training for Swab Sampling

拭子取样培训的关键点

Note that what is written in this section about swab sampling applies appropriately to wipe sampling.
注意，本部分关于拭子取样的描述同样适用于擦拭取样。

Four keys to consistency in swab sampling training are emphasis on consistency of wetting the swabhead, consistency of the swabbing motion (including overlapping strokes), consistency in appliedpressure, and consistency in swabbing of the correct surface area. It is assumed, of course, that thecorrect swab, the correct number of swabs, and the correct wetting solution (if any) for the swab areutilized. A fifth factor for some types of swab sampling (such as sampling involving TOCanalysis) isthe emphasis on preventing external contamination of the swab, such as from the presence of volatileorganics in the atmosphere around the sampling location.
拭子取样培训中强调四个关键的一致性，拭子头部润湿的一致性，擦拭动作的一致性（包括擦拭行程的重叠），用力的一致性，擦拭的表面积一致性。当然，前提是采用了正确的拭子，拭子数量以及润湿拭子的方法（需要时）。某些类型拭子取样的第五个因素（例如取样进行 TOC 分析）是强调防止拭子的外部污染，例如取样位置周围的空气中存在挥发性有机物。

Since swab sampling is not unlike manual cleaning processes in that it depends on a person for ahigh degree for consistency, consideration should be given to have swab samplers retrained and/orrequalified on an established basis. Retraining may involve the same process as for initial training ormay involve only portions of that initial training. Requalification generally involves a repeat of theinitial qualification process. The need for retraining and/or requalification should also be addressedas part of change control for the swabbing procedure as well as when swab sampling “operator error”is suspected in the investigation of a nonconforming result.
拭子取样与手动清洁过程相同之处在于它的一致性高度取决于操作者，应当考虑定期对取样者进行再培训和/或再次资格确认。再培训过程可能与首次培训相同，或者仅仅是首次培训的一部分。资格再确认一般是首次资格确认的一个重复。当擦拭程序发生变更，以及不合格结果调查中怀疑擦拭取样操作错误时，应进行再培训和或资格再确认。

6.6.2 Key Issues for Training for Rinse Sampling

冲洗取样培训的关键点

The major concern for accuracy in rinse samples is to prevent contamination of the rinse sample. Thiscontamination may come from for example, the sampling port, environment around the sampling port,and/or the operator. Steps to prevent contamination may include adequately flushing or cleaning theport prior to taking a sample, as well as avoiding sample contamination due to the use of isopropanolon gloves or use of isopropanol to clean the port (prior to sampling) if TOC is the analytical procedure.
In training rinse samplers to take a grab sample for the final rinse of a CIP cycle, timing of the samplingprocess is critical. Typically, the very last portion of the rinse is sampled but it may be acceptable to samplebefore that time if such sampling represents a worst case. However, once process rinsing is complete,there is no way to go back and collect a rinse sample (unless a separate sampling rinse is performed).

对于冲洗样品准确性，主要是防止冲洗样品被污染。污染可来自取样点、取样点周围的环境和/或操作者。防止污染的措施可包括在取样前对取样点进行充分冲洗或清洁，如果不是采用 TOC 作为分析方法，还应避免用异丙醇消毒手套或使用异丙醇清洁取样点（在取样前）造成的污染。在培训操作者从 CIP 行程的最终冲洗阶段“抓取”样品时，取样时机的控制非常关键。通常从冲洗溶液最后一部进行取样，如果能够代表最差条件，也可在这之前进行取样。然而一旦冲洗过程结束，就无法再回头收集冲洗样品（除非进行一个独立的冲洗取样）。

Since the consistency of rinse sampling is less operator dependent, there may be no need for routineretraining and/or requalification of operators; however, the need for retraining and requalificationshould also be addressed as part of change control for the rinse sampling procedure as well as whenrinse sampling “operator error” is suspected in the investigation of a nonconforming result.
因为冲洗取样的一致性与操作者关系不大，可能不需要对操作者进行例行的再培训和/或资格再确认；然而当冲洗取样程序发生变更，以及不合格结果调查中怀疑冲洗取样操作错误时，应进行再培训和/或资格再确认。

6.6.3 Training for Visual Inspection

目检的培训

Training for visual inspection depends on whether the visual inspection is part of a protocol execution,routine monitoring, or laboratory “limit of detection” determination. In any case, it is preferredto have a visual inspection SOP so that training can be for that SOP. Visual acuity of visual inspectorsfor either type of visual examination should be addressed.
目检的培训取决于目检是否属于方案执行、常规监测或实验室“检测限”研究的一部分。无论如何，必须要有目检 SOP，以便于我们能够根据 SOP 来进行目检培训。无论哪一类型的目检，都需要考虑到目检人员的视力。

For training of visual inspectors in a *protocol execution*, key issues are access to sites for viewing, appropriatelighting, and the ability to discern the difference between residues on the surface and surfaceimperfections. An important element of visual inspection training is to know when to call for furtheranalysis to determine the nature of the residue. For example, if what appears to be rouge is seenon the equipment, the presence of that residue should be noted. Determining whether that residuecauses a failure in the cleaning process is a *separate* decision.
对于方案执行中目检人员的培训，关键点包括观察通道、合适的灯光，以及区分表面残留物和表面瑕疵的能力。目检培训的一个重要方面是知道什么时候需要做进一步分析来确定残留物性质。比如，当看见设备有红锈，需要注明发现了该残留物。需要 单独确定该残留物是否会造成清洁过程的失败。

The procedure for visual inspection for laboratory “limit of detection” determination is generally differentfrom that of visual inspection during protocol execution because the objective is different. Theobjective is to determine at what level a certain residue can be consistently seen across a spiked surfacein order to correlate a visual detectability limit with a level ofknown residue(s) below that spikedlevel. This procedure may be in a separate SOP or may be incorporated in an overall SOP for visualinspection. In addition to the same elements that are included in training for protocol execution, a keyconsideration for training in this procedure, which involves viewing spiked coupons, is a careful distinctionbetween a visually clean surface, a partially soiled surface (in which residue is apparent onlyover a portion of the spiked area), and a “fully” soiled surface. Furthermore, the determination of

a“visual limit” in the laboratory should be done under conditions similar (or worst case) as comparedto visual examination of equipment in a protocol. This includes considerations oflighting, distance,and angle of viewing.
由于目的不同，实验室确定目检“检测限”的程序通常和清洁验证方案执行过程中目检程序不同。确定“检测限”的目的是为了确定某一残留物的水平，在这一水平可一致地观察到涂布在材质试样表面的残留，并将目检“检测限”与已知残留的水平（低于该涂布水平）关联起来。“检测限”确定程序可以作为一个单独的 SOP，或者合并在目检 SOP 中。除了方案执行培训的相同要素外，目检程序培训的一个关键是仔细观察已涂布的材质试样，仔细区分出目检洁净表面、部分脏污表面（仅在部分涂布面上存在明显残留）和完全脏污表面。并且，在实验室中进行“检测限”研究时应该采用与方案执行中设备目检一样（或更差）的条件，包括需要考虑灯光、目检距离和观察的角度。

7.0 Analytical Methods

分析方法

It is essential to a cleaning validation program that the appropriate analytical methods are utilized.Analytical methods must be appropriate in that they can adequately detect and measure the residue(s)of concern. It is also important to understand what can be concluded from the analytical result (e.g.,was the product or cleaning agent measured and were the results acceptable?). The results of testingwill determine if the cleaning cycle is acceptable or needs improvement. This section discusses considerationsin selecting the appropriate test methods, including information on the applicability anduse of both chemical and microbial test methods, and test method validation.
在清洁验证中选择一个合适的分析方法是非常必要的，该适当的分析方法应能够充分检测相关残留物。理解可以从分析结果中得出什么结论也很重要（例如检测的是产品还是清洁剂，结果是否合格？），检测结果决定了清洁方法是否可行或需要进一步改进。本章讨论的内容是怎样选择一个合适的测试方法，包括适用性、化学和微生物测试方法的信息，以及测试方法的验证。

The emphasis in this section will not be so much on describing the features and limitations of methods(although that will be done to a limited extent), as it will be on the *thought process* of decidingwhat information is obtained and when a certain analytical method will be useful. Cleaning processunderstanding is the key to selecting the appropriate analytical method for various stages of cleaningvalidation
本章的重点不是阐述分析方法的特性和局限性（尽管对此也有一定描述），而是判断获得了什么信息以及何时可采用某一特定分析方法的思考过程。对于清洁工艺的理解是在清洁验证不同阶段选择适当分析方法的关键。

7.1 Purposes of the Analytical Methods

分析方法的目的

In a lifecycle approach to cleaning validation, different analytical methods may be appropriate forevaluation of residues at the different stages of the cleaning validation lifecycle. The lifecycle stagesof cleaning validation are design/development, qualification, and validation maintenance. Analyticalmethods may also be used as part of investigations during any lifecycle stage. It is important to considerand evaluate what information one wants to obtain and what information can be obtained fromuse of a given analytical procedure.

在一个生命周期的清洁验证方法里，在清洁验证的不同的阶段可能使用不同的分析方法来评价残留物。清洁验证的生命周期包括设计/开发、确认和验证维护。在生命周期中的任一阶段，分析方法也可以作为调查的一部分。考虑和评估希望以及能够从一个特定分析程序中获得什么信息是很重要的。

For example, in early development work, there may not be adequate information on the nature ofresidues (e.g., is the active ingredient degraded?) and a specific analytical method may not have beenvalidated. However, nonspecific methods may give a reasonably accurate picture of the overall effectivenessof the cleaning process for cleaning process development, even though that nonspecificmethod may or may not be the analytical method chosen for the cleaning validation protocols.

例如，在早期的开发过程中，可能没有残留物的足够的信息（例如活性成分是否降解），而且一个特定的分析方法可能也没有经过验证。然而，在清洁工艺开发时，采用非专属性方法可能有助于较准确地了解清洁工艺的综合效果，即使这种非专属性方法可能是或不是最终清洁验证方案中选定的分析方法。

Another example involves the selection of analytical methods for investigations. For the validationruns (qualification runs), it is usually preferred to have an analytical method that can appropriatelydetermine whether the target residue (e.g., the active ingredient) is at or below the predetermined acceptancelimit for that residue. But for an investigation into a deviation (nonconformance), in certaincircumstances (such as with the use of a nonspecific method in a validation protocol) it may be moreimportant for the investigation to have an analytical method that can qualitatively determine the natureof that residue (e.g., is it active ingredient, cleaning agent or excipient?).

另外一个例子是用于调查的分析方法的选择。在验证（确认）中，通常首选的分析方法应能够适当检测出目标残留物（例如活性成分）是否符合预定的可接受限度。但是，对于一个偏差（不符合）的调查，在特定的条件下（例如在验证方案中使用的是一个非专属性方法），采用一个能够定性检测出该残留物性质（例如，是活性成分、清洁剂还是辅料？）的分析方法则是更为重要的。

It is important to emphasize that *why* an analytical method is being used iscritical for having a robust, science and risk-based approach to cleaning validation. Just because amethod has been used in the past does not necessarily mean it will be useful for a new application.

需要重点强调的是，理解为何选择一个分析方法是建立一个可靠的、科学的和基于风险的清洁验证方法的关键。仅仅因为是过去使用过的分析方法并不一定意味着它可以用于新的应用中。

7.2 Practical Considerations in Selecting Analytical Methods

选择分析方法的实际考虑

In an ideal world, the best method for a given task could be chosen; in the real world, selection ofanalytical

methods may be limited by *practical* considerations. In many cases, it is important not thatthe analytical method be the *best* method available but that it be *adequate* for the intended purpose.In selecting analytical methods, one must consider readily available methodologies within a givencompany. For example, it is not likely that a company will invest in a new analytical method if existingmethods are adequate for the intended purpose. New methods may mean capital equipment purchases,training of analysts and maintenance of the equipment; the related costs should be weighedagainst the expected benefits. For example, total organic carbon (TOC) was not widely considered forcleaning validation until TOC replaced the readily oxidizable substances pharmacopeial method, afterwhich pharmaceutical companies were readily familiar with and comfortable with the technology.

在理想的情况下，应选择最好的分析方法；实际上，分析方法的选择可能会受到实际情况的限制。许多情况下，更重要的不是选择的分析方法是最佳的，而是该方法能够满足预期的目的。在选择分析方法时，必须考虑一个特定公司现有的分析方法，例如，如果现有的分析方法能够满足检测目的，公司就不太可能再投入开发另一个新的分析方法。新的方法可能意味着设备采购、人员培训和设备维护投入，相关的费用需与预期的收益进行平衡。例如，直到 TOC 方法替代了药典方法中的易氧化物检验之后才被广泛应用于清洁验证中，之后制药公司也就很快地熟悉和接受了这项技术。

On the other hand, if a new analytical method is required because existing in-house methods arenot adequate for the intended purpose, then that new method should be considered. These may beimplemented by using contract analytical laboratories or by bringing the new analytical methodologyin-house. A decision on bringing the method in-house versus using a contract laboratory may bebased on business considerations.

另一方面，如果现在的内控方法不足以满足预期的目的，则需要采用一个新的分析方法，这些工作可以在合同实验室完成或建立新的内控分析方法，可基于商业上的考虑决定建立新的内控分析方法还是由合同实验室完成。

7.3 Specific vs. Nonspecific Analytical Methods for ValidationProtocols

验证方案中的专属性和非专属性方法对比

Specific analytical methods are those which measure a certain residue in the presence of *expected*interferences. If the target analyte in a validation protocol is the active ingredient, such interferencesmay include degradation products and related substances, excipients, cleaning agents and cleaningprocess by-products. Examples of specific methods include liquid chromatography (including HPLC,UPLC and TLC) and spectrophotometry (including UV, visible and infrared). Each of these methodsrequires the use of an appropriate reference standard. In contrast, nonspecific analytical methodsmeasure a general property, such as conductivity or TOC, which could be due to a *variety* of analytesor sources.

专属性分析方法是指那些在有预期干扰物存在的情况下仍可以检测特定残留物的方法。如果在验证方案中的目标分析物是活性成分，那些干扰物可能包括降解物和有关物质、辅料、清洁剂和清洁工艺副产物。专属性方法包括液相色谱法（包括 HPLC、UPLC 和 TLC）和光谱法（包括紫外、可见和红外），这些方法都需要使用适宜的对照品。相反的，非专属性方法测量的是一种大致的性质，例如电导率和 TOC，它可能源于多种分析物和不同来源。

Selection of an analytical method may depend on the nature of the residue as it exists after the cleaningprocess. Only if an active ingredient is *not degraded* during the cleaning process (e.g., survivinghigh temperatures and pH extremes in an aqueous environment) does it make sense to use a

specificanalytical method for that active ingredient. If a specific analytical method for an active ingredientwere utilized following a cleaning process that has been demonstrated to degrade that active ingredient,it is likely that residues of the active ingredient would be nondetectable (i.e. not measurable) bythat specific analytical method. In such a case, use of a specific analytical method for the degradant oruse of a nonspecific method (such as TOC) may be considered for measuring residues in a validationprotocol. Alternatively, if limits are established for the degradation product of an active ingredient,then a specific analytical method for the degradant may be considered for use.
分析方法的选择可能取决于清洁工艺后存在的残留物的性质。只有在清洁过程中活性成分没有发生降解（例如，在经过高温和极端的 pH 之后），使用一个专属性的方法测定该活性成分才有意义；如果已知在清洁工艺中活性成分会发生降解，那么使用专属性方法检测活性成分时，可能就不会检测（测量）到活性成分。在这种情况下，验证方案中就应该考虑使用一个专属性测定降解物或采用一个非专属性方法（例如 TOC）测量残留；如果限度是按照活性成分的降解物建立的，也可以考虑采用一个专属性分析方法测定降解物。

It should be recognized that the proper use of a nonspecific analytical method may provide a morerobust demonstration of acceptable cleaning in a validation protocol, because it may have responsesfrom species other than the target residue, yet those responses must be assumed as due to the targetresidue ***(24)***. However, exceeding the residue limit using a nonspecific analytical method provides noinformation on the nature of the failure. The high analytical result may be due to responses from theactive ingredient, the excipients, the cleaning agent, and/or a combination of those species.
应该认识到，在验证方案中，使用适宜的非专属性分析方法更能证明清洁方法的耐用性，因为除了目标残留物外其他成分也会有响应，而这种响应将被假设为源于目标残留物（24）。然而，当检测结果超出限度时，使用一个非专属性分析方法无法为失败提供任何信息，偏高的检测结果可能来源于活性成分、辅料、清洁剂和/或这些成分共同作用造成的响应值。

Nothing in this Technical Report should be interpreted as saying that, as a general principle, specificanalytical methods should be used in preference to nonspecific analytical methods.
本技术报告中的任何内容都不应理解为：一般应优先选择专属性方法而不是非专属性方法。

7.3.1 Regulatory Status of Specific and Nonspecific Methods
专属性和非专属性方法的法规状况

Both specific methods and nonspecific methods have been found acceptable by regulatory authorities.However, one must be careful not to misuse an analytical method. For example, specific methods canbe misused by failing to recognize the degradation of the active ingredient in the cleaning process,and nonspecific methods can be misused by failing to attribute the nonspecific response entirely tothe residue of concern.
无论是专属性方法还是非专属性方法，监管部门都是可以接受的。然而，必须要注意不要误用分析方法。例如，如果不知道清洁过程中活性会发生降解，就可能错误地使用专属性方法；如果非专属性响应不完全源自目标残留物，则可能误用非专属性的方法。

The U.S. FDA cleaning validation guidance states that one should “Determine the specificity andsensitivity of the analytical method used to detect residuals or contaminants” ***(20)***. While some haveinterpreted this to mean that a specific analytical method should be used, a better interpretation isthat irrespective of the type of method selected, make sure it is used appropriately. The EuropeanPIC/S

recommendations state that “The analytical methods used to detect residuals or contaminantsshould be specific for the substance to be assayed….” ***(22)***. This again has been interpreted to meanthat only specific analytical methods should be used. However, it is not applied in that manner sincenonspecific methods are widely used by companies worldwide and have been accepted by the U.S.FDA and European regulatory authorities.

美国 FDA 清洁验证指南要求“对于检测残留或污染物的分析方法，应该验证其专属性和灵敏度”(20)。因此有些人认为应使用专属性的分析方法，但更恰当的说法应该是，不管使用哪种类型的分析方法，要确保能够恰当地使用该方法。欧洲 PIC/S 建议“用于检测残留物或污染物的分析方法对于被分析物应该是专属的”。这再一次被解读为应该使用专属性的分析方法。但是实际并非如此，因为非专属性方法在世界上各公司已经广泛地应用并且被美国 FDA 和欧洲药监当局所接受。

7.4 Most Commonly Used Analytical Techniques

最常用的分析技术

The focus of this section is to discuss the most commonly used analytical procedures in pharmaceuticalcleaning validation ***(25)***. The Task Force believes it was more appropriate to focus on commonuses of analytical methods, based on the stages of cleaning validation where they have been demonstratedto provide relevant information. The features, benefits and limitations of methods are oftensituational and are therefore not covered here.

这一节中我们所要讨论的焦点是清洁验证中最常用的分析方法（25）。专家组认为应基于清洁验证的各个阶段所提供的相关信息，选择常用的分析方法。方法的特性、优点和局限性经常因使用的条件而不同，因此本文不再赘述。

Additional considerations in selecting methods are listed below:

选择方法还要考虑以下内容：

• Availability of instrumentation

可用的仪器

• Speed of analysis

检测的速度

• Specificity of technique

检测技术的专属性

• Sampling limitations (including sampling solvents)

取样限制（包括取样溶剂）

• Detection/quantitation limit

检测限/定量限

• Linearity of response

响应值的线性

• Online adaptability

能否在线检测

• Cost

费用

Most applications in pharmaceutical cleaning validation involve quantitation of residues over a validatedrange. However, in certain situations, pass-fail tests, also known as “go-no go” testing, may beused to establish that the residue is below the acceptance limit. Such testing may be used in

qualificationruns for clinical manufacture (where the effort to fully validate an analytical method over a linearrange may be costly) or for routine monitoring and equipment release based on final rinse solventtesting. A pass-fail test generally does not demonstrate the robustness of the cleaning process unlessthe pass-fail point is significantly below the desired acceptance limit. Since the transition point is arange, the range must be known and its relationship to the limits must be established in the validationprocess. The actual result, although passing, could have been very close to failure and with normalplus/minus variation it could actually represent a failed result.
在制药清洁验证最多的应用是在一已验证范围内定量测定残留物的量。然而，在一些特定的情况下，合格-不合格检测，也被称为“放行-不放行”检测，也可用来检测残留物是否在可接受限度之下。这种检测可以用于临床生产的确认批（如果在线性范围内进行全面验证则成本可能较高）或用于例行监测和设备放行（基于最终淋洗液的检测结果）。合格-不合格检测通常不能证明清洁工艺的耐用性，除非合格-不合格点远远低于所需的可接受限度。由于该转换点是一个范围，因此这个范围必须是已知的，并在验证过程中建立该范围与限度之间的关系。实际的结果，尽管是合格的，可能与不合格结果是非常接近的，考虑到结果的正负误差，可能实际上就已经是不合格的结果了。

For more information on analytical method use in biotechnology manufacture, please consult PDATechnical Report No. 49, *Points to Consider for Biotechnology Cleaning Validation **(2)***.
对于生物制药企业的分析方法的更多信息请参考 PDA 技术报告第 49 号，《生物技术清洁验证要点》（2）。

7.4.1 Liquid Chromatography (LC)
液相色谱法（LC）

LC includes HPLC (High Performance Liquid Chromatography), UPLC (Ultra Performance LiquidChromatography, and TLC (Thin Layer Chromatography). All these methods involve the separationof component by a chromatography procedure and then the measurement of one or more separatedspecies. For HPLC and UPLC, the measurement is typically ultraviolet (UV) detectors, although otherappropriate detectors may be used based on the analyte of interest.
液相色谱法包括 HPLC（高效液相色谱）、UPLC（超高效液相色谱）和 TLC（薄层色谱）。所有这些方法都是通过色谱方法先将各组分分离，再测定各分离组分的量。对于 HPLC 法和 UPLC 法，通常都是采用紫外（UV）检测器进行的测定，根据待测物也可以选择其他适宜的检测器。

HPLC and UPLC methods are typically specific methods, which are widely used for measurementof active ingredients in small molecule-manufacturing (both API and drug product manufacturing).In many cases, HPLC/UPLC methods have been previously developed as a potency assay methodfor the active ingredient, and only need minor modification to make the method suitable for use as amethod for residue determination in qualification runs. Those additional modifications may involveconfirming that the useful range is suitable for residue determinations and that additional “expectedinterferences” that are present in the cleaning system do not interfere with measurement of the activeingredient. HPLC/UPLC methods may not be suitable for measuring residues of an active ingredientif the active ingredient is degraded in the cleaning process, unless the chromatography conditions allowseparation and measurement of degradants of interest.
HPLC 法和 UPLC 法通常为专属性方法，被广泛应用于小分子生产（包括 API 和制剂）中活性成分的测定。多数情况下，HPLC 法/UPLC 法已经被开发成活性成分的含量测定方法，只需要做小的修改即可用于确认时残留物的测定。这些额外的修改包括确认线性范围是否适用于残留物的测定，以

及在清洁系统中存在的“预期的干扰物”是否会干扰活性成分的测定。如果活性成分在清洁过程中发生降解，那么 HPLC 法/UPLC 法可能就不适用于测定活性成分的残留，除非该色谱条件可以将降解物分离并测定出来。

TLC methods may be used for various stages for cleaning of small molecules. For example it may beused for design/development to confirm and characterize degradation of the active. TLC methodsmay also be used for any investigation (at any stage of cleaning validation) to characterize residues.
TLC 方法可以应用于小分子化合物清洁的各个阶段。例如，它可以用于设计/开发阶段以确认和定性活性成分的降解情况。TLC 方法也可以用于调查（在清洁验证的各个阶段）以定性残留物。

7.4.2 UltraViolet/Visible Spectrophotometry (UV/Vis)
紫外/可见分光光度法（UV/Vis）

UV/Vis involves measuring transmission/absorbance of a specified wavelength of light by a solventsolution of the residue. It typically requires a chromophore in the molecule, although it is also possibleto modify the residue to produce a chromophore. For example, it is commonly used in smallmoleculemanufacturing, particularly for API manufacturing where it is not necessary to separate itfrom a matrix to quantify the residue. Because of its simplicity, UV/Vis techniques may be used in thedesign/development, qualification and validation maintenance stages of cleaning validation as well asfor any investigations. UV/Vis has also the possibility of being used in PAT applications for completionof the cleaning steps for small molecule API manufacturing ***(26)***.
紫外/可见分光光度法是通过在特定波长下测定残留物溶液的透过率/吸收值来进行测定的。它通常要求分子中存在一个生色基团，也可以通过衍生法使残留物产生一个生色基团。例如，紫外/可见分光光度法通常被小分子化合物生产企业特别是 API 生产企业所采用，它不需要将残留物分离出来进行定量。由于该方法比较简便，因此可以应用于清洁验证的设计/开发、确认和验证维护阶段，以及各种调查中。紫卜 /可见分光光度法在小分子 API 生产中也可以作为 PAT 技术判断清洁步骤的终点。

7.4.3 Total Organic Carbon (TOC)
总有机碳（TOC）

TOC is applicable to any residue containing significant amounts of organic carbon. The TOC methodis based on oxidizing the carbon present and measuring the carbon dioxide produced. Oxidizingmethods include UV, persulfate, and combustion. Techniques for measuring the generated carbondioxide include conductivity, membrane-based conductivity and infrared. Both online and offline applications
of TOC are possible.
TOC 法可以用于含有大量有机碳的残留物的检测。TOC 法是通过将样品中的碳氧化并测定所生产的二氧化碳的含量来完成的。氧化的方法包括紫外法、过硫酸法和燃烧法，检测产生的二氧化碳的技术包括电导率法、基于膜的电导率法和红外法。在线和离线的 TOC 都是可行的。

For use of TOC, the target residue must have adequate aqueous solubility for the intended purpose.The most common way of applying the TOC method to a cleaning validation testing strategy is toassume that all residues detected are due to the target residue ***(24)***. In manufacturing situations, TOCis commonly used for measuring residues if the target residue (e.g., the active ingredient) is degradedduring the cleaning process. However, it may also be used in situations where the active is not degraded.The rationale for use of TOC in such situations is ease of analytical method development andthe worst-case assumptions inherent in TOC analysis.

对于使用 TOC 法，目标残留物必须具有足够的水溶性。用于清洁验证的 TOC 法通常是将所有的检测到的残留物都假设成目标残留物。在生产过程中，如果目标残留物（例如活性成分）在清洁过程中会发生降解，则 TOC 法是常用的方法。然而，TOC 法也可以用于那些活性分成不发生降解的情况，在这种情况下使用 TOC 法的理由是分析方法易于开发，而且在 TOC 检测中最差条件的假设是始终存在的。

TOC may be used for all stages of cleaning validation, including design/development, qualificationand validation maintenance as well as for investigations.
TOC 也可以用于清洁验证的各个阶段，包括设计/开发、确认和验证维护，以及调查。

7.4.4 Conductivity

电导率

Conductivity measurement is a method to detect dissociated ionic substances in water samples. Forqualification protocols conductivity readings are expressed in micro-Siemens/cm (μS/cm); for controland monitoring of the cleaning solution, conductivity readings are expressed as milliSiemens/cm(mS/cm). It is often used to measure cleaning agent residues (e.g., caustic or acidic agents) and to controlcleaning agent concentration in automated cleaning processes (e.g., CIP). Conductivity readingsare highly influenced by the sample temperature. Temperature adjustment of the sample, automatedtemperature compensation or a conductivity/concentration curve at a specified temperature can beused to standardize the measurements.
电导率测定是通过测定水溶液样品中解离的离子物质来完成的。在确认方案中，电导率读数表示为微西门子/厘米（μS/cm）；用于清洁溶液的控制和监测时，电导率表示为毫西门子/厘米（mS/cm）。电导率法经常被应用于清洁剂残留（例如碱性或酸性试剂）的检测，以及在自动清洁工艺（例如 CIP）中控制清洁剂的浓度。电导率的读数受样品温度的影响很大，样品温度的调整、自动温度补偿以及指定温度的电导率/浓度曲线可以用于测量结果的校正。

To allow correlation of conductivity readings with concentrations of cleaning agent, a dilution curve(conductivity vs. concentration) should be established (at a relevant temperature) by conductivitymeasurements of different dilutions in the relevant range near the acceptance value.
为了将电导率读数与清洁剂的浓度相关联，应建立特定温度下的稀释曲线（电导率对浓度），这可以通过测定特定温度下接近可接受标准的不同稀释浓度的电导率完成。

Conductivity is a nonspecific method that correlates linearly (within a defined range) to the ion concentrationin an aqueous sample. Analytical instruments are robust and can be used on the manufacturingfloor by trained personnel. The method cannot differentiate between different ions. Therefore,as with TOC, all conductivity results above the water baseline should be attributed to the contaminantin question (e.g., the cleaning agent).
电导率是一种非专属性的方法，它在一定范围内与样品溶液的离子浓度线性相关。分析仪器耐用，而且接受过相应培训的人员可以在生产车间进行检测。该方法不会区分不同的离子，因此如同 TOC 一样，所有超过水的基准电导率的结果都是由于污染造成的（例如清洁剂）。

Conductivity is often a function of alkaline or acidic cleaning agent. Measuring conductivity is a goodmeasure of the completion of rinsing, and therefore an indirect measure of good cleaning for routinemonitoring of a cleaning process.

电导率通常说明了碱性或酸性清洁剂的存在，测量电导率是一种判定冲洗终点的好方法，因此对于清洁工艺的日常监控，测量电导率也是间接证明清洁效果的好方法。

Conductivity can also be used for measuring residues of an ionic active ingredient, either in caseswhere the cleaning agent is water alone or in other cases involving ionic cleaning agents if all theconductivity response is attributed to the active ingredient (even though some of the response maybe due to the cleaning agent).
电导也被用于测定离子型活性成分的残留，不管是单独以水为清洁剂，还是使用了离子型清洁剂，只是所有的电导率响应值都应作为活性成分的响应值（即使其中的一些响应值源自清洁剂）。

7.4.5 Organoleptic Evaluation

感观评价

“Organoleptic” evaluation includes visual inspection as well as other evaluations such as smell. Visualinspection is commonly used during all stages of cleaning validation, as it is a minimum requirementunder GMPs for use of equipment for manufacture. Visual inspection is a nonspecific method in thatthe nature of the residue generally cannot be identified except by further analysis.
“感观”评价包括目视和其他评价，例如嗅觉。目视检查通常在清洁验证的各个阶段都有使用，因为目视洁净是生产设备符合 GMP 的最低要求。目视检查是一种非专属性方法，除非做进一步分析，一般无法鉴定残留物的性质。

Training and a detailed documented procedure is required to ensure that “visually clean” from oneoperator to the next is consistent. What one can visually see will vary with distance, angle, lighting,nature of surface, and inspector’s visual acuity. Some equipment surfaces (e.g., piping) are usually notaccessible for visual inspection. The use of optical equipment like mirrors, remote videoscopes, orborescopes can help to facilitate visual inspection.
需要进行培训并建立一个详细的文件，确保不同人员的“目视清洁”是一致的。目检结果受距离、角度、光线、表面的性质，以及检查人的视力影响会有很大不同。使用光学设备例如镜子、远程光纤视镜或管道镜可有助于目视检查。

The visual inspection procedure should specify how operators are to deal with visual observations.Visual inspection may find four different types of visual observations: residue, surface anomalies,foreign object and water. Residue is the *main* concern which would constitute a visual failure whenone is assessing the acceptability of a cleaning cycle. A sample of the residue should be collected forfurther testing, if possible, to assist in the investigation of the cause. Typically, surface anomalies andforeign objects are not considered visual inspection failures for cleaning validation purposes, but mustbe further investigated and corrected, as applicable. Surface anomalies should be noted and a “suitabilityfor use” assessment should be performed to remediate any issue(s) found. Rouge is the mostcommon type of surface anomaly discovered during visual inspection; rouge is generally considereda preventive maintenance problem, not a cleaning process problem. Foreign objects and their removalshould be documented. Also, how the foreign object came to be in the equipment should be investigated.Sometimes a distinction is made between absence of water pooling (“free drained equipment”)and the absence of any visible water droplets (“dry equipment”). Particularly for water pooling, theobservation should be documented, the cause investigated, and the impact on issues such as visualexamination and bioburden proliferation on storage should be addressed.

目视检查程序应当明确检查者怎样处理观察结果。目视检查可以发现四种不同类型结果：残留物、表面异常、异物和水。残留物是主要关注点，当评估清洁行程是否合格时，发现残留物就可能意味着目视检查结果的失败。如果可能的话，应收集样品残留做进一步检测，以协助调查可能的原因。通常，在清洁验证中出现表面异常和异物时，不认为目检结果不合格，但必须进行进一步调查和纠正。应记录表面异常情况，评估“是否适合使用”，并纠正发现的各种问题。红锈在目视检查中是一种最常见的表面异常，它往往被认为是一种预防性维护问题而不是清洁工艺问题。异物及其去除应被记录下来。同样，异物是怎么进入到设备当中也要进行调查。有时应区分无积水（“自排水设备”）和无可视水滴（“干燥设备”），特别是对于积水，应记录观察结果，调查原因，并说明其对目视检查以及贮存过程中的微生物增长的影响。

All equipment surfaces should be visually inspected if possible. Visual inspection may not be performedon the interior of lines and tubing (although outlets may be inspected) on equipment wheredisassembly of the equipment is not practical or possible, or where inspection of the equipment couldpotentially be dangerous to the inspector (e.g., entry into a confined space).
如果可能的话，所有的设备表面被应该进行目检。当无法或不宜拆卸设备时，或者对设备进行目检可能造成人员伤害（如，进入限制性空间）时，可能无法对安装在该设备上的管线和管道内部（尽管可以对出口处进行观察）进行目检。

A training program should be developed for visual inspection. Inspectors typically should be trainedand/or requalified on an established basis. If visual inspection is not possible on an area of concern,it is important to ensure that other sampling methods (such as rinse sampling) can adequately detectpotential residues of concern.
应建立目检培训计划，检查人员应按照要求接受培训和/或进行资格确认。如果对于一些区域无法进行目检，则应确保他取样方法（例如冲洗取样）能够充分地检测出潜在的目标残留物。

Smell as an organoleptic method is generally only used if an unusual smell occurs during sampling ofthe equipment, which would suggest the need for an investigation.
作为一种感观方法，嗅觉检查通常只用于设备取样时有一种特殊气味，应对此进行调查。

7.5 Other Useful Analytical Techniques
其他有用的分析技术

Below are other techniques which may be useful for various stages of cleaning validation.
以下其他技术可能用于清洁验证的不同阶段。

7.5.1 pH

pH is a measure of the hydrogen ion concentration. It can be used as a monitoring process check,particularly when equipment is stored wet in a preservative solution (typically acid or base). pH canalso be used to verify qualitatively the presence of the correct cleaning solution. pH can be used tocomplement conductivity measurements. However, pH is less useful than conductivity for measuringresidues of alkaline or acidic cleaning solutions because pH has a logarithmic relation with hydrogenion concentration, whereas conductivity has a direct, linear relationship with ions. Furthermore,there is not necessarily a direct correlation of conductivity and pH, particularly for neutralized cleaningagents.
pH 是一种测量氢离子浓度的技术，它可以作为工艺监测手段，特殊是当设备贮存在防腐溶液中（通

常为酸性或碱性）时。pH 法也可以用于定性确认是否存在正确的清洁溶液。pH 法也可以作为电导率测量的补充，然而在测量碱性或酸性清洁剂残留时，pH 法不如比电导率法，因为 pH 值与氢离子浓度呈对数关系，而电导率与离子浓度是直接线性相关的。此外，也没有必要将电导率与 pH 值直接关联，特别是对于中性清洁剂。

7.5.2 InfraRed (IR)

红外光谱法（IR）

This includes both FTIR (Fourier Transform InfraRed) and NIR (Near InfraRed). These techniquesare most useful in an investigation where there is a need to identify organic residues that may be present.FTIR has also been combined with a fiber-optic probe for direct quantitative measurement ofresidues on surfaces for qualification protocols ***(27)***.

红外光谱法包括 FTIR（傅立叶变换红外光谱法）和 NIR（近红外光谱法）。当调查中需要对可能存在的有机残留进行鉴别时，这些技术最为有用。确认过程中，可采用 FTIR 联合光纤探头直接测定设备表面残留物的量。

7.5.3 Light Microscopy

光学显微法

Light microscopy, including Scanning Electron Microscopy (SEM), is a method of identifying contaminantson equipment surfaces. In many cases, conventional light microscopy and SEM can becombined with other analytical techniques, such as x-ray diffraction, mass spectrometry, and nuclearmagnetic resonance (NMR). Microscopic techniques alone may identify the physical nature of a residuebut not the chemical nature. One of the practical applications of microscopy is in the evaluationand identification of unknown contaminants on new or used equipment. These techniques are especiallyvaluable in the evaluation of residues in an investigation.

光学显微法包括扫描电镜法（SEM），它是一种可以鉴定设备表面污染物的方法。大多情况下，传统的光学显微法和 SEM 可以与其他分析技术联合使用，例如 X-射线衍射、质谱和核磁共振（NMR）。单独的显微技术可以鉴定残留物的物理性质，但不能鉴定其化学结构，显微法的一个实际的应用是用于评估和鉴定一个新的或旧的设备中的未知污染物，这些技术对于在调查中评估残留物是特别有价值的。

7.5.4 Titrations

滴定法

Titration is another simple analytical method that is often overlooked even though it might providevaluable information in the proper cleaning situation. Titrations may be specific (orthophosphateions) or nonspecific (e.g., for all anionic surfactants). This method is more likely to be used for alkalineor acidic cleaning agent analysis in qualification runs.

滴定法是另一种简单但经常被人忽视的方法，尽管其在适宜的清洁情况下它可以提供有价值的信息。滴定法可能是专属性（磷酸盐）或非专属性（例如，对于所有的阴离子表面活性剂）方法，本方法可能更多地用于确认过程中碱性或酸性清洁剂的检测。

7.5.5 Gravimetric Analysis

重量分析法

Gravimetric analysis can be useful for design/development studies and for qualification runs. It ismost commonly used for determining residues in small-molecule API synthesis where a larger volumeof a

solvent rinse or solvent reflux is evaporated to dryness.
重量分析法可以用于设计/开发和确认中。它多应用于测定小分子 API 合成过程中的残留物，通过将大量冲洗溶剂或回流溶剂蒸干而测得。

7.5.6 Enzyme Linked Immunosorbant Assay (ELISA)
酶联免疫分析法（ELISA）

An ELISA assay is an antigen-antibody type reaction involving the use of specific chemicals developedespecially for the residue involved. Its use is generally limited to biotechnology and biologics manufacturewhere it can be used in the design/development stage to confirm degradation of the activeingredient and in any investigations.
酶联免疫分析法是一种抗原-抗体反应，使用特定的化合物测定残留物。酶联免疫分析法通常局限于生物技术和生物制品生产中，可以用于设计/开发阶段以确认活性成分的降解，以及任何调查中。

7.5.7 Capillary Zone Electrophoresis (CZE)
毛细管区带电泳（CZE）

Also known as capillary electrophoresis (CE), this technique separates residues by charge and frictionalforces in an electrical field. Detection is usually with a fluorescence detector. CZE has been appliedmostly in the biotechnology industry for active ingredients and degraded active ingredients where itcan be used in design/development and qualification stages as well as in investigations.
毛细管区带电泳又被称为毛细管电泳，这项技术是依靠电场里的电荷和摩擦力将残留物进行分离的，通常采用荧光检测器进行检测。CZE 主要被应用于生物技术工业中，在设计/开发及确认阶段检测活性成分及其降解物，以及用于调查。

7.5.8 Atomic Absorption (AA) and Inductively Coupled Plasma (ICP)
原子吸收法（AA）和电感耦合等离子体

Both of these techniques can be used for measuring metals in solution, where the metal is part of aformulation or for unknown residues, such as suspected rouge.
这两种技术都可以用于溶液中的金属，这种金属可以是是处方中的一部分或未知残留物（例如疑似红锈）。

7.5.9 Ion Mobility Spectrometry (IMS)
离子迁移光谱（IMS）

This technique is a type of mass spectrometry which only provides information on the time of flightof the analyzed species. It has been promoted for its short analysis time (a few minutes). It may havemore application for routine monitoring and release.
这项技术是质谱的一种类型，它只提供被分析样本的飞行时间。由于其分析时间较短（几分钟）而被提倡，可以更多地用于日常监测和放行。

7.6 Microbial Test Methods
微生物检验方法

The 1993 U.S. FDA cleaning validation guidance states that “Control of the bioburden through adequatecleaning and storage of equipment is important to ensure that subsequent sterilization or sanitizationprocedures achieve the necessary assurance of sterility”***(20)***. The PIC/S recommendationscall for “the validation of cleaning procedures for the removal of contaminants associated with theprevious

products, residues of cleaning agents as well as the control of potential microbial contaminants”***(22)***. Control of microbial residues is thus an important part of cleaning validation. Microbialresidues include bioburden and endotoxin. Typically bioburden sampling and analysis is performedduring cleaning validation protocols unless there is a documented science-and risk-rationale for omittingsuch sampling and analysis. Science-and risk-based rationales for excluding microbiological testingin protocols may include manufacturing considerations, such as all solvent processing for smallmoleculeAPI manufacture, use of a final alcohol rinse for oral dose drug products, use of subsequentsterilization cycles, and/or demonstration of adequate microbial control in sufficiently similar cleaningprocesses.

1993 年美国 FDA 清洁验证指南中指出“通过充分地清洁和设备存放以控制生物负载，这对确保随后的灭菌和消毒程序达到必要的无菌保证水平是非常重要的”（20）。PIC/S 指南要求“清洁程序的验证内容应包括去除前一产品、清洁剂的残留所带来的污染，以及潜在微生物污染的控制”（22）。因此微生物残留的控制也是清洁验证的一个重要部分。微生物残留包括生物负载和内毒素。通常清洁验证方案中应包含生物负载取样和检测，除非有科学的和基于风险的书面理由表明不需要进行，这可能包括生产上的考虑，例如小分子 API 生产中所有使用溶剂的工艺、口服制剂生产中使用乙醇进行最终淋洗、清洁之后进行灭菌，和/或有证据表明类似的清洁工艺能够对微生物有充分的控制。

7.6.1 Endotoxin

内毒素

Typically, endotoxin testing is performed for cleaning validation runs if the next product has endotoxinspecifications. Endotoxin analytical methods are typically compendial methods. Science-andrisk-based rationales for excluding endotoxin testing in protocols may include manufacturing considerations,such as all solvent processing for small-molecule API manufacture, use of a validatedendotoxin reduction step, and/or demonstration of adequate endotoxin control in sufficiently similarcleaning processes.

通常如果下一个产品质量标准中有内毒素检查项的话，应在清洁验证中进行内毒素检测。内毒素分析方法通常是药典方法。验证方案中不进行内毒素检测需要科学的和基于风险的理由，这可包括生产上的考虑，例如小分子 API 生产中所有的使用溶剂的工艺，有经验证可以减少细菌内毒素的操作步骤，和/或有证据表明类似的清洁工艺能够充分控制内毒素。

7.6.2 Bioburden

生物负载

Testing of bioburden is done through rinse-water sampling, swab sampling and contact plate sampling. Rinse-water sampling typically involves membrane filtration, placement of the membrane onan appropriate agar, incubation, and a count of CFUs. The main rationale for rinse-water samplingfor bioburden is that it provides an overall picture of equipment cleanliness. Also, bioburden testingof rinse water is typically already a qualified method for testing water systems for bioburden. Thebiggest weakness of rinse-water sampling and membrane filtration is that the full range of the acceptancecriteria is not able to be utilized. For example, if 100 ml of rinse water is used for testing with anacceptance criteria of 100 CFU/mL. The typical number of colonies that can be counted is 300 beforeToo Numerous To Count (TNTC) is achieved; this only allows an acceptance criterion of 3 CFU/mLbefore failing to demonstrate that the acceptance criterion is met. In most situations this is not an issue;it may result in the need to test smaller sample volumes (or diluted samples). An alternative is toperform spread-plate or pour-plate microbiological analyses.

生物负载的检测可以采用淋洗水取样、棉签擦试取样和接触碟取样。淋洗水取样后一般采用薄膜过

滤法过滤，再将膜贴在适宜的琼脂培养基上，培养、计数。淋洗水取样检测生物负载的优点是它可以提供设备清洁状况的全景信息。淋洗水生物负载检测通常采用水系统微生物的检测中已确认的方法。淋洗水取样/薄膜过滤检测的最大缺点是没有一个普遍适用的可接受标准。例如，如果取 100ml 淋洗水用于检测，可接受标准为 100CFU/ml，而通常可以计数的菌落数应不超过 300，这就要求如果符合计数标准要求的话样品的可接受标准应为 3CFU/ml。在大多数情况下这并不是问题，可以通过降低样品的取样体积（或稀释样品）来解决。也可以是采用涂布平板阀或倒平板法进行微生物检验。

Two methods for directly measuring on surfaces are swab and contact plate. For swab samples, theswab can be desorbed and a count made by a pour-plate or spread-plate method. Contact plates aredirectly incubated and enumerated. The biggest concern with contact plates and swab procedures ispotentially exposing product contact surfaces to an unknown media or buffer solution from swabs;thus acceptable removal of this media or buffer solution should be demonstrated before manufacturingcan occur. Another concern is that contact plates require flat surfaces.
还有两种可以直接测量表面上生物负载的方法是棉签擦试法和接触碟法。对于棉签擦试法，应将棉签上的菌释放出来，通过涂布法或倾注法进行计数。接触碟法则可直接培养并计数。接触碟法和棉签擦试法最大的问题是可能将产品接触表面与未知培养基或棉签中的缓冲溶液相接触，因此在生产前应确认培养基或缓冲溶液是否已清除。接触碟法的另一个问题是需要设备表面是平整的。

Most companies use analytical techniques for bioburden involving incubation in an appropriate mediumand counting of CFUs. Such a procedure has the disadvantage of only providing a number forCFUs and not individual cells. Sampling and processing of the test sample may affect the reportednumber of CFUs due to disruption of aggregated cells. In addition, while it is common to reportbioburden counts below 20 CFU as quantifiable numbers, it is recognized that enumeration below 20CFU is not scientifically established. Another alternative is to use rapid instrumental microbiologicalprocedures. PDA Technical Report 33, *Evaluation, Validation and Implementation of New MicrobiologicalTesting Methods* should be consulted for a discussion of rapid methods ***(28)***.
大多数公司生物负载检测，需要在适宜的培养基中培养并计数。这种方法的缺点是只能提供菌落数而不是单个细胞数量。由于可能会破坏细胞，取样和检验可能影响报告的计数结果。另外，虽然生物负载报告结果通常小于 20CFU，但一般说来计数结果如果低于 20CFU，则说明你建立的方法是不科学的。另外一种方法是使用快速仪器法检测微生物，PDA 技术报告 33《新微生物检验方法的评价、验证和执行》可以作为讨论该快速检验方法的参考。

7.7 Analytical Method Validation
分析方法验证

This section focuses on analytical method validation for “chemical” residues. Typically endotoxinmethods are compendial methods and do not require formal validation but require a confirmation fortheir application of use or suitability. Microbial methods that are approved microbiology laboratorymethods do not require additional method validation.
这一节我们关注“化学”残留的分析方法验证。通常内毒素检验方法都是药典方法，不需要进行正式的验证，但需要确认其适用性。经批准的微生物检验方法也不需要额外的方法验证。

7.7.1 General Principles
一般原则

Since one key part of cleaning validation is setting residue limits and then measuring (using an analyticalmethod) the actual residues left on surfaces after cleaning, it is critical that the analytical methodbe appropriately validated. Method validation is typically accomplished using the criteria in ICH Q2(R1) ***(29)***. However, the types of assays listed in ICH Q2 do not explicitly cover cleaning validationmethods. One approach is to essentially validate analytical methods, much like an "Assay" in ICH Q2,establishing accuracy, precision, specificity, linearity and range, with added determination of limit ofquantitation/ limit of detection (LOD/LOQ). LOD/LOQ must be below the acceptance limit for thesample, and ideally is significantly below the acceptance limit so that the robustness of the cleaningprocess can be established. In addition to the ICH Q2 parameters, sample stability as a function ofstorage conditions (time, temperature, vial for storage, etc.) may be evaluated if there is a significantinterval between sampling and analysis. Specific methods should address possible interferences fromother species, such as cleaning agents, which might occur only in the cleaning process.
由于清洁验证的一个关键点就是确定残留限度，然后再测定（通过分析方法）清洁后残留在设备表面的残留物，很关键的一点就是分析方法应经过适当的验证。通常方法验证应按照 ICH Q2（R1）（29）进行。然而，在 ICH Q2 中所列出的含量测定的验证并没有明确涵盖清洁验证中的分析方法。一种方法是按照 ICH Q2"含量"进行全面的验证，包括准确性、精密度、专属性、线性和范围，以及定量限（LOQ）/检测限（LOD）。LOD/LOQ 必须低于样品的可接受限度，而且最好是远低于可接受限度，以确保清洁程序的耐用性。除了 ICH Q2 中规定的参数外，如果取样和检测时间间隔比较大时，应评估贮存条件（时间、温度、贮存的小瓶，等）对样品稳定性的影响。专属性方法应关注可能只有在清洁工艺中使用到的其他物质（例如清洁剂）可能带来的干扰。

In cases where a nonspecific method is utilized, it is not necessary to compensate for the lack of specificity by "other supporting analytical procedures" (as suggested in ICH Q2). The reason for this isthat for cleaning validation purposes, the limit value is not a target (as it is for a potency assay); ratherthe limit is a value *not to be exceeded*. As long as these other species that contribute to the nonspecificresponse do so in a positive manner (thus increasing the response value), and as long as the total measuredvalue is attributed to the target residue, such complementary methods suggested by ICH Q2are not required. Furthermore, it is not required to correlate nonspecific methods with a specific analyticalmethod except to the extent that accuracy in the method validation of the nonspecific methodmay be established using a known standard where the concentration or activity is established by aspecific analytical method. While Detection Limit and Quantitation Limit are not part of the "Assay"requirement in ICH Q2, it is critical that these values be at or below the pre-established limit for theresidue (otherwise it would not be possible to claim that residues were below predetermined limitvalues). However, it is not necessary to drive detection or quantitation limits as low as possible; havingdetection or quantitation limits of 10% or less of the residue limit in the analytical sample is ideal(but not always possible) to establish the robustness of the cleaning process. Assay capability shouldtake into account both the target/limit and the process capability, and provide relevant measurementsfor both.
当采用非专属性方法时，没有必要采用"其他分析方法"（ICH Q2 的建议）对缺少专属性进行补偿，这是由于对于清洁验证而言，限度值不是一个目标（如需要精确测定的含量），而是不能超出该限度值。只要其他物质是增加非专属性响应值的，而且只要总的响应值都归结于目标残留物，那么 ICH Q2 中所建议的补充方法就是不需要的。而且，也没有必要用一个专属性方法去关联非专属性方法，除了非专属性方法验证中准确性研究可能采用一个已知标准物质，而该标准物质的浓度或活性是采用一个专属性方法建立的。尽管 ICH Q2 中对于含量测定的验证并不需要确定检测限和定量限，关键是检测限/定量限应接近或低于设定的残留物限度（否则你很难说明测得的残留物是低于限度值

的)。然而，也没有必要让检出限或定量限过低，为了建立具有耐用性的清洁工艺，理想的检测限或定量限应不超过残留限度值的 10%（但这并不总是可能的)。含量测定应同时考虑目标值/限度和工艺的能力，并提供相应的测定结果。

When performing carryover calculations it should be ensured that the analytical methods that will beused for cleaning validation are sensitive enough to meet the acceptance criteria. To provide reliableresults for carryover calculations, the results should be equal to or above the LOQ. Results betweenthe LOQ and the LOD typically show a higher-than-acceptable variation of the results obtained andare typically reported as less than LOQ.
在进行残留计算时，应确保用于清洁验证的分析方法足够灵敏，以符合可接受标准。为了获得可信的残留量，检测结果应等于或大于 LOQ。在 LOQ 和 LOD 之间的检测结果，通常具有过高误差，一般报告为低于 LOQ。

For companies that use a pass/fail analytical method for meeting cleaning validation limits, analyticalmethod validation is less extensive. In such a procedure, the only conclusion of the analyticalprocedure is whether the experimental sample is less than or equal to or above the pass/fail value.Accuracy and precision are typically performed only at the residue limit but linearity and range arenot performed. Note that in this case, the pass/fail value selected should take into consideration anyapplicable correction factor due to the sampling method recovering less than 100% from the surface.Such pass/fail methods do not allow collection of relevant data to support a process capability determinationto establish action or alert levels for routine monitoring. Pass/fail analytical proceduresare more likely to be used in manufacture of early clinical trial materials where a cleaning verificationmode is employed. However, such methods can also be used for qualification runs and for routinemonitoring.
对于使用合格/不合格方法来进行清洁验证的公司，不需进行全面的分析方法验证。在该方法中，只需要报告样品的结果是低于或等于或高于合格/不合格限度值。准确性和精密度的验证通常只需要在残留限度水平进行，不需要进行线性和范围的验证。注意在这种情况下，合格/不合格限度值的选择应考虑从设备表面取样时的回收率低于 100%时，需要进行适当的校正。如果想通过收集相关数据建立警戒限或行动限进行日常监测以说明清洁工艺的能力，则不能使用这种合格/不合格的方法。合格/不合格分析方法可能更多地用于需要进行清洁效果确认的早期临床产品的生产，然而这类方法也可以用于清洁确认和日常监测中。

Analytical method validation protocols may only include validation of the residue in solutions. It mayalso include sampling recovery studies, although those sampling recovery studies may be performedas separate studies apart from the analytical method validation.Acceptability of variability of results for parameters, such as accuracy and precision for chemicalmethods at typical residue levels, are generally much broader than in a typical potency assay. Relativestandard deviation (RSD) requirements of 15-20% are typical.
分析方法验证方案可以只包括残留物溶液的验证，也可以包括取样回收率研究，尽管取样回收率研究可以独立于分析方法验证而单独进行。各验证项目（例如在一典型的残留物水平化学方法的准确性、精密度）的结果的变动范围一般要远宽于含量测定的要求，通常相对标准偏差（RSD）要求为 15-20%。

7.7.2 Compendial Methods
药典方法

Compendial methods do not require separate analytical method validation provided those methodsare used

within the parameters in the compendia. For example, a compendial method for endotoxinis generally appropriate for measuring endotoxin in final rinse water samples. However, suitability ofuse of compendial methods should be addressed.
在规定的参数范围内使用药典方法不需要再单独进行分析方法验证，例如使用药典测定内毒素的方法就可以用来测定最终淋洗水中的内毒素。然而，应该说明使用药典方法的适用性。

When using swab or rinse samples with a compendial analytical method, items that should be considered for suitability of use include the validated range, possible interferences from the cleaning process,possible interference from the swab, and recovery of residue from the swab (see **Section 6.1.3).**
当使用药典方法检测棉签擦拭或淋洗样品时，需要考虑方法的适用性，包括验证的范围、清洁工艺可能带来的干扰、棉签的干扰和从棉签回收残留物时的回收率（见 6.1.3 节）

When using TOC in rinse-water samples (a compendial method), additional work should be done tosupport its applicability for test samples where the TOC values could be above 500 ppb or where alinear range is to be established. Just performing system suitability as specified in the USP requirementmay not be adequate to demonstrate that the TOC analytical procedure could accurately analyzesamples at 1 ppm or 5 ppm. For that reason, analytical method validation as for any other methodshould be considered. An additional reason for formal method validation for TOC in rinse-watersamples is that the USP method is essentially set up as a pass/fail test, not as a quantitative assay.
使用 TOC（一种药典方法）测定淋洗水取样时，如果 TOC 的结果可能大于 500ppb 或需要建立线性范围时，仍需要做一些额外的工作以证明该 TOC 方法适用于测试样品。只是按照 USP 要求进行系统适用性测定，不能充分证明 TOC 方法可以准确测量浓度为 1ppm 或 5ppm 的样品。因此，可以考虑其他方法和方法验证。另一个使用 TOC 测定淋洗水样品需要进行正式方法验证的原因是 USP 方法实质是一种合格/不合格的测试方法，而不是一个定量的含量测定方法。

7.7.3 Visual Inspection
目视检查

Method validation in this case is actually the determination of a quantitative “visual limit” wherevisual examination is the *sole* sampling/analytical method and “visually clean” is used as the *sole acceptancecriterion* for the given residue in the *absence* of swab or rinse sampling for that residue. If visualexamination is used to supplement swab or rinse sampling, such determination of a visual limit is notrequired. A visual limit *under specified viewing conditions* can be determined by spiking coupons of theequipment surface materials with solutions of the residue at different levels (in μg/cm2) and having apanel of trained observers determine the lowest level at which residues are clearly visible across thespiked surface. The significance of such a visual limit is that if equipment surfaces are determinedto be visually clean under the same (or more stringent) viewing conditions in a cleaning validationprotocol, the level of the residue is below the visual limit. Appropriate viewing conditions includedistance, lighting and angle. The visual limit depends on the nature of the residue as well as the natureof the surface (e.g., stainless steel vs. PTFE).
对于目视检查，方法验证实际是建立一个定量的“可视限度”，而目视检查是唯一的取样/分析方法，在没有棉签和淋洗取样的情况下，“目视清洁”是目标残留物的唯一的可接受标准。如果目视检查只是作为棉签/淋洗取样的补充，则不需确定目视限度。特定观察条件下的目视限度可以通过将不同浓度的（$\mu g/cm^2$）残留物溶液涂布在材质试样表面，然后让接受过培训的观察者来确定材质试样表面上有明显可见残留的最低残留水平。这种目视限度的意义在于，在清洁验证方案相同的（或更严

格的）观察条件下设备表面如果是目视清洁的，则说明残留物的水平是在目检限度之下。适宜的观察条件包括距离、光线和观察角度。目视限度取决于残留物的性质和设备的性质（例如，不锈钢或PTFE）。

7.7.4 Bioburden Methods

生物负载法

Approved and qualified microbiological lab procedures do not require additional method validationfor use in cleaning validation programs. However, suitability for use of such methods in the presenceof cleaning process chemicals should be addressed ***(30)***.

在清洁验证中，经过批准和确认的微生物检验方法不需要进行额外的方法验证。然而，应当说明存在化学清洁剂时使用这些方法的适用性。

7.7.5 Transfer to another Laboratory and Use of Contract Laboratories

方法转移到另一个实验室和合同实验室的使用

Other laboratories (other than the laboratory that originally validated a method) can be utilized toperform an analytical method for cleaning validation purposes. In such cases, a method transfer protocolshould be established and executed to determine that the other laboratory can suitably analyzesamples using that method. If a method is developed by a contract laboratory and qualification runsamples are analyzed by that contract laboratory, then no transfer protocol is required. It is preferablethat analytical method validation protocol be reviewed and approved by the pharmaceutical companyprior to execution of that protocol. Care should be used in the transfer protocol to first determinewhether the measurements between the two laboratories are practically significant before any determinationof statistical significance is performed ***(31)***. If an analytical method has been developed andvalidated *previously* by the contract laboratory, then the pharmaceutical company should review thatprotocol and the final report to determine the acceptability of the method for its (new) intended useas well as perform an audit of the contract laboratory.

其他实验室（即不是原来进行方法验证的实验室）也可以进行清洁验证的相关检测，此时，应当建立一个方法转移方案，验证其他实验室能够采用该方法进行样品检测。如果方法是由合同实验室开发的，并且样品检测也在合同实验室进行，此时就不需要进行方法转移了。方法验证方案在执行前应得到药品生产企业的审核和批准。在方法转移方案的执行中应注意的是，在进行显著性差异判断前，首先要看看不同实验室之间测定的结果是否存在较大差异（31）。如果分析方法之前是在合同实验室开发和验证的，药品生产企业应审核验证方案和最终的报告，以确定该方法是否适用于使用目的，并进行合同实验室审计。

8.0 Maintenance of Validated State

验证状态维护

A key part of the validation lifecycle for any system is maintenance of the validated state. A variety of terms are used within the industry for those activities that follow the cleaning process design/development and successful execution of the formal validation protocols. The term used in this Technical Report for those activities is “validation maintenance”; other related terms used in the industry include “continued process verification”, “ongoing process maintenance”, “ongoing process control”,“monitoring”, and “continued process control”. Validation maintenance is critical for cleaning validation because a lapse, shift, and/or change in the validated state has the potential to adversely impact the quality, safety and purity of subsequent batches of the same or different products. The main tools for ensuring the continued maintenance of the validated state are change control, periodic monitoring and data trending review. Additionally, training is an important area of control for cleaning processes, and it is one of the primary mechanisms for controlling manual cleaning consistency.
任何系统的验证生命周期的一个重要部分是验证状态的维护。行业内有多种术语描述那些在清洁工艺设计/开发和正式清洁验证方案成功执行之后的活动。本技术报告中所使用的术语是“验证维护”，行业内使用的其他相关术语包括“持续工艺确证”和“持续工艺维护”“持续工艺控制”“监视”以及“持续工艺控制”。验证维护是清洁验证的关键点，因为已验证状态的偏离、漂移和/或变更对后续生产的相同或不同产品的质量、安全和纯度存在潜在不良影响。变更控制、定期监测和数据趋势回顾是保证验证处于持续维护状态的主要工具。此外，培训是清洁工艺的一个重要控制领域，同时也是控制手工清洁一致性的主要机制。

In each of these areas, knowledge of the operational parameters and/or design space (see Section 3.0) should be applied. Furthermore, application of risk management principles should be used for selection of validation maintenance practices for a given facility or process. Risks to be addressed include not only product quality risks. Note that for formal risk management assessments, the risk focus should be on risks to patients and product quality. However, risks related to business operations and operator safety may be the rationale for certain validation maintenance practices. For example, monitoring of conductivity in the recirculating cleaning solution line may be based primarily on quality concerns. However, provided that such monitoring of the recirculating cleaning solution is done, monitoring of detergent level in a drum may be based primarily on a business risk to prevent interruptions in manufacture. Activities (and the frequency of those activities) to be conducted during validation maintenance should be initially selected during the design/development and qualification stages. However, they may be modified based on new information and/or data collected during routine commercial manufacture. Examples of such information include newly discovered sources of variation or consistent trending data. Maintenance of the validated state should include the cleaning process and equipment, including preventive maintenance and calibration for the equipment being cleaned and the equipment used for cleaning.
应在每一领域中，应用操作参数和/或空间设计知识（参见 3.0 章）。此外，对于给定的厂房或工艺，应采用风险管理的原则选择验证状态维护工具。要解决的风险不仅仅包括产品质量风险。应该注意的是对于正式风险管理评估，应关注对患者和产品质量的风险。然而，商业运作和操作人员安全的相关风险也可作为某些验证维护操作的理由。例如，对清洁溶液循环管路电导率的监测可能主要基于质量的考虑。然而，假如已对循环管路中清洁溶液进行质量监测，那么监测桶内清洁剂的液位可

能主要是基于商业风险，以防止生产中断。在验证维护期间所要开展的活动（以及那些活动的频率）应在设计/开发和确认阶段进行初步选择。然而，可根据在商业生产中收集的新信息和/或数据对它们进行修改。这些信息可包括新发现的变异来源或趋势一致的数据。验证状态的维护应包括清洁工艺和设备，包括对被清洁设备和用于清洁的设备的预防性维护和校准。

8.1 Critical Parameter Measurement
关键参数测量

It is of utmost importance to understand the control range of critical parameters used to define thecleaning process. Typically, these include cleaning agent concentration, temperature, flow rate andtimes for all processing steps. During the design phase, an appropriate level of understanding of theprocess and its variability should be obtained to design a cleaning process capable of addressing thisinherent variability. Once the process is well defined, there are a variety of control strategies that maybe used.
理解用于定义清洁工艺的关键参数的控制范围是极其重要的。通常，这些参数包括所有操作步骤中清洁剂的浓度、温度、流速和时间。在设计阶段，对工艺及其变动性的适当理解有助于设计一个能解决这种内在的变动性的清洁工艺。一旦充分地定义了工艺，就可以使用不同的控制策略。

One control strategy is to set minimum and/or maximum values for each of the critical cleaning parametersduring a cleaning cycle. In this approach, each of the steps of the cycle has a defined provenrange or threshold (lower threshold or upper threshold) that should be measured and maintained duringeach execution of the cleaning cycle, and each parameter should be within that range or withinthat threshold. This approach has an advantage in that it is straightforward to implement and controland demonstrates proper performance of the cleaning process on each cleaning run.
其中一种控制策略是在清洁过程中设定每一个关键清洁参数的最小和/或最大值。在本方法中，清洁过程中的每一步都有经过证明的明确范围或阈值（低阈值或高阈值），在每次执行清洁程序时应对其进行测量和维护，同时每一个参数都应在该范围内或在该阈值内。本方法优点是易于实施和控制，并证明清洁工艺的每一次执行结果都符合要求。

Measurement of parameters for purpose of feedback for process control (such as process completion)is discussed separately in Section 11.3 on Process Analytical Technology.
在 11.3 章工艺分析技术章节单独讨论了用于工艺控制（如工艺完成）反馈的参数测量。

8.2 Process Alarms
工艺警报

Another practice for validation maintenance is alarming of critical parameters or events. Alarms forprocess parameters and/or events are typically based on a quality risk approach but there may bealarms based on business or safety concerns. In an automated cleaning cycle, alarms may be basedon a variety of parameters, such as temperature of the wash and rinse solutions, online analyticalresults of the recirculating wash solution, pressure at the spray device, flow through various circuits,and online analytical results of the final rinse. These are typically automated alarms, in which a lightflashes, a buzzer sounds, or the cleaning process is aborted, with the generation of a failure record.When using measurement probes for alarm purposes, the device should have appropriate accuracyand should be maintained in current calibration. There may also be other “nonautomated” alarms, inwhich observations by an operator trigger a response (e.g., visual observation by an operator that acleaning detergent drum is empty).
另外一个验证维护的做法是关键参数或事件的警报。工艺参数和/或事件的警报通常是基于质量风险，

但也有警报可能基于商业或安全考虑。在自动清洁行程中，警报可能基于多个参数，如洗涤和冲洗溶液的温度、循环洗涤液在线分析结果、喷淋装置的压力、不同的回路，以及最终冲洗水的在线分析结果。通常采用自动报警装置，发出警报时灯光闪烁、发出嗡鸣声或中断清洁工艺，并生成失败记录。用于报警的的测量探头应有适当准确性，并保持在校准状态。也可以采用其他“非自动”警报，由操作人员进行观察并触发响应（如：一位操作人员目视观察到清洁剂桶空了）。

There are a variety of approaches to cleaning the equipment on which an alarm occurred. The causeof the alarm should be investigated. This may be done as part of a Corrective and Preventative Action(CAPA) program. One strategy is that on specified alarm conditions, the cleaning cycle may berestarted. For example, if inadequate cleaning agent concentration occurred (as indicated by an alarmon the wash cycle conductivity), the cleaning cycle can be restarted from the beginning after appropriateactions are taken to ensure that the alarm does not reoccur and that the cleaning effectivenesswill not be adversely affected. This is a conservative approach and ensures a complete cleaning cycle isperformed, but care should be taken that alarms are noted and trended to ensure cycle performance isnot trending towards being ineffective and to better correct repetitive problems. Alternately, the stepin which the alarm occurs may be restarted. This approach strikes a balance between ensuring cycleperformance and minimizing cleaning time as the entire cycle does not have to be repeated. Automatedalarming is generally not done in manual cleaning operations. However, if cleaning agent dilutionis confirmed by conductivity, or cleaning agent temperature is confirmed by temperature measurement,measurements outside the specified range can serve as an “alarm.” In all cases, it should be ensuredthat cycles performed during validation are not “best case” due to alarm conditions. For example,if equipment is soiled and during the validation runs of the cleaning cycle, alarms occur that result inmultiple additional rinse steps being completed, this cycle may no longer be representative or worstcase but may be a best case.

有多种方法清洁发生了警报的设备。应调查引发警报的原因。可将此作为纠正和预防措施（CAPA）计划的一部分来完成。一种策略是在规定警报条件下，重新开始清洁行程。例如：如果清洁剂浓度不够（由清洗过程中电导率警报所显示），可在采取适当措施保证警报不再发生以及清洁有效性不会受到不良影响以后，从头开始清洁行程。这是一种保守方法，能保证执行完整的清洁行程，但应注意的是要记录警报并进行趋势分析以保证清洁工艺不会趋于无效，以及更好地纠正重复性问题。或者重复发生警报的那一步操作，因为不必重复整个清洁行程，该方法在清洁效果和清洁时间最小化之间取得了平衡。通常不会在手动清洁操作中实行自动警报。然而，如果用电导率法确认清洁剂被稀释，或通过测量温度确认清洁剂温度，那么测量值超出指定范围外可以作为一个“警报”。在任何情况下，都应该保证在验证期间，所执行的清洁行程不会因为警报而成为“最佳条件”。例如:如果设备受到污染并在清洁验证中，发生导致多次额外冲洗步骤的警报，那么该清洁行程可能不再具有代表性或不是最差条件而可能是最佳条件。

8.3 Change Control

变更控制

A change control system is critical for ensuring maintenance of the validated state for cleaning processes.The change control system should cover all key parameters and components of the cleaningsystem to ensure that all changes with a potential to impact maintenance of the validated state areevaluated. This includes not only changes in the cleaning process but also changes in equipment andchanges in the manufacturing process (e.g., a change in temperature in a manufacturing process) thatmight affect the performance of the validated cleaning process. Quality preapproval and tracking ofchanges are key requirements for this system.

变更控制系统是保证清洁工艺的验证状态维护的关键。变更控制系统应涵盖清洁系统所有重要参数以及组件以保证可能影响验证状态维护的所有变更都得到了评估。这不单包括清洁工艺变更，还包括可能影响清洁工艺的性能的设备变更和生产工艺变更（如：生产工艺中温度变更）。质量部门的预批准和变更追踪是该系统的关键要求。

The change control system should provide for a review of each change by an interdisciplinary team.This should include a review of current validation for the equipment being changed, and dependingon the nature of the change, may result in laboratory, pilot scale and/or commercial scale evaluations.This may also involve a review of the relevant sections of any risk assessment previously done.Significantly major changes may result in the decision that the new cleaning process requires separatevalidation as a new process. There are some important considerations for designing the test plan toverify changes; review of the process design considerations will assist in this evaluation. First, controlparameters should stay within their validated ranges. If changes are made to extend or widen avalidated range, an evaluation should be made to determine the nature and extent of testing (if any)necessary to change that range. For example, if the pump on a CIP skid is validated to deliver water between 60 and 70 liters per minute, and the desired change is to increase the flow rate to 70-80liters per minute, new validation testing is required to verify that the pump is capable of deliveringthe desired flow before validation of the cleaning cycle can occur. Second, the acceptance criteria foranalytical methods should remain unchanged from the previous validation unless there is a justifiedreason for the difference. This is to ensure that changes result in maintenance of the validated staterather than creation of a new state, which may require significant testing to ensure it is still validated.Finally, reduced sample sites and/or fewer analytical methods may be appropriate in many cases toconfirm validation maintenance based on a change. For example, if the effect of the change is only onbioburden then it may be appropriate to evaluate only bioburden in studies that evaluate the effectsof the change. These differences should be justified in the testing plan/protocol.
更控制管理系统应规定由一个跨领域团队审核每项变更。这应包括待变更设备的现行验证状态，同时取决于变更的性质，还可能需要进行实验室、中试规模和/或商业规模的评估。还应包括对先前所做的任何风险评估的相关部分的审核。主要变更可能会导致对新的清洁工艺进行单独验证。设计确认变更的试验计划时有几项重要考量；对清洁工艺设计的回顾将有助于进行评估。首先，应保持控制参数在其已验证范围内。如果所做变更是为了延伸或扩大验证范围，那么应进行评估以确定变更该范围必须进行的试验（如果有）的性质和范围。例如，如果 CIP 模块上的泵经验证的送水量为 60-70 升/分钟，拟将流速增加到每分钟 70-80 升，那么在清洁验证前应对泵进行新的验证试验，以证实其能达到需要的流速。第二，除非有合适理由，否则分析方法的可接受标准仍应与先前验证一致。以此来保证变更能维持已验证状态，而不是创造一个新的状态，该新状态可能需要进行大量的试验来保证其仍然处于已验证状态。最后，在许多情况下，根据变更具体情况减少取样点和/或减少分析方法可能适用于证实验证状态维护。例如：如果变更的影响仅作用于生物负载，那么在评价变更的影响的研究中可仅限于生物负载。这些不同点应在试验计划/方案中予以说明。

8.4 Routine Monitoring

例行监测

Another tool for ensuring maintenance of the validated state is a risk-based routine monitoring program.A routine monitoring program may provide analytical data to be trended (see Section 8.5below), such as by SPC. In most cases involving automated processes, the data are provided by theautomated equipment itself. For example, data may be generated by the CIP skid on wash-solutionconductivity, final rinse conductivity, temperatures, times, flow rates and pressure. In other cases,separate sampling may be established for data

collection, such as rinse analysis by UV/Vis, HPLC, orTOC. Visual examination after each cleaning process is another type of routine monitoring. Visualinspection after each cleaning process typically does not involve disassembly of equipment solely forthe purpose of that inspection.
保证已验证状态维护的另一种工具是基于风险的例行监测计划。例行监测计划可提供用于趋势分析的分析数据（参见 8.5 章），如通过 SPC。在绝大多数涉及到自动化工艺的情况中，数据都是由自动设备自身提供。例如：洗涤液电导率、最终冲洗液电导率、温度、时间、流速和压力数据可由 CIP 模块提供。在其它情况中，可单独取样以收集数据，如采用 UV/Vis, HPLC 或 TOC 进行冲洗液分析。每次清洁后进行目测是另外一种类型的例行监测。对于每次清洁后的目视检查，通常不需要仅仅是为了进行该检查而拆卸设备。

A documented risk-based approach should be used to optimize compliance in an efficient manner.This could include leveraging family or grouping approaches, reduced sample sites and reducedanalytical methods. Leveraging in this manner is most common on cleaning processes which weregrouped for qualification purposes but it may also be done for cleaning processes which were qualifiedseparately. In both cases, all members of the group should be considered for routine monitoringactivities in a risk-based approach. When defining these approaches, the inherent risk associated witha given cleaning process and historical experience/data should be considered. For example, whenperforming the initial validation on process equipment, residues of an active ingredient may be measuredvia a variety of swab and rinse samples. However, with the proper data analysis, it may beappropriate to measure using only rinse sampling during routine monitoring. However, it may beappropriate for cleaning of highly hazardous drug active ingredients (as compared to cleaning ofdrug active ingredients that are not highly hazardous) to include more sampling for residues as partof routine monitoring after completion of the qualification runs.
应采用文件化的基于风险的方法，以更有效地符合法规要求。这可以包括利用分类或分组法、减少取样点、减少分析方法。这种方式最常用于进行分组确认的清洁工艺，但是也可用于单独进行确认的清洁工艺。在这两种情况中，应基于分组中的所有清洁工艺的风险考虑，进行例行监控。对制订这些方法时，应考虑到与特定清洁工艺相关的固有风险以及历史经验/数据。例如：当进行工艺设备的首次验证时，可通过多个擦拭和冲洗样测量活性成分的残留。然而，通过恰当的数据分析后，在例行监测期间可只测量冲洗样本。但对于高危害活性成分（同非高危害药品比较）的清洁，完成确认以后，在例行监测中应取更多的残留样品。

8.5 Data Trending and Review

数据趋势分析和回顾

Trending of cleaning cycle performance, analytical data from routine monitoring, and alarms are anotherrecommendation to ensure continued cleaning cycle performance. Data that is trended can becontinuous data (such as final rinse water analysis) or discrete data (“yes/no” data such as occurrenceof an alarm). When trending any of these data sets, procedures should be in place to initiate an investigationwhen adverse trends are observed even if ineffective cleaning cycles have not occurred. Trendingof cleaning cycle performance data is important for identifying potential cleaning cycle issuesbefore they result in ineffective cleaning cycles. For example, a slowly increasing trend in the final rinseanalytical result may not be indicative of an ineffective cleaning process. However, such a trend shouldrequire an investigation of the cause. In the example given, it may be that the spray device is becomingclogged, in which case it should be cleaned, and appropriate steps should be taken to preventclogging in the future. On the other hand, it may be a result of a fouled sensor, such as a conductivitysensor. Alarm monitoring and trending will help indicate cycle failure although alarm data will

notproactively identify potential issues. The incidence of all alarms should still be trended to determine ifadditional process controls are required to reduce the frequency of alarming. Data trending may alsoserve as an important input for a continuous improvement program.
保证持续清洁行程性能的另一个建议是对清洁行程性能、例行监测分析数据和报警进行趋势分析。趋势分析的数据可以是连续数据（如最终冲洗水分析结果）或离散数据（“是/否”数据，如警报的发生）。当对这些数据组进行趋势分析，发现不良趋势时，即使没有出现清洁不合格的情况，也应有规程来启动调查。清洁行程性能数据的趋势分析对于在出现无效清洁前识别这些潜在的清洁问题是很重要的。例如：最终冲洗液分析结果的缓慢增长趋势可能无法预示无效清洁。然而，需要对这一趋势进行原因调查。在给出的例子中，喷淋设备可能发生堵塞，在这种情况下应该清洁喷淋设备，同时采取合适的步骤来预防其再次堵塞。另一方面，它可能传感器（例如电导率传感器）变脏的结果。尽管警报数据不会提前识别潜在问题，但警报监测和趋势分析有助于提示清洁过程失败。仍然应对所有警报的发生率进行趋势分析来确定是否需要采取额外工艺控制来减少警报发生频率。数据趋势也可以作为持续改进计划的一项重要输入。

For data trending, there should be appropriate criteria established for action and/or alert levels. It isadvisable to obtain guidance from a statistician to determine the appropriate number of data pointsnecessary to obtain a statistically relevant data set. These values are typically less than any pass/failacceptance criteria established for the qualification runs. Statistical process capability studies, basedon multiple (e.g., 20-25) data points, may be used to establish action/alert levels. Since such extensivedata may not be available for initial commercial manufacture, data from development runs and/or sufficiently similar cleaning processes may be used to establish tentative action/alert levels. Appropriatetechnical judgment should be utilized in establishing action/alert levels that are practicallysignificant and not just statistically significant. For example, consistently obtaining “zeroes” for rinsebioburden data for the cleaning process may not alone be sufficient to require a “one-time” value of3 CFU to be a significant event which needs an investigation.
对于数据趋势分析，应建立适当的纠偏限和/或警戒限。明智的做法是从统计员那里寻求指导，确定所需的适当数据点数，以组成具有统计学意义的数据组。这些值通常小于确认过程中建立的合格/不合格所对应的可接受标准。基于多个（如 20-25）数据点的统计过程能力研究，可用于建立纠偏限/警戒限。因为最初商业生产可能没有如此大量的数据，所以可以使用开发和/或足够相似的清洁工艺的数据来建立临时的纠偏限/警戒限。应该使用适当的技术判断建立具有实际意义而不仅仅是统计意义的纠偏限/警戒限。例如：仅冲洗液生物负载持续为“零”可能不足以将一个“一次性”的 3CFU 结果作为一次需要调查的显著事件。

8.6 Evaluation of Cumulative Changes
累积变更的评估

Review of the cumulative impact of changes on a system should be considered. Such a review maybe initiated based on data/events from the cleaning process or may be time-based. One approach isto include a review of cumulative changes for every change control event. This review should provideevidence that the cleaning cycle continues to meet specified requirements despite multiple smallchanges, each of which was appropriately approved. It is possible that many minor changes (eachdeemed to have no impact on the validated state) could have an impact when considered in total. Thisreview of cumulative changes may involve two approaches. First, a documented analysis (i.e. reviewof the changes and the impact these changes will have on other parts of the process) of the changesshould be undertaken. Second, process performance and alarms should be monitored to ensure continuedmaintenance of the validated state and

system performance.
应考虑回顾所有的变更对一个系统累积影响。可以基于清工艺数据/事件或基于时间发起这样的回顾。一种方法是在每一变更控制事件中都增加对累积变更的回顾。这种回顾应提供证据证明清洁行程能持续符合要求，尽管发生了多个微小变更（每一个微小变更都经过适当批准）。有可能许多微小变更（每一个都视为对验证状态无影响）放在一起考虑时就可能对验证状态产生影响。这种累积变更的回顾有两种方法。首先，应对变更进行分析（即：回顾变更和这些变更的将对工艺其他部分产生的影响）并记录。其次，应监测工艺性能和警报以保证对验证状态及系统的性能的持续维护。

8.7 Training

培训

Training after the initial qualification runs should be done to help assure maintenance of the validatedstate. One type of training may involve training on a procedure revised for either clarification or fora cleaning process change. Another type of training is retraining of a previously trained operator becauseof suspected operator error. A third type of training is retraining on a regular basis for manualcleaning processes. This latter training may be done on a regular basis to avoid process “creep”. Ofcourse, training of any new (previously untrained) operators should also be done. Training shouldcover cleaning process operators, sampling personnel, and analytical personnel as applicable.
首次确认后应进行培训以确保已验证状态的维护。其中一类培训是对相关程序进行修订后的培训，这些修订是因为需对文件内容作进一步说明或清洁工艺的变更。另一种是对先前受过培训的操作人员进行再培训，因为怀疑这些人员操作错误。第三种培训是对人工清洁工艺的定期再培训，这种定期培训可以避免工艺“微小变化”带来的影响。当然，应培训所有新的（之前未受训的）操作人员。培训对象应包括清洁工艺的操作人员、取样人员和相关分析人员。

8.8 Periodic Review

定期回顾

As part of lifecycle validation, it is common practice to perform an overall periodic review of thevalidation state. The frequency of such a review will depend on a risk assessment. Such a review typicallyinvolves a review of data collected as described in Sections 8.1 through 8.7 above. In addition, ittypically involves a review of any changed regulations as well as any change in common industry orinspectional practices that might be considered part of current Good Manufacturing Practice. This periodicreview should be documented and should include a conclusion as to the validation status of thecleaning process. It may also include recommended or planned improvements in the cleaning process.
作为生命周期验证的一部分，通常对验证状态进行总体的定期回顾。该回顾的频率取决于风险评估。该回顾通常通常包括回顾按照 8.1 到 8.7 章要求收集到的数据。另外，通常还包括回顾任何法规的修订，也包括回顾行业或检查规范的变更，这些规范可能被视为 cGMP 的一部分。应记录该定期回顾且应包含关于清洁工艺验证状态的结论。也可以包含对清洁工艺的建议或计划的改进。
Historically, it was considered acceptable to perform periodic revalidation on cleaning processes inlieu of routine monitoring and periodic review. However, the approach of revalidation yields a muchless robust picture of the state of control of the cleaning process and may be more resource-intensive.Revalidation as a concept is no longer used by some regulatory agencies because of a preference for alifecycle validation approach. Under a lifecycle validation approach, a significant change in a cleaningprocess involves not the revalidation of the previous process, but rather validation of a new process.Such validation of a new process, however, may rely on data from the old process based on it beingsufficiently similar.
历史上，用清洁工艺的定期再验证来代替常规监测及定期回顾被认为是可以接受的。然而，再验证

的方法无法获得一个具有耐受性的清洁工艺控制状态，而且可能消耗更多资源。由于倾向于生命周期的验证方法，一些监管机构已不再使用再验证的概念。按照生命周期的验证方法，清洁工艺的重大变更导致的不是对先前工艺的再验证，而是对新工艺的验证。然而，因为新旧工艺足够相似，新工艺的验证也可能基于旧工艺的数据。

9.0 Documentation

文件

Documentation is pivotal to cleaning process knowledge management. Documentation of cleaning validation activities will vary with individual company practices. This is particularly the case in terms of where data, reports and other documents are stored and how they are retrieved. There might be variations among companies in terms of determining at what stage of validation (i.e., design/development, qualification, and validation maintenance) those documents are considered. All data and documents relevant to a determination of the extent of control and consistency of a cleaning process should be appropriately controlled and consistent with GMP regulatory requirements and with the company's quality system. This system should be such that those documents can be readily retrieved. This documentation should be part of, or consistent with, a company's quality management system. A procedure on documentation, with specifics for cleaning validation documents, should be considered for knowledge management.
文件是清洗过程中知识管理的关键。清洁验证的文件因各个公司的做法有所不同会有所差异。对于数据、报告和其他文件的储存和如何追溯，则尤为如此。不同的公司对各验证阶段（即，设计/开发，确认，及验证维护）要求形成的文件也会不同。所有与确定清洗过程的控制程度和一致性有关的数据和文件需受到适当的控制并符合 GMP 法规和公司的质量管理体系的要求。这些文件应易于追溯并作为为公司质量管理体系的一部分或与其保持一致。应建立文件管理程序，特别是清洁验证文件，以便进行知识管理。

This section will cover documentation for a high-level cleaning validation master plan and/or policy, for design/development, for qualification, and for validation maintenance. Figure 9.5-1 contains the typical steps in a cleaning validation process flow where appropriate documentation should be considered.
本节讨论的文件包括高层次的清洁验证主计划和/或方针、设计/开发、确认和验证维护文件。图 9.5-1 包含了清洁验证流程中需建立适当文件的典型步骤。

9.1Cleaning Validation Master Plans

清洁验证主计划

It is good practice to have a document or documents near the top of the cleaning validation documentation hierarchy that broadly define the expectations for a cleaning validation program. This document is often called the "cleaning validation master plan". Such a master plan is not a regulatory requirement but is a practical "requirement" in order to facilitate regulatory inspections as well as to ensure consistency of execution within a facility.
应建立高层次的清洁验证文件，概述对清洁验证计划的要求。这个文件通常被称为“清洁验证主计划”，法规没有要求必须建立清洁验证主计划，但为了便于监管机构的检查，以及为了确保执行的一致性，在实际工作中应建立清洁验证主计划。

The plan should provide a description of responsibilities and activities for the planning and execution of cleaning validation. This is best accomplished by a specific cleaning validation master plan. The cleaning validation master plan could be described in detail or referenced as a separate document in the overall site validation master plan. The cleaning master plan may be all-encompassing. An alternative approach is to

have a high-level cleaning validation policy and then have a cleaning validation master plan that has more detailed explanations of the validation requirements. This approach is common for multinational companies where a cleaning validation policy is set at the corporate level.Individual sites will prepare master plans consistent with that policy, but with requirements more appropriate for the manufacturing situation at that site. If this approach is used, care should be utilized in the higher level policy so as not to set policy requirements that may not be appropriate for every site.These documents are living documents that should be reviewed and updated as needed and on a defined frequency specified in the master plan.A report to the plan may be written periodically to summarize the major activities executed under the plan during that interval.

该主计划应描述清洁验证策划和执行的职责和活动。最好制定在一个专门的清洁验证主计划中。可以详细描述清洁验证主计划或将其作为一个单独文件引用在验证总计划中。清洁验证主计划可能包含所有因素。另一种方法是建立一个高层次的清洗验证方针，然后用一个清洁验证主计划对验证要求做更详细的解释。跨国公司通常采用这种方法，在集团层面建立清洁验证方针，各子公司编制的主计划须与集团方针相一致，但应更适合于各公司的实际生产情况。如果使用这种方法，制订高层次验证方针时应注意提出的要求不适用于各公司的具体情况。这些文件应根据需要以及验证主计划中规定的频率进行审核和更新。可以定期撰写主计划实施报告，总结在这段时期内根据验证主计划进行的主要活动。

The cleaning master plan will describe the overall plan, rationale and methodology to be used in performing cleaning validation. The plan should provide a high-level description of the cleaning validation philosophy and strategy that will support the validation activities performed at the site. Detailed procedures on the execution of cleaning validation will be in individual protocols. The plan will define the efforts required to ensure the cleaning program complies with current Good Manufacturing Practices (CGMPs). The validation activities are documented according to the requirements of the plan to provide sufficient scientific rationale to assess the suitability of the cleaning program in order to consistently clean equipment to the required specifications. During a regulatory inspection, an inspector may ask to review the master plan and then look at the specific validation protocols and final reports to determine if the plan is appropriate and to assure that the elements of both the plan and individual protocols are being followed.

清洁验证主计划描述了进行清洁验证的总体的验证计划、基本原理和方法。该计划应从较高层次对清洗验证的理念和策略进行描述，用于支持各公司验证活动的实施。清洁验证的详细实施步骤应在单独的验证方案中进行描述。该计划将定义确保清洁程序符合 cGMP 所需的努力。应根据该计划要求对验证活动进行记录，为评估清洁程序的适宜性提供充分的科学依据，使设备清洁持续符合预定要求。监管部门检查时，检查员会对主计划进行审阅，然后查看具体的验证方案和最终的报告来确定计划是否适当，并确保主计划和各验证方案的所有要素都得到执行。

9.1.1 Elements of a Comprehensive Plan

验证主计划的要素

The master plan should address each important aspect of the cleaning validation program. Elements of a master plan and the appropriate details provided for those elements will depend on the practices of the specific facility.One approach is to include more detail in the master plan while another approach is to include that level of detail for procedures consistent with the master plan. Elements of a master plan may include, but are not limited to, the following topics:

清洁验证主计划应涵盖清洁验证计划的各个重要方面。一个主计划的要素和这些要素的适当细节将取决于各公司的具体操作。一种方法是将更多细节描述在主计划中，而另一种方法是将同等细节写

入程序中，而主计划则引用这些程序。主计划的要素可以包括，但不限于：

•Purpose of the plan
主计划的目的

•Scope of the cleaning validation program
清洁验证程序的范围

•Designation of responsibilities
职责的划分

•List of equipment to be validated
待验证的设备清单

•Definitions and glossary of terms
定义和术语表

•Means of cleaning documentation (e.g., procedures and records)
清洁文件（例如，程序和记录）

•Prerequisites to cleaning validation (e.g., equipment and utility qualifications)
清洁验证的先决条件（例如，设备与设施的确认）

•Spray device coverage testing
喷淋装置覆盖测试

•Use of various cleaning systems (e.g., CIP, COP, mechanical washers or manual cleaning)
各种清洁系统（如，在线清洗，离线清洗，机械清洗机或手动清洗）的使用

•Cleaning reagents and mechanisms
清洁剂和作用机理

•Cleaning cycle development requirements
清洁行程开发要求

•Cleaning equipment lists
清洗设备清单

•Product list
产品列表

•Cleaning SOPs
清洁标准操作规程

•Precleaning methods
预清洗方法

•Conditions for use of artificial or surrogate soils
人工或替代污物的使用条件

•Definition and use of “worst-case conditions” associated with a cleaning process (e.g., flow rates or step durations)
清洁工艺的“最差条件”（例如，流速或操作步骤的持续时间）的定义和使用

•Description of family approach and grouping of products/equipment/systems based on similarities, including an approach to determine “worst-case product” based upon attributes that impact cleaning (e.g., solubility of all components in the “soil”)
根据产品/设备/系统的相似性对其分类/分组进行描述，包括根据影响清洁的特性来定义“最差条件产品”的方法。（例如，污物中各组分的溶解度）

•Use of dedicated or shared equipment; single use (disposable) equipment
使用专用或共用的设备，一次性使用（一次性）的设备

•Definition of circumstances in which cleaning verification is preferred or acceptable (e.g., clinical stages)

定义首选或接受“清洁效果确认”的条件（例如，临床阶段）

•Strategies and definitions for indirect product contact surfaces
间接接触产品表面的策略和定义

•Cleaning of components and single-use equipment
组件和一次性设备的清洗

•Use of quality risk management to determine the scope and extent of validation activities
使用质量风险管理来确定验证活动的范围和程度的

•Establishment of design space based on cleaning parameters and use in ongoing monitoring
基于清洁参数建立设计空间，并用于持续监测中

•Use of mock, blank, or placebo runs
使用模拟，空白或安慰剂进行验证

•Equipment hold study approaches (e.g., dirty hold, clean hold or storage hold)
研究设备保持时间的方法（例如，生产后保持时间，清洁保持时间或储存效期）

•Microbial contamination (e.g., bioburden and endotoxin)
微生物污染（如生物负载和内毒素）

•Sampling techniques (e.g., visual inspection, rinse sampling or swab sampling)
取样技术（如目视检查，冲洗取样或棉签擦拭取样）

•Training/qualification for sampling techniques
取样技术培训/资格确认

•Analytical methods (e.g., validation and recovery requirements)
分析方法（例如，验证和回收率要求）

•Rationale for the use of product-specific assays and nonspecific assays
选择专属性和/或非专属性含量检测方法的理由

•Rationales and formulas for limits for process residues, microbial contaminants and cleaning agents
工艺残留、微生物污染和清洁剂限度的制订原理和公式

•Validation maintenance (including routine monitoring, change control, and periodic review)
验证维护（包括日常监测，变更控制和定期回顾）

•Attachments/appendices (e.g., various tables or lists of items within the realm of the plan such as a responsibility matrix)
附件/附录（例如，在主计划中的不同表格或项目清单，如职责矩阵）

•Requirement for reassessment of cleaning validation master plan
清洁验证主计划的再评估要求

•Roadmap or summary of current status and upcoming plans
现状和计划的路线图或摘要

•References
参考

Note that this is a comprehensive list. Some items listed may not be applicable to a given manufacturer. Some items may be maintained by a manufacturer in a system outside the cleaning validation master plan.
请注意，这是一个全面的列表。列出的某些项目可能并不适用于一个特定的生产厂家。生产商可能将某些项目放在清洁验证主计划之外的系统中进行维护。

9.1.2Harmonization of Site Cleaning Validation Programs
不同公司清洁验证计划的协调

For a product made at more than one site, where appropriate, the cleaning requirements should preferably be the same. However, if the process equipment scale, the type of cleaning equipment available, analytical equipment, and/or cleaning process is different (e.g., CIP skid vs. manual), the programs can only be harmonized to a limited degree. The acceptance criteria may differ for any limit that is based on batch size and equipment surface area. The same would also apply to some degree if a contract manufacturer were making the same product. However, there is an additional consideration in that the contractor is also obliged to follow its own master plan. A contract manufacturer may validate their cleaning process using techniques and procedures that differ from those of the sponsor but the resulting validation must be compliant and must meet appropriate regulatory expectations. Any critical differences should be addressed upfront in a quality agreement with the sponsor. The ultimate responsibility for the cleaning validation does reside with the sponsor.

对于同一产品在一个以上的地点生产的情况，清洁要求应尽量是相同的。然而，如果工艺设备的规模，清洗设备的类型，分析仪器，和/或清洁过程是不同的（例如，在线清洁模块与手动清洁），只能在有限的程度上对验证计划进行协调。根据批量的大小和设备的表面积确定的可接受标准可能会有不同。如果由合同制造商生产相同的产品，这在一定程度上也是适用的，同时，合同制造商还应执行自身的主计划。合同制造商可以使用不同于委托方的技术和程序对清洁程序进行验证，但验证结果必须符合相关规定和监管要求。所有关键的差异应在前期与委托方在质量协议中予以明确。清洁验证的最终责任由委托方承担。

9.2Documentation for Design/Development

设计/开发文件

In a risk-based environment, it may be appropriate to begin the design/development stage of cleaning validation with a risk assessment to provide a rationale for the development plan as well as to identify CQAs and CPPs. This assessment will be different for an entirely new cleaning process as compared to a consideration of an existing cleaning process for a new product.

在清洁验证设计/开发的初始阶段应进行适当的风险评估，为清洁验证开发计划提供理论基础，并确定 CQAs 和 CPPs。对于一全新的清洁工艺的评估与在现行的清洁工艺中新增品种所进行的评估是不同的。

The output of laboratory studies (if any) will typically include initial selection of the cleaning agent, cleaning agent concentration (if applicable), temperature and time of the washing step (see Section 3.0). It may also include stress studies to identify the robustness of those selected parameters. Laboratory studies may also be used to determine the nature and/or characteristics of residues (such as degradation of the API) following the cleaning process. Reports for laboratory studies should have clear conclusions with references to documentation for supporting data. The output of lab studies may also be leveraged to aid in equipment design.

实验室研究的输出（如果有）通常包括清洁剂，清洁剂浓度（如适用），各清洁步骤温度和时间（请参见第 3.0 节）的初步选择。它也可能包括恶劣条件研究，以确定所选定参数的耐用性。实验室研究也可以用于确定清洁后残留的性质和/或特性（如 API 的降解物）。实验室研究报告应有明确的结论并引用相关数据文件。实验室研究得出的结果还可用于设备设计。

The output of pilot-scale studies (if any) will typically include a confirmation and/or modification of the basic cleaning parameters, plus an evaluation of any engineering issues (such as dead legs) that may affect

the selection of those cleaning parameters. Reports for pilot-scale studies should have clear conclusions with references to documentation for supporting data.
中试研究的结果（如有）通常都会包括对基本清洁参数的确定和/或修改，以及对可能影响清洁参数选择的工程问题（如死角）的评价。中试研究报告应有明确的结论并引用相关数据文件。

Any studies on full-scale equipment are generally performed to collect data not practical in a pilot-scale or lab-scale study, to investigate any possible issues where lab-scale data may not reflect accurately performance on full-scale equipment, and/or to confirm the performance of the cleaning process on full-scale equipment prior to qualification runs. Reports for full-scale studies should have clear conclusions based on documented supporting data references. For studies on full-scale equipment, cleaning verification should be performed in order to release the equipment for subsequent manufacture of a commercial product.
在大生产设备中进行研究以收集中试或实验室研究中不易获得的数据，对实验室研究数据无法反应的大生产设备性能进行调查，和/或在确认开始之前证实清洁程序应用于大生产设备时的情况。在大生产的设备中进行的研究报告应有明确的结论并引用支持性的数据文件。使用大生产设备进行研究时，应进行清洁效果确认以证明该设备可用于后续商业化产品的生产。

Clinical batches may be made on pilot-scale and/or full-scale equipment. The cleaning verification data from such studies should also be leveraged to support conclusions of the design/development report.
临床批次可能在中试规模和/或大生产规模的设备中生产。从这些研究获得的清洁效果确认数据也应该被利用来支持的设计/开发报告的结论

The output of design/development stage should be both a development report (also called a technology transfer report) and a draft cleaning process procedure (SOP). It may also include a risk assessment report based on the cleaning procedure, although this risk assessment may be done as an initial step in the Qualification stage.
设计/开发阶段得出的结果应该包括一份开发报告（也称为技术转移报告）和一个清洁程序的草案（SOP）。还可能包括一个基于清洁程序的风险评估报告，虽然这种风险评估也可作为确认的第一步。

9.3Documentation for Qualification
确认文件
Documentation for the Qualification stage starts with Commissioning and IQ/OQ protocols/reports on the equipment utilized for cleaning (assuming that Commissioning, IQ and OQ for the equipment to be cleaned are already done as part of the process validation). The emphasis for this stage is design and execution of the protocols for the validations runs (sometimes called process performance qualification, or PPQ, runs). Validation runs should not be considered experiments to gain new information but are a confirmation of what is known. Documentation that may be needed prior to preparation of the protocol may include:
确认阶段的文件始于清洗设备的试车、IQ/OQ 方案/报告（假设待清洁设备的调试，IQ 和 OQ 已经作为工艺验证的一部分完成）。这一阶段的重点是验证方案（有时也称为工艺性能确认）的设计和执行。验证过程不是为了从实验中获得新的信息而是对已知信息进行确认。在制订验证方案前需准备的文件包括：

•Validation strategy, including rationale for product and/or equipment grouping

验证策略，包括产品和/或设备分组的基本原理
•Draft cleaning SOP, including CPPs
清洁 SOP 草案，包括关键工艺参数
•Acceptance criteria and how those criteria were established
可接受标准，以及这些标准建立的依据
•Analytical methods and their validation
使用的分析方法和分析方法的验证
•Sampling methods and sampling sites (locations)
取样方法和取样点（位置）
•Sampling recovery studies
取样回收率的研究
•Selection of protocol challenges, including hold times
挑战方案的选择，包括保持时间
•Rationale for the selection of number of validation (PPQ) runs
验证（PPQ）运行次数选择的理由
•How equipment cleaning is to documented
设备清洁的记录方法
•Responsibilities for execution of the protocol
方案执行的责任
•Training of operators, samplers and analysts on applicable procedures
操作者、取样人员和分析人员的培训记录
•Plans for validation maintenance (see Section 8.0)
验证维护计划（参见 8.0 节）
•Plans for equipment and product disposition during the protocol execution.
方案执行过程中设备和产品的处置计划

Note that the number of validation (PPQ) runs should be based on cumulative knowledge based on data collected during the development and qualification stages, and ordinarily is not based on a statistical evaluation.
请注意，验证(PPQ)运行次数应基于在开发和确认阶段收集的数据所积累的知识而不是一般的统计分析。

The next document developed is the protocol itself. One approach is to include all the documentation covered in the prior paragraph in the protocol itself while another approach is to only put in the details critical to execution of the protocol and have references in the protocol to the supporting rationales/data that are in separate documents.
接下来形成的文件是方案本身。可以将所有文件包含在方案里面，也可以只将执行的关键细节纳入方案，并在方案中引用那些单独的支持性（原理/数据）文件。

Interim reports may be written for each validation (PPQ) run. The last document developed for this stage is the final report, summarizing the results of protocol execution with a conclusion as to the state of control of the cleaning process. The final report should also include documentation of conclusions of any investigations of deviations. It may also include recommendations for improvements, including changes in the validation maintenance program.

可以对每次验证（PPQ）进行小结。这一阶段制定的最后一个文件是验证报告，在报告中总结方案执行的结果并给出清洗过程的控制状态的结论。所有的偏差调查结论应包含在最终的报告中。它可能还包括改进的建议，包括验证维护计划的调整。

9.4Documentation for Validation Maintenance

验证维护文件

Documentation for the validation maintenance stage will depend on activities selected for this stage.It should include reports related to the following activities, as applicable:

验证维护阶段的文件取决于这个阶段选择进行的活动。它应该包括以下活动相关的报告（如适用）：

•Alarms and alerts, including investigations and corrective/preventive actions

报警和警报，包括调查和纠正/预防措施

•Routine monitoring, including trending of data and evaluation of such trending (may include statistical evaluation)

例行监控，包括数据趋势和对这些趋势的评估（可包括统计分析）

•Change control

变更控制

•Deviations, including investigation and corrective/preventive actions

偏差，包括调查和纠正/预防措施

•Evaluations of cumulative changes (which might be as a result of a deviation investigation or a periodic review)

评估累积的变更（这可能是偏差调查或定期回顾的结果所致）

•Training and retraining

培训和再培训

•Periodic cleaning process review

清洁工艺的定期回顾

•Risk assessments relating to any process changes or shifts.

对任何相关的工艺变更或漂移进行风险评估

Cleaning log records (such as cleaning log books or cleaning batch records) are generally a GMP requirement and should also be considered.

清洁日志（如清洁记录簿或批清洁记录）通常是 GMP 要求之一，应予以考虑。

9.5Other Documentation Considerations

其他文件的注意事项

Whenever a risk assessment is performed, it is critical that risk communication be made to departments and/or functions affected by the risk assessment. Documentation of events, deviations, failures, and/or investigations involving a cleaning process should follow approved practices within a company for such documentation.

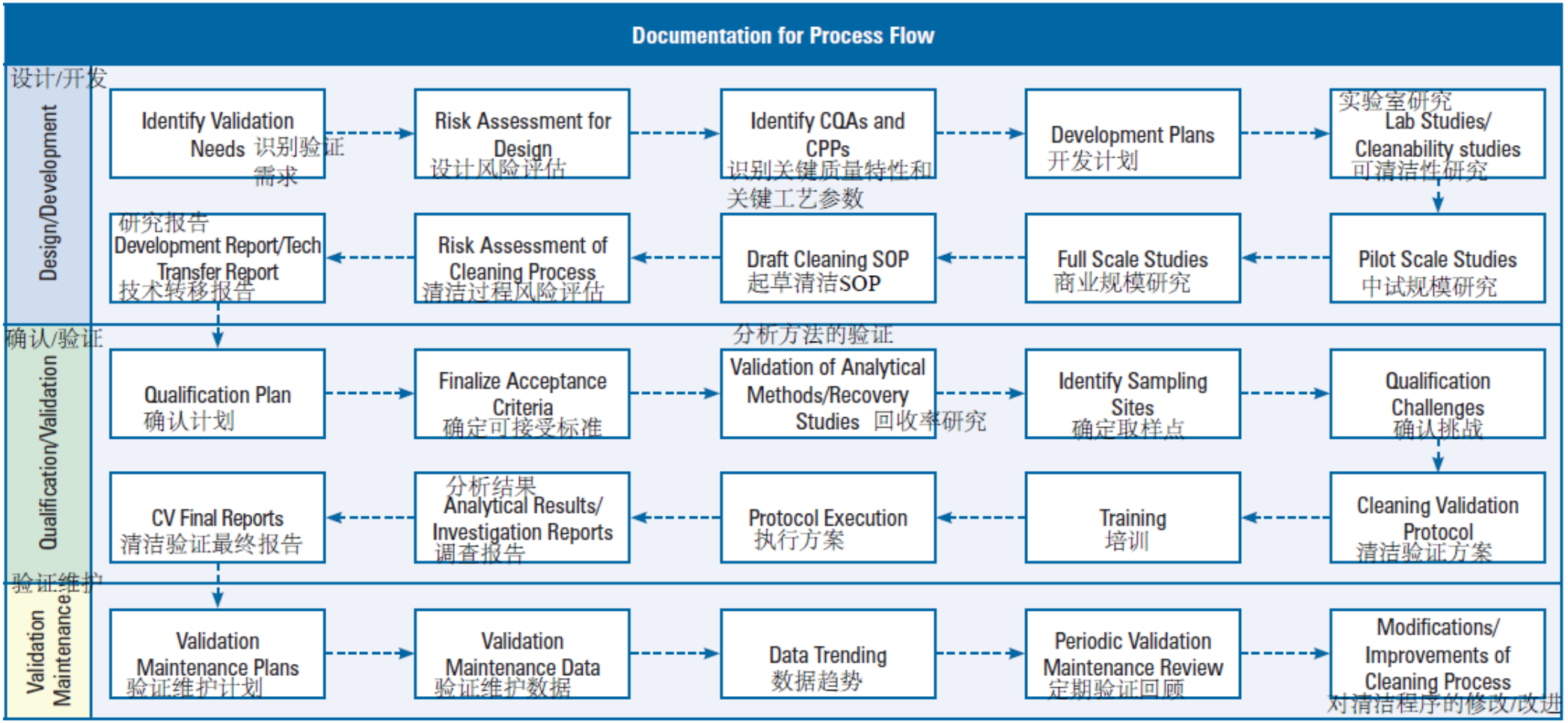
每次进行风险评估时，与受影响的各部门和/或职能单位沟通风险评估结果是很关键的。与清洁工艺相关的事件、偏差、失效和/或调查的记录应遵循公司批准程序的记录要求。

Cleaning validation final reports may not be part of a regulatory filing. The requirement for completion of cleaning validation will vary by regulatory authority and nature of the product. In the USA, CDER likes to

at least see a plan for cleaning validation as part of the PAI, but CBER requires cleaning validation summaries as part of the BLA filing.
清洁验证最终报告可能不是一份监管文件中的一部分。由于监管机构和产品的性质的不同，对清洁验证的要求也有所不同。在美国，药品评价与研究中心喜欢将清洁验证计划作为 PAI 的一部分，但 CBER 要求将清洁验证作为 BLA 申请的一部分。

Documentation for cleaning verification follows the same principles as for cleaning validation except that the extent of design/development may be as appropriate for a one-time cleaning activity.
清洁效果确认文件与清洁验证遵循相同的原则，除了设计/开发程度应适用于一次性的清洁活动。

Figure 9.5-1Documentation for Process Flow
图 9.5-1 工艺流程文件



10.0 Special Considerations

注意事项

10.1 Cleaning Agents

清洁剂

A variety of cleaning agent options is available. These include water, organic solvents, commodityalkalis and acids, and formulated detergents.

可以选择各种不同的清洁剂。这其中包括水、有机溶剂、市售酸和碱，以及配方洗涤剂。

10.1.1 Types

类别

10.1.1.1 Water

水

Although the typical use of water is in the prerinsing, post rinsing, and preparation of use-dilutions,water is also used as a sole cleaning agent for readily water-soluble residues. As a general rule, thequality of water used in the final rinse should be at least as good as the water used in the manufacturingof the drug product. The water quality used in cleaning should also meet the chemical, microbiologicaland endotoxin levels as appropriate for the application.

虽然水通常用于前冲洗、冲洗后和使用稀释液的配制中，但是对于易溶于水的残留物，水也可以单独作为清洁剂使用。通常情况下，用于最终冲洗的水质至少与药品生产用水相当。清洁用水的质量还应该符合适用其用途的化学、微生物和内毒素限度要求。

10.1.1.2 Organic Solvents

有机溶剂

Organic solvents, such as methanol, are used for cleaning in small-molecule API synthesis processes.Solvents are chosen based on the solubility of the manufacturing soils in the solvent. The cleaningprocess typically involves agitating the solvent in the reactor vessel, circulating it through pipes,and refluxing the heated solvent through overhead risers and condensers. The issue of flammabilityshould be considered for organic solvents. Organic solvents, like isopropyl alcohol, are also used in finishedpharmaceutical manufacturing for manual cleaning of parts and to facilitate drying of surfaces.

有机溶剂，例如甲醇，用于小分子 API 合成工艺中的清洁。溶剂的选择基于生产中形成的污物在溶剂中的溶解性。清洁工艺通常包括将溶剂在反应罐中搅拌，通过管道循环，采用高架立管冷凝回流受热挥发的溶剂。对于有机溶剂应该考虑易燃性问题。有机溶剂，如异丙醇，也用于制剂生产过程对部件进行手工清洁，以利于表面干燥。

10.1.1.3 Commodity Alkali

市售碱

A commodity alkali, such as sodium hydroxide, is often used for the alkaline wash step. The high pHand alkalinity of sodium hydroxide solutions may enhance solubility of organic process residues and,in some cases, facilitate hydrolysis. Sodium hydroxide is also widely available, relatively inexpensiveand, being a single component containing no organic carbon, is relatively easy to analyze and validatefor cleaning-agent removal. The higher pH of sodium hydroxide also facilitates the precipitation ofsalts or oxides of such ions

as calcium, magnesium and iron if those ions are present during the cleaningprocess. However, commodity cleaners, such as sodium hydroxide, may have limited effectivenessfor tenaciously adhered or baked-on residues. They also have limited wetting characteristics and soilsuspendingability.
市售碱，例如氢氧化钠，常常用于碱洗步骤。氢氧化钠溶液的高 pH 值和碱度会提高有机合成工艺残留物的溶解度，在有些情况下，还会促进水解。氢氧化钠也广泛易得，价格相对较低，组分单一而不含有机碳，易于检测，也容易对清洁剂的去除进行验证。如果在清洁过程中存在钙、镁离和铁之类离子，氢氧化钠的高 pH 值也会促使这些离子的盐或氧化物形成沉淀。但是，市售的清洁剂中，如氢氧化钠，对于强烈吸附或干燥的残留的清洁效果有限。它们还有一定的吸潮性和污物悬浮能力。

10.1.1.4 Commodity Acids
市售酸

An acid washing step may be used alone for cleaning. The addition of an acid wash step after the causticwash/rinse may overcome precipitation and buildup of inorganic compounds, improve rinsing,and help broaden the spectrum of soils cleaned (although at the expense of adding another cycle). Inaddition, maintaining a clean surface and limiting the deposition and buildup of iron oxides or othercontaminants may help minimize the potential for stainless steel corrosion and rouge formation.
在清洁中可能采用单独的酸洗步骤。在碱洗/冲洗之后增加酸洗步骤可以防止无机化合物形成沉淀和聚集，提高冲洗效果，并扩大可清洗的污物范围（虽然增加了额外的步骤）。此外，维持表面清洁和限制铁氧化物或其他的污染物的沉淀和聚集，有助于降低不锈钢腐蚀和形成红锈的可能性。

10.1.1.5 Formulated Detergents
配方洗涤剂

Formulated detergents are multicomponent cleaning agents that take advantage of several differentcleaning mechanisms, thus providing broader spectrum effectiveness. In addition to the mechanismsof alkalinity and hydrolysis offered by a commodity caustic, a formulated alkaline detergent mightprovide improved wetting and soil penetration, emulsification, chelation of calcium, iron oxide orother inorganic ions, and might facilitate dispersion of particulates in the wash step.
配方洗涤剂是具有多种成分的清洁剂，利用不同清洁机制，因而具有更广泛、有效的清洁作用。除了具有市售碱的碱性作用和水解作用外，配方碱洗涤剂可能提供更好的润湿和污物渗透性，乳化作用，钙离子、金属氧化物或其他无机离子的螯合作用，并可能促进清洗步骤中颗粒的分散。

10.1.2 Factors in Selection
选择因素

A number of factors need to be considered when selecting cleaning agents for CGMP applications.These include:
选择清洁剂时应该考虑很多的因素，这其中包括：

10.1.2.1 Broad Spectrum Effectiveness
广泛的有效性

The cleaning agent should be effective at removing the residues that may range from single componentsto complex mixtures of various chemistries that constitute a product’s active ingredients,excipients, degradants, and other contaminants. A broad-spectrum cleaner may also facilitate moreeffective grouping strategies.
清洁剂应能有效去除单组分残留，或不同化学物质组成的复杂混合物残留，该混合物残留包含了产

品的活性成分、辅料、降解产物和其他污染物。广谱清洁剂还有利于有效地进行分组。

10.1.2.2 Substrate Compatibility

与底物的相容性

The cleaning agent should be compatible with the various equipment substrate materials, such asstainless steel, polymers, glass, and soft metals.

清洁剂应该与各种设备底物材料具有相容性，如不锈钢、聚合物、玻璃和软金属。

10.1.2.3 Stability and Shelf Life

稳定性和货架寿命

To ensure consistent performance after transportation and storage, cleaning agent stability and shelflife under those exposure conditions should be considered.

为了确保运输和储存后的性能一致，应该考虑暴露条件下清洁剂的稳定性和货架寿命。

10.1.2.4 Analyzability

可分析性

Cleaning agents should be analyzable and quantifiable down to the acceptance criteria established.

可对清洁剂进行质量分析，并应符合已建立的可接受标准。

10.1.2.5 Disposal

处置

Cleaning agents should meet the local waste water discharge requirements such as limits on pH,phosphates and heavy metals. When organic solvents are used, air emission requirements may needto be considered.

清洁剂应该满足当地的污水排放要求，例如 pH、磷酸盐和重金属限度。当使用有机溶剂时，还需要考虑废气排放要求。

10.1.2.6 Safety

安全

Particularly for cleaners used for manual cleaning applications, appropriate personal protective equipmentmay be required.

尤其对于手工清洁中清洁剂的使用，应该采取适当的人员防护措施。

10.1.2.7 Toxicity

毒性

Cleaning agent toxicity is not only important for personnel safety during cleaning, but also is used indetermining the residue limit and consequently cleaning process efficiency.

清洁剂的毒性不仅对于清洁中的人员安全很重要，还将用于确定残留限度和清洁工艺的效率。

10.1.2.8 Rinsability

可冲洗性

Cleaning agents should be free-rinsing. Cleaning agents that foam can be difficult to rinse and mayalso cause pump cavitation in CIP systems and COP washers.

清洁剂应该易于冲洗。起泡的清洁剂很难冲洗干净，还可能导致 CIP 系统和 COP 清洗机的泵气蚀。

10.1.2.9 Quality

质量

Cleaning agents should have a specification, be lot-traceable, and preferably be manufactured usingCGMP practices with appropriate change control policies.

应建立清洁剂的质量标准，每批均具有可追溯性，最好 按照 CGMP 规范生产，并有合适的变更控制程序。

10.2 Nonproduct Contact Surfaces

非产品接触表面

Nonproduct contact surfaces may be defined in different ways by manufacturers. For surfaces with noproduct contact (e.g., floors, walls, outsides of process equipment), there should be cleaning procedures.However, these cleaning processes are generally less critical and do not require cleaning validation. Cleaning for these nonproduct contact surfaces may be repeated in full or in part if the cleaningprocess results in visible and/or gross levels of residual soils.

不同的生产商对非产品接触表面的定义可能不同。对于没有产品接触的表面（例如，地面、墙面、工艺设备外表面），应该有相应的清洁程序。但是，这些清洁工艺通常没有那么关键，不需要进行清洁验证。如果清洁后仍有可见和/或明显残留污物，应重新对非产品接触表面进行全面或部分清洁。

There are other nonproduct contact surfaces which may contact the product *indirectly,* such as by avector or by an airborne route. These are sometimes called “indirect product contact surfaces”. Examplesof these types of surfaces might include lyophilizers, equipment used solely to manufactureand transfer buffers, media, and excipients, and stopper bowls. These indirect product contact surfacesshould be included in the cleaning validation program. However, because of the limited impactof these indirect product contact surfaces, requirements for cleaning validation, such as limits, maybe different from cleaning validation for *direct* product contact surfaces. A risk assessment should beutilized to define the requirements, which will depend on the specifics of the manufacturing situation.For example, for highly hazardous drug active ingredients, cleaning validation of nonproduct contactsurfaces may be performed in order to document any potential of airborne transfer to another productas well as for operator safety reasons ***(12).***

还有些非产品接触表面，可能间接接触产品，例如通过载体或空气。有时称之为“间接产品接触表面”。这类表面可能包括冻干机，单独用于生产或转移缓冲液、介质、辅料的设备、胶塞桶。间接产品接触表面应该包括在清洁验证计划中。但是，因为这些间接产品接触表面的影响有限，清洁验证的要求，例如限度，可以与直接产品接触表面的清洁验证不同。应该进行风险评估，根据生产条件的具体情况，确定清洁验证要求。例如，对于高危的药品活性成分，为了证明残留通过空气转移至其他产品的可能性，以及出于操作者安全考虑，应进行非产品接触表面的清洁验证（12）。

See **Section 10.9** for information related to secondary packaging equipment surfaces.

对于外包装设备表面相关的信息请见 10.9 节。

10.3 Process Analytical Technology

过程分析技术

Process Analytical Technology (PAT) is defined by the U.S. FDA to be “a system for designing, analyzing,and controlling manufacturing through timely measurements (i.e. during processing) of critical qualityand performance attributes of raw and in-process materials and processes, with the goal of ensuringfinal product quality”***(32)***. The U.S. FDA further notes that “the term ‘analytical’ in PAT is

viewedbroadly to include chemical, physical, microbiological, mathematical, and risk analysis conducted in anintegrated manner." The use of a PAT approach may replace traditional validation approaches.
美国 FDA 定义过程分析技术（PAT）为"一个用于生产设计、分析、控制的系统，通过即时测定（例如在处理过程中）原料、中间体和工艺的关键质量和性能属性，保证最终产品质量"（32）。美国 FDA 进一步说明"应宽泛地理解 PAT（过程分析技术）中的术语"分析"，它综合了化学、物理学、微生物学、数学和风险分析的方法"。可用 PAT 方法取代传统的验证方法。

Much has been published about PAT in general and about PAT in many processes; the reader shouldinvestigate current literature for a general background on PAT. However, there are limited publicationsabout PAT in cleaning processes and cleaning validation as compared to PAT for other manufacturingoperations. The use of a feedback loop from the analytical measurement to control a cleaningprocess or cleaning process step is the point of using PAT. It should be noted that consistent with PATprinciples, the timely measurement could be in-line, online or at-line.
对于 PAT 的一般要求和不同过程的 PAT 应用有很多出版物。读者应该调研最新文献以获取 PAT 基本知识。但是，相对其他生产操作来说，关于 PAT 在清洁工艺和清洁验证中的应用的出版物有限。通过分析结果的反馈回路控制清洁工艺或清洁步骤是使用 PAT 的关键。应该注意为了与 PAT 原则保持一致，即时测试可以采用 in-line、on-line 或 at-line 的方式。

10.3.1 Timely Measurements
即时测试

"Timely measurements" have long been used in cleaning processes to assist in the design of *rinse cycletimes* in automated CIP systems. For example, a common practice in the design of the rinsing processusing cleaning solutions or products with high conductivity values has been to measure conductivityof the final rinse as a function of rinse time. If evaluated over several cleaning process runs in thedesign phase, a minimum time to consistently complete the rinsing process can be effectively determined.A safety factor (additional time) may be included as part of this determination. While such astudy in the design phase would be appropriate for a PAT application, unless it combines the timelymeasurement with a feedback mechanism to control the cleaning process during commercial cleaningprocesses, it would not be considered to be a PAT. As described *in this paragraph*, the purpose ofthe timely measurement is not to control the rinsing process but to assist in selecting a *fixed* rinse time.
长期以来，在自动 CIP 系统中，"即时测试"被用于帮助设计冲洗行程时间。例如，在采用高电导率的清洁溶液或产品设计冲洗工艺时，通常的做法是测量不同冲洗时间的最终冲洗液的电导率。对设计阶段的几个清洁过程进行评估，可以有效地确定一个最短时间，以获得一致的清洁效果。。确定该最短时间时可引入安全因子（适当增加一些时间）。尽管可以在设计阶段对 PAT 应用进行此类研究，但并不认为它就是一个 PAT，除非在大生产过程中将即时测试与反馈机制结合起来对清洁工艺进行控制。如本段所述，即时测试的目的不是用于控制冲洗工艺而是帮助选择一个固定的冲洗时间。

10.3.2 PAT for Cleaning Process Control
清洁工艺控制

The more relevant use of PAT for cleaning processes is the use of a timely measurement to define thecompletion of a cleaning process. In this case, the achievement of a certain analytical measurement isa controlling mechanism for completion of that process. In the situation referred to previously aboutmeasuring conductivity online, if it is possible to determine through experimentation and modeling thatthe achievement of a certain conductivity correlates in a statistically significant and operationally

meaningfulmanner with the end of the rinsing process, conductivity could be employed in a PAT approach.That is, the rinse time is not fixed but could be variable depending on the time needed to achieve thatpredetermined conductivity value. In addition, consistent with PAT principles, it would be expected thatthe achievement of that conductivity value would be within a defined time window. The U.S. FDA PATguidance ***(32)*** states "Within the PAT framework, a process end point is not a fixed time; rather it is theachievement of the desired material attributes. This, however, does not mean that process time is notconsidered. A range of acceptable process times (*process window*) is likely to be achieved during the manufacturingphase and should be evaluated, and considerations for addressing significant deviations fromacceptable process times should be developed." In both cases, a final conductivity is recorded and a finalrinse time is recorded. However, in the traditional approach, time is the step-controlling parameter andconductivity is the monitoring parameter. In a PAT approach, conductivity could be the step-controllingparameter and time would be the monitoring parameter. Lack of achieving the desired conductivitywithin the time window should result in an investigation under a CAPA program.
清洁工艺相关的 PAT 应用更多是使用即时测试去确定清洁工艺的完成。在这种情况下，获得某个分析结果是工艺完成的一个控制机制。如上述关于在线测定电导率，如果通过实验和模型有可能确定某个电导率可以与冲洗工艺的终点相关联，并且该关联具有统计学意义和可操作性，那么电导率测定可作为 PAT 的一种方法。也就是说，冲洗时间不是固定的，可以根据达到预定的电导率值所需的时间而定。此外，与 PAT 原则一致，可以预见达到该电导率值所需时间在规定时间窗以内。US FDA PAT 指导原则（32）提到"在 PAT 框架内，工艺终点不是固定时间，而是达到预期物料属性。但是，这并不是意味着可以不考虑工艺时间。生产过程中很可能出现一个可接受的工艺时间范围（时间窗），并应对其进行评估，应建立出现工艺时间显著偏差时应该采取的处理方法"。在这两种情况中，应记录最终的电导率和最终冲洗时间。但是，在传统的方法中，时间是步骤控制参数，而电导率是监控参数。在 PAT 方法中，电导率可以是步骤控制参数，时间为监控参数。如果在时间窗内没有达到预期的电导率，应该启动 CAPA 调查。

Another example of a PAT application for cleaning is in the use of organic solvent cleaning in smallmoleculeAPI synthesis. In this situation, the active ingredient in the solvent may be measured usingonline UV spectroscopy. The achievement of a low absorbance value, corresponding to the limit ofthe active in the rinse or solvent reflux sample, may be used to determine the process completion.
另一个 PAT 应用于清洁的例子是小分子 API 合成中采用有机溶剂进行清洁。在这种情况下，可以采用在线 UV 光谱扫描测定溶剂中的活性成分。当达到一个低的吸光度值，该值相当于活性物质在冲洗液或溶剂回流样品中的限度，就可以确定清洁工艺的完成。

Sometimes there is an objection to the use of PAT in this way because it seems to violate the cleaningvalidation principle of not cleaning until clean (or testing until the equipment is clean). However, oneof the features of PAT is that traditional rules of what is done for validation may not apply. As noted inthe U.S. FDA's 2011 Process Validation guidance, "In the case of a strategy using PAT, the approachto process qualification will differ from that used in other process designs" (***10***).
有时候对于采用这种 PAT 的方式会有异议，因为其似乎已经违背了清洁验证原则，即不得反复清洁直至符合要求（或者重复测试直到符合设备清洁要求）。但是，PAT 的一个特征是传统的验证理论已不再适用。US FDA2011 工艺验证指导原则中指出，"在使用 PAT 的控制策略时，工艺确认的方法将与其他工艺设计中使用的方法不同"（10）

10.3.3 Additional Considerations for Online Measurements

对于在线检测的额外考虑

It should be clarified that online methods by themselves do not necessarily constitute PAT. As discussedpreviously, online measurements (such as UV spectroscopy or conductivity) of a final rinse canbe a routine monitoring tool in a cleaning process step *without* controlling a process step. Such onlinemeasurements, even though they don't control process completion, may be used as a means of cleaningverification after each cleaning event.

需要澄清的是在线方法本身不一定是 PAT 的组成部分。如此前讨论的，最终冲洗液的在线检测（如紫外光谱或电导率）可以作为清洁工艺步骤中的例行监测工具，而不是控制工艺步骤。这类在线检测，即使没有用来控制工艺结束，也可以作为每次清洁后清洁效果确认的一种方法。

10.4 Clean Hold Considerations

"清洁保持"注意事项

Following cleaning, equipment that is to be reused should be stored in a manner to protect it fromcontamination during storage. Clean hold time is the time from the end of cleaning until subsequentuse of the equipment, which may be product manufacture or may be a steam-in-place (SIP) cycle."Clean hold time"is different from "dirty hold time" in that dirty hold time should be evaluated inthe basic cleaning validation protocol as a worst-case condition or challenge. Clean hold time may beincluded as a second part of the basic cleaning validation protocol or may be considered as a separateprotocol (apart from the basic cleaning validation protocol). The cleaning process validation studyand the clean hold time study are related in that the data for bioburden at the end of the cleaningprocess also serve as the "time zero" bioburden data for the clean hold study.

清洁后，待使用设备的保存应能避免其受到污染。清洁保持时间为设备清洁结束至下一次使用的时间，可能用于产品制备或者进行在线灭菌（SIP）。"清洁保持时间"与"生产后保持时间"不同，生产后保持时间应该在基本的清洁验证方案中予以评价，并作为一种最差条件或挑战。清洁保持时间可以作为基本清洁验证方案的第二部分，或者作为一个单独的方案（与基本清洁验证方案分开）。清洁工艺验证研究和清洁保持时间研究具有一定关联性，因为清洁结束时生物负载数据也可作为清洁保持研究的"零时"生物负载数据。

The major concern with the clean hold time is the possibility of recontamination from external sourcesand the possibility of microbial proliferation because the equipment is wet with water during theclean hold period. The major *regulatory* concern is the control of microbial proliferation during thestorage of equipment. If the microorganisms that proliferate are Gram-negative bacteria then issueswith endotoxin may also arise. External sources of recontamination can be prevented by closing thedry equipment or by wrapping the dry equipment in plastic (or storing in plastic bags). Selectionof an area for storage (including temperature and humidity) is also important for preventing externalrecontamination. Water in the equipment can come from lack of drying at the end of cleaning,condensation of water onto equipment surfaces from humid air because of a temperature drop, andexternal sources (such as splashing water onto cleaned equipment because the equipment is storednext to a wash sink).

对于清洁保持时间，需要重点关注的是外部污染的可能性和微生物繁殖的可能性，因为设备在清洁保持期间是潮湿的。法规方面应关注设备储存期间对微生物繁殖的控制。如果繁殖的微生物为革兰氏阴性菌，还可能导致内毒素的产生。可以通过干燥并密封设备或用塑料膜包裹干燥的设备（或存储在塑料袋中）防止外来污染。存储区域的选择（包括温湿度）对于防止外来污染也是非常重要的。设备中有水可能由于清洁结束时没有干燥，或者由于温度下降导致空气中水分凝结在设备表面，以及外来的（例如水溅至已清洁设备上，因为设备放在一个清洗水槽旁边）。

Criteria used to determine acceptability after storage under defined conditions may include lack ofmicrobial proliferation, endotoxin level and visual examination. A major regulatory concern is thecontrol of microbial proliferation during the storage of equipment. While based on a risk assessmentit may be possible to justify not measuring bioburden for a clean hold time before a sterilization process,it may be prudent to measure bioburden after the clean hold time to ensure that the subsequentsterilization is not excessively challenged. This is also important from the standpoint of the controlof pyrogens from Gram-negative bacteria, which may not be removed or inactivated by sterilizationprocesses. An additional issue is to insure that plastic wrap or bags are intact and not compromisedduring the clean hold storage. Storage instructions should be specified in a control document, such asthe cleaning procedure or approved storage procedure.
用于确定设备在规定条件下储存后的可接受标准应该包括没有微生物繁殖，内毒素和目检符合要求。法规方面主要关注的是设备储存期间的微生物繁殖控制。尽管基于风险评估，对于灭菌之前的清洁保持时间，可不测定生物负载，明智的做法是在清洁保持时间之后测量生物负载，以确保接下来的灭菌工艺不会被过度挑战。从控制革兰氏阴性菌产生热原的角度来说，这也是很重要的，因为热原无法通过灭菌工艺去除或者灭活。另一个问题是确定塑料包裹物或袋子是完整的，在清洁保持期间不会破损。储存要求应该规定在受控文件中，例如清洁程序或批准的存储程序。

The best procedures are to store cleaned equipment in a dry state or in a solution that inhibits themicrobial proliferation. If equipment is to be stored in a dry state, manufacturing controls should bein place to ensure that equipment is sufficiently drained and dried upon completion of the cleaningprocess, as well as to minimize the amount of condensed water accumulation in the equipment *after*cleaning due to equipment cooling. In addition, it is preferred that equipment be stored in a mannerto prevent external recontamination. If stored in a dry state and if protected from external contamination(e.g., by sealing the equipment or by covering any openings with appropriate “GMP” covers),formal studies to demonstrate lack of microbial proliferation may not be necessary. Based on soundscientific principles, microorganisms will not proliferate on clean, dry surfaces. If stored in an inhibitingsolution, the solution should be known to inhibit microbial growth (such as dilute caustic) or datashould be developed to demonstrate inhibition. Recirculation of the storage solutions may also assistin microbial growth inhibition. Procedures should be in place to adequately remove that inhibitingsolution from equipment prior to use.
最好的方法是将已清洁设备干燥后存放或保存在一种可以抑制微生物繁殖的溶液中。如果拟将设备干燥后存放，应确保设备充分排水，在清洁工艺结束时立即进行干燥，以及减少清洁后设备冷却导致的冷凝水的量。此外，设备的储存方式最好能防止外来污染。如果存储在干燥状态并能防止外来污染（例如，密封设备或用合适的“GMP”覆盖物盖住任何的敞口之处），就不必进行正式研究以证明没有微生物繁殖。基于合理的科学原则，微生物无法在干净干燥表面上繁殖。如果储存在抑菌性溶液中，应确定溶液可以抑制微生物生长（例如稀碱溶液）或者应该获得数据以证明其抑菌性。储存溶液的循环也有助于微生物生长抑制。应建立程序在设备使用之前充分去除抑菌性溶液。

If the equipment is stored with a possibility of water in all or parts of the equipment, there are two commonstrategies to control microbial proliferation during the storage of equipment. One strategy is toestablish an acceptable time between the end of cleaning and the beginning of the next use (which maybe sterilization, sanitization, or a manufacturing process step) by performing a clean hold validation. Aftera predetermined storage time, sampling by a suitable method is performed and the post-hold data is comparedto the data at the beginning of storage. If rinse sampling is used, it should be ambient

temperaturewater so that what is measured is the bioburden remaining on surfaces (the use of a hot water rinse mayreduce the bioburden in the rinse solution). Bioburden (and possibly endotoxin) levels in the equipmentare measured to ensure that levels would not challenge the sterilization or sanitization procedures orexceed in-process manufacturing specifications. Since purified water or WFI is not an ideal medium forbacterial growth, another approach is to require the use of the cleaned equipment within a short timeperiod, such as one shift or 24 hours, such that microbial proliferation is not likely to occur.
如果设备储存时其全部或部分可能有水，有两个常用的策略以控制设备储存过程中微生物繁值。一个策略是通过清洁保持验证，确定清洁结束至下一次使用（可能是灭菌、消毒或生产）之间的可接受时间。在一个预定的储存时间后，通过合适的方法取样，将清洁保持时间后的数据与储存开始时的数据进行比较。如果使用冲洗样品，应该使用常温水，使得测定的结果能够代表设备表面上的生物负载（使用热水冲洗可能减少冲洗溶液中的生物负载）。测定设备上的生物负载（和内毒素，适当时）水平以确保该水平不会挑战灭菌或消毒程序或超过中间过程控制标准。由于纯化水或注射用水不是细菌生长的理想培养基，另一种方法是在较短时内使用已清洁设备，如一个班次或 24 小时后，这样就不太可能会有微生物繁殖。

If clean hold validation is not performed, or if the validated clean hold time is exceeded, a validatedwater (usually hot purified water or WFI) flush may be used before sterilization, sanitization, and/or use of the equipment to reduce microbial proliferation that might have occurred during storageto an acceptable level before further manufacturing or processing on the equipment. After the waterflush, sampling (by rinse, swab or plating) is performed. Bioburden (and optionally endotoxin) levelsin the equipment are measured to ensure that levels would not challenge the sterilization or sanitizationprocedures or exceed in-process manufacturing specifications. Another approach is to performadditional bioburden sampling to document that microbial proliferation has not occurred.
如果没有进行清洁保持验证，或者已经超过了验证的清洁保持时间，在进行灭菌、消毒和/或使用设备之前，可以采用已验证的水冲洗法（通常使用纯化水或 WFI），在下一步生产或设备处理之前，将储存期间可能发生的微生物繁殖降低至可接受水平。水冲洗以后，取样（通过冲洗，擦拭或接触碟法），测定设备中的生物负载（和内毒素，适当时）水平以确保该水平不会挑战灭菌或消毒程序或超过中间过程控制标准。另一个方法是进行额外的生物负载取样，并记录没有微生物繁殖。

For clean hold time studies using rinse water fed from process lines, a few common approaches forestablishing the acceptable amount of rinse water to use are based on the minimum working volumeof the system or the minimum CIP rinse based on the design. Bioburden values in rinse sampleshould be compared to the measured bioburden values based on the equivalent rinse sampling at thebeginning of storage. It is preferable to collect the entire volume of rinse solution and agitate it fora specified period of time to ensure homogeneity before collecting the sub-sample for testing. Thiscollection of the entire rinse sample may be done in the process vessel itself or in an external vessel.
当采用来自工艺管道的冲洗水进行清洁保持时间研究时，确定冲洗水用量的通用方法是基于系统最小的工作容积或基于设计的最小的 CIP 冲洗量。冲洗样品中的生物负载应该与在储存开始时采用相当的冲洗取样方法测得的生物负载进行比较。在采集用于检测的子样品之前，最好收集所有的冲洗溶液，搅拌规定时间以确保均一性。所有冲洗液可以收集在工艺容器内或者是一个外部容器中。

Validation of clean hold studies on a given piece of equipment is applicable to all products using thatequipment and to all cleaning processes for that equipment, provided the final state of the cleanedequipment and the storage conditions are consistent. If a validated clean hold time is exceeded,

anassessment should be made as to the need for corrective action. Appropriate corrective actions beforeuse or further processing may include cleaning the equipment again using a validated cleaning processor using a validated hot water rinse (as described above) to bring bioburden to an acceptable level.If any changes to the equipment, manufacturing processes and/or cleaning procedures are made, theimpact of these changes on the clean hold studies should be evaluated.
对于一个指定设备的清洁保持研究适用于所有的使用该设备的产品和该设备的所有清洁工艺，只要清洁设备的最终状态和储存条件是一致的。如果超过了验证的清洁保持时间，应该进行评估以确定是否需要采取纠正措施。在使用和进一步处理之前，合适的纠正措施可以包括使用已验证的清洁工艺重新清洁设备或者使用已验证的热水冲洗（如上述）至生物负载降至可接受水平。如果对设备、生产工艺和/或清洁程序有任何变更，应该评估变更对清洁保持研究的影响。

If cleaned equipment is to be stored for an extended period of time in an area that is not controlled, itis even more important that the equipment be stored in a dry state because of possibilities of significantbacterial or mold proliferation. In any case, there should be a procedure in place to deal with thereturn of such equipment to active use. This may be an individual determination on a case-by-casebasis, it may be treating the equipment as if it exceeded the dirty hold time, or it may be treating theequipment as if it exceeded the clean hold time. A risk assessment for the specific facility will helpdetermine which option is utilized.
如果拟将已清洁设备长时间储存在一个不受控的区域内，那么比较重要的是设备应干燥储存，因为有细菌或霉菌大量繁殖的可能性。任何情况下，都应该有程序规定在什么条件下才能使用该设备。可以基于具体情况做出决定，也可以像超过生产后保持时间一样对设备进行处理，或者像超过清洁保持时间一样对设备进行处理。对于特定的公司应该通过风险评估确定采用哪种方式。

10.5 New and Used Equipment
新设备或使用过的设备

Introducing additional equipment into a firm’s established cleaning validation program presents severalissues which will require careful consideration. Factors such as equipment design, materials ofconstruction, modes of operation and product-contact surface area are likely to influence decisionson how the incoming equipment will fit and on what steps should be taken to integrate the equipmentinto the cleaning program. Additionally, whether the equipment is of new construction or wasobtained as a used piece of equipment should be considered when developing steps to utilize theequipment. These considerations for new and used equipment may also be applicable to equipmentthat has been repaired or refurbished.
将额外的设备引入至已建立的清洁验证计划时，需要仔细考虑几个问题。例如设备设计、材质、操作方式和产品接触表面面积很可能会影响如何以及在哪个工艺步骤将其整合至清洁计划中。此外，当确定采用该设备的工艺步骤时，应该考虑该设备是新的还是使用过的。这些对于新设备和使用过的设备的考虑也适用维修的或翻新的设备。

10.5.1 New Equipment
新设备

When adding new equipment to a cleaning program, some points to consider are as follows.
当引入新设备至清洁计划中时，应该考虑如下几点：

10.5.1.1 Cleaning Procedure Development
清洁程序的开发

If the new equipment is sufficiently similar to existing equipment, design/development for the newequipment may leverage knowledge from that existing equipment. If the new equipment is not similarto existing equipment, additional cleaning development work may be required. The design characteristicsand operational parameters of the new equipment may present hard-to-clean areas or operatingranges not previously encountered in existing equipment.
如果一台新设备与现有设备足够相似，新设备的设计/开发可以采用现有设备的知识。但是如果新设备与现有设备并不类似，则需要额外的清洁开发工作。新设备的设计特性和操作参数使得可能会存在难以清洁的区域，或新设备的操作范围在现有设备中没有遇到过的。

10.5.1.2 Post-Installation Cleaning

安装后清洁

Following the installation of the new equipment, cleaning is typically required in order to remove anygrease, dust or other debris. Manufactured product residues are not usually a concern at this point.The effectiveness of this cleaning may be shown using a visual inspection, water-break evaluation, awhite-glove (or black-glove) test, and/or various chemical tests (such as TOC and conductivity). Thiscleaning is not typically validated, but is verified (see **Section 4.4** on “Cleaning Verification”).
在新设备安装以后，通常需要清洁以去除油污、灰尘或其他的碎屑。此时产品残留通常不在考虑之列。采用目测、设备表面水膜评价或白手套（或黑手套）检查、和/或各种化学测试（例如 TOC 和电导率）确定清洁的有效性。这些清洁通常不需验证，但是需要进行效果确认（见 4.4 节“清洁效果确认”）。

10.5.1.3 Grouping Impact

对分组的影响

If a firm employs a grouping approach regarding equipment, the addition of new equipment into theproduction facility may have an impact on established equipment groups. See **Section 4.3** “Grouping/Family Approach” for more information.
如果一个公司对设备采用了分组的方法，那么增加新的设备会影响已经确定的设备分组。更多的信息见 4.3 节：“分组/分类的方法”。

10.5.1.4 Limit Calculation Impact

对限度计算的影响

The addition of new equipment into an established train, line or group may have an impact on acceptancelimits based on the increase or decrease of product-contact surface area. Calculations should bereviewed for any impact and any changes implemented through a change control program.
在已建立的设备组、生产线或分组中引入新设备时，由于增加或减少产品接触面积，可能会对可接受限度产生影响。对于通过变更控制计划实施的任何变更或产生的任何影响，应对限度计算进行复核。

10.5.2 Used Equipment

使用过的设备

When adding used equipment to a cleaning validation program, the points noted in the previous sectionabout new equipment apply. An additional point to consider for used equipment is equipment history.It is desirable to have as much information as possible about the compounds that were previouslymanufactured in the equipment. Some information of interest would be the type of compound

(e.g.,pharmaceutical or pesticide) and the hazards and/or toxicity of the compounds. That information maybe used to determine an acceptable cleaning process for the used equipment, and to set acceptancelimits for those compounds for a cleaning verification evaluation following the cleaning process.
当将使用过的设备引入至清洁验证计划中时，在此前章节中提到的引入新设备时应考虑的几点也同样适用使用过的设备。对于使用过的设备还需考虑的一点是设备历史。应尽可能多地获得以前在该设备中生产的物料有关信息。一些有用的信息可能包括物料种类（例如药品或杀虫剂）和危害性和/或物料的毒性。这些信息可以用于确定已使用设备的合适的清洁工艺，以及建立这些物料残留的可接受限度，以便在清洁结束后进行清洁效果评估。

If little to no information about the previous compounds is available, it may be possible to identifypotential manufactured products by FTIR analysis of swabbed surfaces. Additional surface modificationsteps (e.g., descaling, pickling, passivation, reglassing, repolishing) may be taken to assure thecleanliness of the equipment. An evaluation of cleanliness may also entail TOC analysis (as a generalmeasurement of equipment cleanliness) and/or FTIR analysis of sampled surfaces (to confirm removalof any potentially objectionable organic residues identified in the precleaning FTIR analysis).The justification for a firm’s decision should be captured in a documented risk-consideration. In somecases, the additional cost of the steps taken for used equipment may negate any cost benefit; therefore,this consideration should be made well in advance of the purchase.
如果关于此前生产的物料信息很少或者没有，则可以采用 FTIR 分析表面擦拭样品，识别以前可能的生产产品。也可以采用额外的表面处理步骤（例如除锈、酸洗、钝化、再磨光、再抛光）以确保设备清洁。对清洁的评价可以采用 TOC 分析（作为设备清洁测试的通用方法）和/或 FTIR 分析表面取样（以确认在清洁前 FTIR 分析确定任何可能有害残留已经去除）。应通过书面的风险分析说明公司决策决定的依据。有时，为了应对已使用设备带来的风险而采取的步骤将产生额外的费用，可能抵消采购成本优势，因此，在购买之前应该仔细考虑。

10.6 Measurement Systems Analysis (MSA)
测试系统分析（MSA）

The identification and measurement of variation in the process are needed to determine if the system isperforming as desired and if not, to provide insights into what must be better controlled in order to meetspecifications. The purpose of measurement systems analysis is to measure, understand and control thevariation caused by measurement systems. By separating out this source of variation, the impact of variationin the parameters or aspects being measured can be understood in relation to the cleaning method.
Before beginning a MSA it is extremely important:
应确定并测量工艺中的变动，确保系统是按照预期进行，如果没有按照预期进行，则需要考虑应加强哪一方面的控制，以符合标准要求。测试系统分析的目的是测试、理解和控制由测试系统自身引起的变动。通过将这种变动来源区分出来，就可以很好地理解清洁工艺参数或被测量对象的变动对清洁方法的影响。在开始测试系统分析前，以下工作尤为重要：

- To clearly define the parameters or aspects to be controlled
  清晰确定需要控制的参数或对象
- To identify tests capable of achieving the measurements needed
  确定能够获得所需测量结果的测试方法
- To understand measurement requirements (bias, gage Repeatability and Reproducibility (R&R),

accuracy, stability, linearity, etc.)
理解测试需要（偏差、计量器具重复性和重现性（R&R），准确度、稳定性、线性，等等）

It can be very wasteful and stressful to achieve an unnecessarily low level of measurement sensitivity.For example, if lower limits of detection are quite good compared to the threshold level specification,then statistically significant differences between two tests, provided both are well below the thresholdfor acceptance, often have no operational significance. Be careful not to confuse the process of MSAfor the overall goal: a safe and robust cleaning process that consistently meets its target values.
达到一个不必要的低测试灵敏度，是一件非常浪费和困难的事。例如，如果同残留可接受标准相比，方法的检测限较低，那么两个测试结果之间的统计学显著性差异通常不具有实际操作意义，假如两个测试结果都远低于残留可接受标准。注意不要将 MSA 过程同总体目标（一个安全且具有耐用性的清洁工艺，可以一致地达到目标值）相混淆。

10.6.1 MSA Components
MSA 的组成

The measurement system variation for continuous data can be broken down into the sum of twocomponents: R&R. Such studies examine the precision of a measurement system but not the accuracy.
对于连续数据的测试系统，变动可以分解为两个组成的总和：重复性和重现性。这些研究考察了测试系统的精密度而不是准确度。

Repeatability is an estimate of short term variation of the error that occurs when successive measurementsare made under the same conditions.
重复性是在相同条件下进行持续测定时，对误差的短期变动的估计。

Reproducibility is an estimate of the variation in the average of measurements made between operatorsusing the same equipment or between laboratories performing the same assays and it capturesthe precision of the different groups (labs or operators).
重现性是当两个操作者采用相同设备或两个实验室进行相同试验时，对二者测定的平均值之间的差异的估计，其考察了不同组（实验室或操作者）之间测试结果的精密度。

10.6.2 Attribute R&R
特性 R&R

Attribute R&R are used for discrete data often with binary outcomes and distributions (e.g., pass/fail, good/bad, yes/no). In these studies the focus is on analysis of the ability of the evaluator to detectnonconformance. This is called *effectiveness*. The effectiveness of different evaluators is comparedwhen assessing reproducibility and how biased the evaluator is towards acceptance or rejection. Theprobability of false negatives/positives is also calculated, which results in the ability to measure biastowards one outcome or the other.
特性 R&R 用于通常具有二元结果与分布（例如合格/失败，好/坏，是/否）的离散数据。这些研究重点要分析评价指标检测出不符合的能力，这称为有效性。在评价重现性以及评价指标如何偏离向接受或拒绝时，比较不同评价指标的有效性。也计算假阳性/阴性的可能性，该结果可用于测量偏向这一结果或是那一结果。

10.6.3 Minimizing Variations

变异最小化

There are guidelines for acceptable levels of variation for continuous data as well as attribute levels(effectiveness, bias (False Acceptance/Rejection)) ***(33)***. However the main goal is, as always, to achievean acceptable level of control for the system in question based upon a previously agreed upon set ofcriteria that make sense from a business and patient safety perspective.Ideally,the bulk of the variationthat one measures should come from the items being tested, not the test methods themselves.
关于连续数据以及离散数据（有效性，偏差（误接受/拒绝））的变动的可接受水平，请参加相关指南（33）。但是主要目标都是基于此前批准的标准（考虑到商业和患者安全），达到对系统控制的可接受水平。理想情况是，一个测试的偏差很大程度上应来自被测试对象，而不是测试方法本身。

Many actions can be taken to improve the precision of measurements.
可以采取很多措施改善测试精密度

- Regular maintenance and calibration of equipment
  定期维护和校正设备
- Maintaining and updating SOPs
  维护和更新 SOPs
- Meaningful operator training
  有效的操作培训
- Mapping or charting the process to identify sources of variation (noise)
  绘图或图示流程以确定变异的来源（噪音）
- Alternative measurement systems for the aspect in focus
  备选测试系统
  - analytical method with greater resolution (discrimination)
    分析方法有更大的分离度（区分能力）
  - development of better standards for comparison
    开发更好的比较标准
  - ensure random sampling/test performance when collecting data
    当收集数据时应确保随机取样/检验性能
  - change from manual to automated system
    将手动改为自动系统

10.6.4 MSA and Cleaning Validation Strategy

MSA 和清洁验证策略

In cleaning validation carryover calculations, safety factors are always included in order to cover uncertaintiesdue to cleaning as measured by visual inspection, assumptions about surface area, or thesystem in general. Sometimes one is faced with the dilemma of needing to have measurable limits andthus being unable to apply the safety factor best practice would indicate. Within this framework ofuncertainty, one must create a control strategy whose capabilities are sufficient to ensure patient safety.
在计算清洁验证残留时，通常会引入安全因子，以涵盖由于目检、假定的表面积或系统总体导致的不确定性。有些时候，需要找到可测定的限度，而这样就无法应用最佳规范所要求的安全因子。必须建立一个控制策略，能够在这一不确定性范围内保证患者安全。

MSA is a statistical tool that aids both the analytical methods of detection for carryover as well as

theprocess parameters monitored in the control strategy for the cleaning process. Once the MSA for theanalytic is under control, one can use the same MSA techniques to measure the variation within thecontrol strategy. For example, one can answer the question about whether the pressure fluctuationsmeasured at the spray ball are responsible for or correlated to the trends in TOC from rinse tests or isthe variation simply due to the system used for pressure measurements? One can thus systematicallyaddress critical process parameters for better control. Should these investigations prove fruitless, thenone must re-examine the assumptions in the risk assessments and control strategy that lead to theprioritization of these process parameters.

MSA 是一个统计学工具，可用于检测残留的分析方法和清洁工艺控制策略中监控的工艺参数。一旦 MSA 处于受控状态，可以采用相同的 MSA 技术测定控制策略范围内的变异性。例如，可以回答关于喷淋球处测得的压力波动导致了冲洗溶液的 TOC 趋势变化或者与冲洗溶液的 TOC 趋势有关，还是该变化仅仅由于压力的测试系统造成的？这样就可以系统地控制关键工艺参数。如果这些调查没有结果，那么必须重新检查风险评估和控制策略中的假定，对这些工艺参数进行优先排序。

10.7 Cleaning for API Manufacture

API 生产的清洁

Equipment for multiproduct intermediate and API manufacturing can be exposed to a large varietyof substances and agents (e.g., solvents, reagents, catalysts, cell cultures and processing aids). Detailedwritten procedures should be established to enable effective and reproducible cleaning of these residuesand subsequent release of the equipment for next use. Acceptance criteria for residues and the choiceof cleaning procedures and cleaning agents should be justified on the basis of being practical, achievableand scientifically sound. For equipment producing later stage intermediates and final APIs, cleaningprocedures will therefore need to be developed and validated to remove manufacturing residues thatmay include raw materials, un-isolated intermediates, by-products, degradants and the product itself. Itshould be noted that equipment used solely for some raw materials that are Generally Recognized asSafe (GRAS) and for raw materials or intermediates, visual inspection alone may be appropriate if allparts of the equipment are visually inspectable. For API manufacturing, lack of adequate cleaning mayimpact not only potential cross contamination of the next product, it may also impact the processing ofthe next product (e.g., if residual materials interfere with subsequent process reactions).

用于生产多品种中间体和 API 的设备会暴露于不同的物质和试剂（例如：溶剂、试剂、催化剂，细胞培养物和工艺助剂）中。应该建立详细的书面程序，以有效和重现地清洁残留，并放行设备用于下一次使用。残留物的可接受标准以及清洁程序和清洁剂的选择，应该具有实用性、可实现性和科学合理性。对于用于生产后一阶段的中间体和最终 API 的设备，需要开发并验证清洁程序，以去除生产残留，可能包括原材料、未分离的中间体、副产物、降解产物和产品本身。应该注意的是，对于专用于那些通常被认为是安全的原料（GRAS）、其他原料或中间体的设备，如果该设备的所有部分都可以目测检查，则可仅进行目视检查。对于 API 生产，缺少合适的清洁会导致下一个产品潜在的交叉污染，还会影响下一个产品的加工（例如，残留物质干扰随后的工艺反应）。

The need for limits for residual organic solvents should be evaluated and can utilize a risk assessment.For example, some residual organic solvents evaporate upon drying of the equipment. If there aremeasures in place (e.g., equipment drying or flush with next process solvent) that may mitigate therisk for residues of residual solvents then analytical limits may not be necessary. If necessary, limitsfor residual organic solvents may be derived from ICH Q3 guidance ***(19)***. Limits for other residuesexpected to be present after cleaning must also be established. For some residues, such as earlier intermediates,dose, toxicity, or

acceptable daily intake information may not be established or available.For other residues, such as proteins or unstable residues, degradation may occur to produce multipleother residues, some of which may not be characterized. For these cases, other approaches to theestablishment of limits may be necessary. Industry benchmarking data may be used to determine ifthere are common limits applied for these cases. For any limits approach used, the rationales and riskassessments used to establish that approach should be documented and approved.
应采用风险评估评价是否需要建立有机残留溶剂限度。例如，设备干燥时，一些残留溶剂会挥发。如果有措施（例如，设备干燥或用下一种工艺溶剂冲洗）可以减轻溶剂残留的风险，那就没有必要建立分析限度。如有必要，残留溶剂的限度可根据 ICH Q3 指导原则（19）得出。应建立清洁后其他可能存在残留的限度。对于一些残留，例如，较早的中间体，也许没有剂量、毒性或可接受的日摄入量信息。对于其他残留，例如，蛋白质或不稳定残留，可能会降解产生其他多种残留，其中一些可能无法鉴别。对于这些情况，需要采用别的方法建立限度。工业基准数据可以用于确定这些情况是否可以采用通用的限度。对于所采用的任何限度建立方法，应记录该方法建立的依据和采用的风险评估，并得到批准。

Facilities and manufacturing systems for intermediates and APIs should be designed to facilitate cleaningas appropriate to the type and stage of manufacture. Equipment used for API manufacturing is often large,closed and complex. It often includes a significant amount of process piping and large-scale vessels, dryers,condensers and/or chromatography columns. For this reason, visual inspection of much of the equipmentmay not be possible due to inaccessibility. Equipment design for cleanability is a significant factor in theease and reproducibility of cleaning for these types of large closed systems. Design factors of particularimportance can include equipment and pipe sloping for drainage, elimination or minimization of deadlegs,adequate pump size for turbulent flow of cleaning solutions, and the use of spray coverage devices.
根据生产类型和生产阶段，中间体和 API 的厂房和生产系统的设计应该便于清洁。用于 API 生产的设备通常较大、密闭而复杂。通常包括大量的工艺管道和大体积容器、干燥器、冷凝器和/或层析柱。由于无法接近，不太可能对大部分设备进行目测。对于这类大型密闭系统，设备的可清洁性设计对于清洁的重现性和简易性是非常重要的。尤为重要的设计因素包括设备和排水管道的坡度、盲管的消除和最小化、适当的泵体积以使清洁溶液处于紊流状态、以及喷淋装置的使用。

Quality risk-assessments should be used to determine the need for microbiological specifications (ifany) after cleaning, if any. The harsh chemical environment (e.g., pH extremes, use of organic solvents,high temperature processes) that is often associated with small-molecule intermediate and APImanufacture may eliminate the risk to product quality from microbiological proliferation. Wheremicrobiological specifications have been established for the cleaning, facilities should be designed tolimit exposure to objectionable microbiological contaminants. Equipment cleaning and/or sanitationstudies should address microbiological and endotoxin contamination for those processes where thereis a need to reduce total microbiological count or endotoxins in the API or other processes wheresuch contamination could be of concern (e.g., aqueous-based processing of non-sterile APIs used tomanufacture sterile products).
应该采用质量风险评估以确定是否需要建立清洁后的微生物质量标准（如果有）。小分子中间体和 API 生产中苛刻的化学环境（例如：极端的 pH，有机溶剂的使用，高温处理），可以消除由于微生物繁殖导致的产品质量风险。如果已经建立了清洁后的微生物质量标准，设施的设计应能避免致病微生物污染。对于那些需要降低 API 中微生物总数和内毒素的工艺或其他需要关注此类污染的工艺（例如用于生产无菌药品的非无菌 API 采用液体工艺生产），设备清洁和/或卫生研究应该包含微生

物和内毒素污染的研究。

Cleaning validation at product changeover should be directed to situations or process steps wherecontamination or carryover of materials poses the greatest risk to API quality ***(34)***. Cleaning validationis typically performed on equipment used to produce later stage intermediates and APIs. SeeICH Q7 Table 1 for guidance on where cleaning validation may be expected ***(34)***. For equipment usedin early intermediate production, it may be unnecessary to validate equipment cleaning procedures.In these cases, cleaning verification for multipurpose equipment is still required. Validated analyticalmethods used to verify the equipment cleaning should be used. If product/processing residues aredemonstrated to be removed by subsequent purification steps, this may be considered in a documentedrisk assessment to determine the level of cleaning and cleaning validation necessary.
在更换产品时的清洁验证应该关注那些物料携带或污染会给 API 质量带来最高风险的情况或工艺（34）。清洁验证通常在生产较后阶段中间体和 API 的设备上进行。对于何时进行清洁验证，见 ICH Q7 表 1（34）。对于前一阶段中间体生产的设备，没有必要验证这些设备的清洁程序。在这些情况下，需要对共用设备进行清洁效果确认。用于确认设备清洁效果的分析方法应经过验证。如果产品/工艺残留被证明可以通过后续的纯化步骤去除，应在书面的风险评估中予以考虑，并确定清洁的程度和所需的清洁验证。

Cleaning procedures should be monitored at appropriate intervals after validation to ensure that theyremain effective when used during routine changeovers. Depending on equipment design and complexity,it is typical for API equipment cleanliness to be routinely monitored by analytical testingand/or visual examination, where feasible, after each cleaning after cleaning validation is completed.This is often associated with the higher risk of some API cleaning circumstances (e.g., large closedequipment that cannot be easily visually inspected and the fact that contamination of one batch ofAPI can often implicate many batches of drug product). This routine cleaning monitoring after eachcampaign for multipurpose equipment is often accomplished via rinse sampling and testing for largeclosed equipment.
在验证以后应定期对清洁程序进行监控，以确保例行更换品种时，清洁程序仍然有效。基于设备设计和复杂性，在清洁验证后的每一次清洁后，通常应采用分析测试和/或目测检查，对 API 设备的清洁状况突进行例行监控。这通常关系到较高风险的一些 API 清洁环境（例如大的密闭设备，不易目测检查，而且每批 API 的污染会影响很多批的制剂）。对于共用设备每次阶段性生产后的例行清洁监控通常通过对大型密闭设备冲洗取样和检测来完成。

For more information on biotechnology API manufacture, see PDA Technical Report No. 49 ***(2)***.
对于更多的生物技术 API 生产的信息，见 PDA 技术报告 No.49（2）。

10.8 Topical Drug Products

局部用药品

The major issue with topical drug products relates to how limits are set. The approach to settinglimits depends on the systemic availability of the drug active ingredient when applied to the skin.Some topical products, such as drug patches, are actually transdermal delivery mechanisms to allowsystemic availability of the drug active ingredients. While for other topical drug products, the effect ofthe drug active ingredient is limited to the skin itself and there is generally no, or very low, systemicavailability of the drug active ingredient.
局部用药的主要问题是如何制定限度。设定限度的方法取决于药物活性成分应用到皮肤上的全身利

用度。一些 局部用药,如贴剂,实际上活性成分是通过经皮给药机制发挥作用。而对于其他局部药品，活性成分的作用仅限于皮肤本身，通常没有或仅有极低的活性成分的全身利用度。

10.8.1 Topical Drug Products with Systemic Availability
具有全身利用度的局部药品

Limits for topical drug products where the drug active ingredient is topically designed to be availablesystemically are established based on a typical carryover calculation based on a safe level in the nextproduct. That safe level may be established on either a fraction of the dose or on a toxicological evaluation **(see Section 5.0).** A significant difference may be the portion of the active in the topical drugproduct that is systemically available from the cleaned topical product versus the portion of the activeingredient that is systemically available when that active ingredient is present as a residue in the nexttopical product. In the absence of specific information, it may be assumed as a worst case that the residue of the cleaned active is 100% systemically available when in the next product. As with othercarryover calculation based on the therapeutic dose, the minimum dose of cleaned active ingredientand the maximum dose of the next product should be adjusted based on factors such as the numberof applications per day (or per other time period) and the amount of product applied per application.

对具有全身利用度的局部用药，其限度应基于在下一产品中的安全水平计算出的典型残留量而建立。这个安全水平可以建立在剂量的一部分或毒理学评价之上(见 5.0 节)。一个显著的差异可能是在具有全身利用度的局部用药中的部分活性成分是来自被清洁的局部用药，而另一部分具有全身利用度的活动成分作为残留出现在下一局部用药产品中。缺乏详细的信息，可以假设其为最差条件，即存在于下一产品中的被清洁的活性成分残留具有 100%的全身利用度。同其他基于治疗剂量残留计算一样，被清洁的活动成分的最小剂量和下一个产品的最大剂量应根据每天(或每个其他时间周期)的应用次数和每次用量等因素进行调整。

Another factor that may be considered in setting limits in this situation is dermal irritation of the activeingredient. In most cases, this will not be a limiting factor, but it may be considered, particularlyif the active ingredient, which is the residue, is not systemically available when present in the nexttopical drug product.

在这种情况下，设定限度时需要考虑的另一因素是活性成分对皮肤的刺激性。在大多数情况下，这不会是一个限制因素，但它可能被考虑，特别是当残留的活性成分在下一个局部药物产品中不呈现全身利用度时。

10.8.2 Topical Drug Products with No or Limited Systemic Availability
不具有或具有有限全身利用度的局部用药

For some topical drug products, the therapeutic effect is limited to the skin to which the drug productis applied. An example of such a product is sunscreen (a drug product in some countries, such as theUSA). If the therapeutic effect of the active ingredient is so limited then a modification of a traditionalcarryover calculation may be utilized. The reason is that a “dose” for such topical drug products isgenerally not well defined, as the “use instructions” may typically read “Apply to the affected area.”

对于一些局部药物产品，治疗效果仅限应用于应用了药物的皮肤。例如防晒霜(在一些国家被作为药品，比如美国)。如果有效成分的治疗效果仅限于局部，那么可以对传统的残留计算方法进行调整。原因在于这种局部用药的“剂量”一般不是很好确定，因为“使用说明”通常是“应用于受影响的区

域。”

10.8.2.1 Adjusted Calculation

调整计算方法

A traditional carryover calculation bases the limit on a minimum dose of active ingredient of the productthat is cleaned and a maximum dose of the next drug product. However, in this situation (wherethe effect of the active ingredient is limited to the skin it is applied to) it is not necessary to considerthe minimum dose of the cleaned active ingredient as application to a very small area (such as 100 cm^2)and the maximum dose of the next product as application to the entire body (such as 1.6 m^2). Thosecalculations can be used but they result in extremely low limits. However, the relevant safety concern iswhat happens if 0.001 of the amount of active applied to a given area (such as 100 cm^2) appears in thenext drug product which is also applied to the same surface area (in this example, 100 cm^2). Becausethe therapeutic effect is limited to the skin surface the drug product is applied to, limits can be based on0.001 of the concentration of the active ingredient from the cleaned product in the subsequently manufacture drug product (suitably modified by application conditions which will be discussed shortly). Inother words, if the drug product which is cleaned contains 0.5% drug active ingredient, then the safelevel in the next drug product is 0.001 of that concentration, or 0.0005% (5 ppm).

传统的残留计算方法是基于被清洁产品活性成分的最小剂量和下一产品的最大剂量。但在这种状况下（活性成分的效果仅限于应用该药品的皮肤)，则不必考虑被清洁的活性成分的最小剂量（应于于非常小的区域，如 100cm^2）和下一产品的最大剂量（应用到整个身体，如 1.6m^2)。可以这样进行计算，但得到的限度极低。但是,如果应用到一个给定的区域(如 100 cm^2)的活性成分的千分之一量出现在下一个药物产品中，该下一产品也应用于相同的表面面积(在这个例子中，100 cm^2)，会有什么安全顾虑呢？因为治疗效果是限于应用了药物的皮肤表面，限度可以基于被清洁产品的活性成分在随后生产药品中浓度的千分之一(适当地修改应用条件不久将要讨论的)确定。换句话说，如果被清洁药物含有 0.5%的药物活性成分，那么下一产品中的安全水平是该浓度的 0.001 倍，或 0.0005%(5 ppm)。

10.8.2.2 Modification Based on Frequency of Application

基于应用频率的修改

Carryover calculations should be modified first based on the frequency of application. For example,if the cleaned product is applied a minimum of once per day and the second product is applied amaximum of three times a day, then the limit should be lower by a factor of 3 (with a resulting limitof 0.00016% in the example given). If the first product is applied a minimum of three times a day andthe second product applied a maximum of once per day, then the limit may be higher by a factor of 3(resulting in a limit of 0.0015% in the example given).

残留的计算首先应该基于应用频率进行修改。例如，如果被清洁产品是每天应用至少一次，下一产品每天最多 3 次，那么限度应该应除以 3(在上述例子中，限度为 0.00016%)。如果第一个产品是一天应用至少三次,第二个产品每天应用最多一次，那么限度应乘以 3 倍(在上述例子中，限度为 0.0015%)。

10.8.2.3 Modification Based on Amount Applied per Surface Area

基于单位表面积应用量的修改

A second modifying factor is based on the amount applied per surface area. This is sometimes difficult toassess. However, if it is clear that one product is applied at a significantly higher amount per surface areathen that factor should also be considered. For example, if the cleaned product is typically applied at a

rate of 2 mg/cm2 and the second product typically applied at a rate of 4 mg/cm2, the concentration limit inthe basic example given would be lower by a factor of 2 (resulting in a concentration limit of 0.00025%).
第二个修改因子是基于单位面积的用药量。这是有时很难评估。然而，如果一个产品单位表面积的用量明显很高，则需要考虑这个因素。例如，如果被清洁产品用量通常为 2mg/m^2，第二种产品用量为 4mg/ cm^2，上述例子中浓度限度应降低 2 倍(浓度限度变成 0.00025%)。

One approach is to establish a therapeutic dose of topical preparation in terms of area of applicationcovered by one fingertip unit (FTU), which is defined as the amount of topical preparation ointmentdose delivered from a tube with a 5-mm diameter nozzle, applied from the distal skin-crease to thetip of index finger an adult forefinger (35). One FTU measures approximately 0.5g. As the averagehuman adult area covered by 1 FTU is 286 cm2, approximately 1.75 mg of the topical formulation isapplied per each square centimeter of the skin surface area.
一种方法是依据一个指尖单位(FTU)覆盖的应用面积建立局部用药的治疗剂量，FTU被定义为从一个带有 5mm直径喷嘴的管子挤出的局部药膏制剂的量，从成人的食指远端褶皱皮肤开始应用至食指指尖(35)。一个FTU大约为 0.5 克。因为 1 个FTU覆盖的成人体表面积是 286m^2，大约 1.75mg的局部用药应用于每cm^2的皮肤表面。

10.8.2.4 Additional Considerations
其他注意事项

If a firm has a policy or procedure for a default limit(such as 10 ppm of the cleaning active in the nextdrug product), then the calculated limit (considering the modification discussed in Sections 10.8.2.2and 10.8.2.3) should be compared to that default limit and the lower of the two values utilized forsubsequent calculations.

如果一个公司有默认限度政策或程序(比如下一产品中含 10 ppm 的被清洁活性成分)，则应将计算得出的限度(考虑 10.8.2.2 和 10.8.2.3 节所讨论的修改)同默认值进行比较，并采用较低的数值用于后续计算。

In addition, if there is evidence that the active ingredient in the cleaned product would be systemicallyavailable if it were present in the vehicle (excipients) of the next product, then the calculation in 10.8.1may not be applicable. In such a case, either the calculation in 10.8.1 should be considered or the orderof manufacture may be restricted.
此外，如果有证据表明被清洁产品的活性成分在下一产品中呈现全身利用度，则 10.8.1 所述的计算方法可能不适用。在这种情况下，或者考虑按照 10.8.1 进行计算或限制生产的顺序。

10.8.3 Additional Safety Considerations
其他的安全注意事项

If active ingredients used in topical preparations produce adverse skin irritation effects, hypersensitivity,and/or possible photosensitivity reactions, those considerations should be evaluated to determinewhether more stringent residue limits should be established.
如果用于局部给药制剂生产的活性成分有皮肤刺激性、过敏、和/或可能的光敏性反应，应对此进行评估来确定是否应该建立更严格的残留限量。

10.8.4 Additional Cleaning Considerations
其他清洁注意事项

Topical drug products may present cleaning challenges because of the nature of the excipients usedand the high viscosities of the drug product. In place of a water prerinse, it may be necessary to physicallyremove gross amounts of product left on equipment surfaces using a plastic scraper or a nonwovenwipe. Particularly if the excipients are designed to make the topical drug product “waterproof ”,more stringent cleaning process conditions, such as higher temperatures or higher concentrations ofcleaning agents, may be required for effective cleaning.

因为所使用辅料的性质和制剂的高粘度，局部给药制剂可能给清洗带来挑战，。除了用水进行预冲洗，还可以使用塑料刮板或无纺布抹布去除设备表面的残留物。特别是当辅料的设计旨在使局部给药制剂能够“防水”，可能需要更严格的清洗工艺条件，如高温或更高的浓度清洁剂，以进行有效的清洗。

10.9 Animal Drug Products

动物药品（兽药）

Cleaning validation for animal drug products is basically the same as for human drug products. Themain complication is in setting limits because one product (the cleaned product) may be for one animalspecies and the next product manufactured in the cleaned equipment may be for a different species. Forexample, the cleaned product may be dosed only to horses and the next product dosed only to dogs. Inthis situation, a toxicological assessment to determine a safe limit should be considered for the effect ofthe active ingredient of the cleaned product (dosed only to horses) as if it were used for dogs. All relevanttoxicology and safety information should be considered; for example, drugs that may be residuesin products for cows may have restrictions not based on toxicity to the cows but because of concernsabout safety of the cow’s milk. These concerns may also apply to facilities that make both human andanimal drugs. Limits based on toxicological evaluations are discussed in Section 5.0.

动物药品清洁验证与人用药品基本上是一样的。主要的问题是在残留限度的建立，因为一个产品(被清洁产品)可能用于一种动物而设备清洁后生产的下一个产品可能用于另一种动物。例如，被清洁产品剂量仅用于马，下一个产品仅用于狗。在这种情况下，应针对被清洁产品活性成分（仅用于马）进行毒理学评估来确定一个安全限度，就像它是用于狗的。应考虑所有相关毒理学和安全信息；例如，用于奶牛的产品中的残留限度可能不是基于对奶牛的毒性，而是基于牛奶的安全考虑。这些考虑可能也适用于人用药物和动物药物的共用厂房。基于毒理学评价的限度在 5.0 节做了讨论。

10.10 Packaging Components and Packaging Equipment

包装组件和包装设备

10.10.1 Primary Packaging Components

内包装组件

Product contact surface of primary packaging closures and containers should be free of materials thatcould adulterate the drug product to the extent that fitness for use would be compromised. An evaluationof suitability may include considerations of manufacturing process residues, cleaning agents/solvents, particles, bioburden and/or endotoxin.

内包材密封件和容器与产品接触的表面应不得掺杂异物，导致药品不再适合预定用途。适用性评估可能包括考虑制造过程残留、清洁剂/溶剂、粒子、微生物和/或内毒素。

10.10.1.1 Oral Dosage Forms Primary Packaging Components

口服剂型内包装组件

Cleaning of containers and stoppers used for oral dosage forms is based on a risk analysis. The riskshould

be assessed and appropriate cleaning levels defined that will control the risks to acceptablelevels. Cleaning of containers for solid oral dosage forms, related to risk analysis, could be limitedto removing of solid material by blowing a stream of compressed filtered air into the bottles whileinverted. From a microbial perspective, most solid oral drug products will not allow microorganismsto proliferate, due to the extremely low water activities of these types of products.
用于口服制剂的容器和塞子的清洁应基于风险分析。应对风险进行评估，并确定适当的清洁水平，将风险控制在可接受的水平。固体口服制剂容器的清洁，涉及到风险分析的，可仅限于用经过滤压缩空气吹扫倒置的瓶子，将固体异物去除。从微生物的角度来看，由于这些类型的产品具有极低的水活性，大多数固体口服制剂不利于微生物繁殖。

Some consideration could be provided for the cleaning of containers for liquid oral dosage forms evenif the liquid does inhibit growth of microorganisms, due to presence of components, like preservativesor sugar at high concentrations, or a final terminal heat treatment.
应关注液体口服制剂容器的清洁，即使液体制剂本身确实能够阻止微生物的生长，因为存在组分如防腐剂或高浓度的糖，或有最终的终端热处理步骤。

10.10.1.2 Parenteral Dosage Forms Primary Packaging Components
注射用药物内包装组件

Cleaning of containers and stoppers used for parenteral dosage forms is based on a risk analysis. Therisk should be assessed and the cleaning levels validated at the acceptance criteria. Since the parenteralcontainer/closure components are in contact with the drug product, similar cleaning qualification considerationsas for direct product contact surfaces for manufacturing equipment should be addressed.
用于注射剂的容器和胶塞的清洁应基于风险分析。应进行风险评估，清洁程序应经过验证并符合可接受标准。因为注射剂容器/密封组件与药品直接接触，其清洁确认应与直接接触产品的生产设备的清洁确认类似。

For cleaning processes used as a depyrogenation step for container/closure components, the qualificationshould demonstrate successful endotoxin removal (36). The efficiency of the cleaning processto depyrogenate can be assessed by spiking containers or closures with known quantities of endotoxin, followed by measuring endotoxin content after cleaning. The studies are typically performed byapplying a reconstituted endotoxin solution onto the test surfaces and allowing the solution to air dry.
对用于容器/密封件除热原的清洁工艺，应确认其可以成功去除内毒素（36）。可通过在容器或密封件上涂布已知量的内毒素，在清洁后测定内毒素含量，以评估清洁工艺去除热原的效率。该试验中，通常将复溶的内毒素溶液涂布在待测试表面，并自然晾干。。

Positive controls (test surfaces with applied endotoxin but without the endotoxin reduction process)should be used to measure the percentage recovery in the test method. Data should demonstrate thatthe cleaning process reduces the endotoxin content by at least a 3-log reduction in a spiking study.
应采用阳性对照（在待测试表面上涂布内毒素，但不进行可能降低内毒素的工艺）来测量检验方法的百分回收率。内毒素涂布试验中，研究数据应能证明清洁工艺可以降低内毒素含量至少 3 个对数单位。

Container washer qualification should start by using a spray coverage test to verify all the surfaces areefficiently rinsed. The cleaning performance qualification should consider removal of residues

comingfrom the surface treatment (if applicable) and/or particles (which, as an example, could comefrom burned glass molding lubricant as well as glass particles if breakage occurs before wash).
容器的清洁确认从采用喷淋覆盖测试来确认可有效冲洗所有表面开始。清洁效果确认应考虑去除来自表面处理（如适用）的残留和/或颗粒（例如，来自玻璃成型中润滑剂燃烧产物，以及清洗前容器破裂产生的玻璃颗粒）。

For closures (such as stoppers), the cleaning performance qualification should consider removal ofresidues coming from the closure manufacturing process, like the lubricant and cleaning agent used,as well as particles.
密封件(例如塞子)的清洁效果确认应该考虑去除来自密封生产过程的残留物，如使用的润滑剂和清洁剂，以及颗粒。

10.10.2 Packaging Equipment
包装设备
Packaging equipment may be categorized into primary and secondary equipment
包装设备可以分为内包装设备和外包装设备.

10.10.2.1 Primary Packaging Equipment
内包装设备
Primary packaging equipment may exert direct impact on the quality of the finished product. Examplesof such equipment may include oral, topical and aseptic liquid fillers, tablet fillers, oral powder fillers,tube fillers, blister machines and other filling machinery that has parts with direct finished dosage productcontact. The cleaning processes and validation practices for primary equipment should not differ fromthe same practices utilized for direct impact manufacturing equipment as they present similar risk of crosscontamination. Auxiliary equipment such as hoppers, tubing, piping, conveyors, cappers, cottoners andother product contact surfaces should be cleaned and validated the same as associated filling equipment.The design of packaging equipment should consider “gentle handling” of finished product to minimizepossible attrition and breakage in the case of solid dosage products and possible adsorption of liquids. Thecleaning of dedicated primary packaging lines may not require validation. Consideration should be givento design of the lines and cleaning procedures to minimize validation efforts. While there is a possibilityof preferential transfer of residues from the primary packaging equipment to an initial portion of thepackaged product, this risk may be reduced by discarding an initial portion of processed product
内包装设备可能直接影响成品的质量。这类设备可能包括口服、局部给药和无菌液体灌装机、片剂充填机、口服粉末充填机、装管机、泡罩包装机和其他充填设备，这些设备的部分部件与成品直接接触。内包装设备的清洁工艺及其验证应同直接接触产品的生产设备相同，因为他们有类似的交叉污染风险。辅助设备如料斗、管道、传输带、轧盖机、装棉机和其他产品接触表面的清洁和验证应同相关充填设备一样。包装设备的设计应使其“轻柔地操作”成品，以尽可能地减少固体制剂产品的磨损和破损和可能的液体制剂吸附。专用的内包装生产线可能不需要进行清洁验证。包装线和清洁程序的设计应能减少验证工作量。虽然残留有可能从内包装设备优先转移至下一被包装产品的初始部分，可以将最初生产的部分产品废弃来降低该风险。

10.10.2.2 Secondary Packaging Equipment
外包装设备
Secondary packaging equipment, such as induction sealers, retorquers, labelers, palletizers and

othersimilar equipment that does not have direct impact on the quality of the product, should be designedto allow only minimal inevitable residuals generated by the packaging process. However, appropriateattention should be given to document cleaning of this secondary equipment.
外包装设备，如感应封口机、拧盖机、贴签机、堆垛机等类似的设备，它们对产品质量没有直接影响，其设计应能将包装过程不可避免的残留降至最低。然而，应适当注意对外包装设备的清洁过程进行记录。

Once the drug substance is sealed in its primary packaging, the risk of cross-contamination is generallyrelatively low. Cleaning processes should be used on the packaging lines after primary packaging,but do not require cleaning validation. The main concern with cross-contamination is a compromisedprimary package (such as a broken vial or a crushed bottle) that might release product that transfersto the outside of the primary packaging of a different product. Depending on the hazard propertiesof the product, its presence on the outside of the primary packaging of a different drug productmay be an unacceptable risk. Cleaning processes for such situations should be considered. However,because contamination of the next product may only involve contamination of the outside of theprimary package, the requirements for cleaning validation should be assessed based on risk to patientsor to people handling the vials from that external contamination on the primary package. In thosecases where the risk is significant (such as a genotoxic API), a dedicated line or a cleaning step knownto remove, deactivate or degrade that active drug should be considered. Degradation processes mayappropriately be confirmed in a laboratory study demonstrating degradation or inactivation of thehighly hazardous API.
一旦药物密封在内包装中，交叉污染的风险就变得相对较低。内包装之后的包装线需进行清洁，但不需要进行清洁验证。主要的交叉污染顾虑是一个不完整的内包装(如破瓶或碎瓶)，会释放出产品至另一产品的内包装的外部。根据产品的风险属性，它的存在于另一产品内包装的外部可能是一个不可接受的风险。应考虑这种情况的清洁程序。然而，由于只是污染了下一产品内包装的外部，是否需要进行清洁验证应基于内包装的外部污染对患者或者操作瓶子的人所带来的风险而确定。当风险很高（如基因毒性 API)，应考虑采用专用生产线或已知能够去除、灭活或降解活性成分的清洁工艺。可通过实验室研究确认降解工艺能够降解或灭活高危险性的 API。

10.11 Tubing and Hoses

管道和软管

Tubing and hoses have diverse transfer applications in pharmaceutical manufacturing operations.Types may vary from flexible plastics to fixed stainless steel piping. Conditions for use may be singleormultiple-use. Biocompatibility and inertness of the tubing with the contact material is a primaryconsideration prior to use. The regulatory standards on transfer tubing and hoses used in manufacturingprocesses are covered under compliance with U.S. FDA standards 21 CFR Part 177.2600 (37). Thisrule is applied in combination with ISO 10993-1 (38) standard for medical devices and USP class I-VIplastics tests (39).
管道和软管在药品生产中有多种形式应用。应用类型可能会从弹性的塑料管路到固定不锈钢管道而不同。可能单次使用或多次使用。在使用前，应该考虑与物料接触管路的生物相容性和惰性。用于制造业过程的传输管路和软管应符合美国 FDA 标准 21 CFR 177.2600(37)部分。该法规和 ISO 10993 - 1(38)一起被用于医疗器械和 USPI-VI 等级塑料的测试(39)。

The procedure for cleaning should be effective for exposing all product contact surfaces and the internalbore of tubing to the cleaning detergent and rinsing solution or water. A key for cleaning of

tubingand hoses is to assure turbulent flow throughout as well as to assure proper sloping for drainage forfixed tubing. Visual inspection of the internal bore of the tubing/hose to evaluate the efficiency forremoval of residue may be performed with the aid of video devices, such as a borescope. It is recommendedto drain tubing and hoses of any water/resident solution when not in use. Tubing/hosescleaned in place attached to the main equipment receive the same cleaning regimen as the equipment.Although priority is given to the attached equipment when selecting the cleaning detergent and procedure,evaluation of the impact on the cleaning and storage (hold time) conditions of tubing/hosesshould be considered. Shorter tubing length may benefit cleaning ability, drainage and storage management.CIP cleaning equipment or automated hose washers often may be utilized and qualified toconsistently perform cleaning of tubing or hoses.
清洁程序应能有效地将所有产品接触表面和内部孔道暴露在洗涤剂和冲洗溶液或水中。管路和软管清洁的一个关键是保证充满湍流以及确保适当坡度利于固定管路的排水。可在视频设备如管道镜的帮助下，目视检查管路/软管内部孔道，以评估残留去除效率。建议在不使用的时候，将管路和软管中的水/溶液排尽。采用在线清洁的主要设备的附属管路/软管，同设备一样进行清洁。虽然在选择洗涤剂和清洁程序时，会优先考虑所连接的设备，也应其对管路/软管清洁和存储（清洁保持时间）条件的影响。管路越短越利于清洁、排水和存储。通常可以采用 CIP 清洗设备或自动软管清洗机对管路或软管进行清洗，并应经过确认，以获得一致的清洁效果。

Design of the tubing and hoses should take into consideration welded or permanently embeddedfittings for ease of cleaning. If removable end fittings are used, they should be removed during eachcleaning cycle. If not dried before storage, tubing/hose should be stored on the slope (to allow drainage)and should be covered using hose-end covers of spun-bonded polyolefin or similar materials toreduce the risk of microbial and/or particulate contamination during storage.
管路和软管的设计应考虑采用焊接或永久嵌入配件以便于清洗。如果使用可拆卸的终端配件，应在每次清洁时将其拆下。如果存放前没有干燥，应将管道/软管倾斜存放（利于排水），并用纺粘聚烯烃或类似材料的管帽来减少存储过程中微生物和/或微粒污染的风险。

Based on the material of composition, the indicators of damage (such as pressure testing) should bepredefined for the tubing under the conditions of use. Qualification for use of product contact tubingand hoses should include an assessment of the useful lifetime for the manufacturing operation.The assessment should integrate a visual component of inspecting tubing periodically for signs oftear, pitting and disintegration, with wear characteristics, such as particulate shedding detected undersubvisible conditions.
基于管路的材质，应预先确定实际使用条件下管路损伤指标(如压力测试)。接触产品管路和软管的确认应包括对其在生产中的使用寿命进行评估。应该将采用可视组件定期管路的撕裂、点蚀和剥落的现象与磨损特性，如显微条件下检查到的颗粒脱落，整合在一起进行评估。

10.12 Excipients

辅料

The excipients used for a drug product should be considered in the cleaning validation program. Oneissue for excipients is the possible effect on cleaning of a drug product. This effect is generally morepronounced for solid dosage products, where the excipient may be a coating or other functional materialdesigned to retard dissolution. This is one reason why some companies prefer to use a laboratorycleaning study, as compared to only evaluating the solubility of the active ingredient, to determine thedifficulty of cleaning of different products in a grouping approach.

在清洁验证计划中应考虑制剂使用的辅料。问题是辅料可能影响制剂的清洁。对于固体制剂，这种影响通常更为明显，在固体制剂中辅料可能是作为包衣或其他功能材料以降低溶出的速度。这就是为什么有些公司喜欢使用实验室清洗研究，来确定分组中难以清洁的产品，而不是只评估活性成分的溶解度,。

Unless the excipient has some kind of unusual toxicity, limits are generally not set for excipients ina cleaning validation protocol. A case where limits may be set for excipients is where the excipientis known to have a significant effect on the performance of the next manufactured product, such ascomplexing with the API to reduce bioavailability. However, it should be recognized that in all cases,residues of excipients after cleaning should be such that the equipment is visually clean. A surfacewhich is not “visually clean” due to a high level of an excipient should be generally considered a cleaningvalidation failure.
除非辅料有某种不寻常的毒性，清洁验证方案中一般不设定辅料的限度。当已知辅料对下一个生产产品的性能有重大的影响时，才需要设定辅料的清洁限度，如与 API 结合降低了生物利用度。然而，应注意在所有情况下，清洁后辅料残留应满足设备目视洁净的要求。一由于大量辅料存在造成表面不符合目视洁净要求，则通常认为清洁验证是失败的。

10.13 Dedicated Equipment
专用设备

Equipment for pharmaceutical manufacturing and packaging may be dedicated for processing onlyone product. Some points to consider regarding cleaning validation of dedicated equipment are coveredbelow.
药品生产和包装设备可专用于一个产品。专用设备清洁验证要点如下：

10.13.1 Reasons for Dedication
专用的原因

Reasons for dedication of equipment may be quality driven (such as to avoid cross-contamination ofone active ingredient into another product) or may be based on business considerations (such as forproduction efficiency). Regulatory agencies recommend dedicated equipment and/or facilities in certainsituations. For example, the PIC/S recommendations state that “Dedicated equipment should beused for products which are difficult to remove (e.g., tarry or gummy residues in bulk API manufacturing),for equipment which is difficult to clean (e.g., bags for fluid bed dryers), or for products witha high safety risk (e.g., biological or products of high potency which may be difficult to detect belowan acceptable limit)” (22). That PIC/S document also states that “For certain allergenic ingredients,penicillins, cephalosporins or potent steroids and cytotoxics, the limit should be below the limit of detectionby best available analytical methods. In practice this may mean that dedicated plants are usedfor these products.” Additionally, the ANVISA Resolution – RDC No. 17 states that “There shouldbe used segregated facilities and dedicated to the production of certain medications such as certainbiological preparations (e.g., live microorganisms) and the highly sensitizing materials (e.g., penicillin,cephalosporin, carbapenem and other beta-lactic derivatives) in order to minimize the risk of seriousdamage to health due to cross contamination”, and further that “The production of certain highlyactive products, such as some antibiotics, certain hormones, cytotoxic substances should be held insegregated areas” (40). Finally, there are the U.S. FDA draft recommendations about dedication forbeta-lactams (41).
设备专用的原因可能是质量原因(例如避免产品之间的交叉污染)或基于商业考虑(如为了提高生产效率)。对于某些情况，监管机构建议使用专用设备和/或厂房。例如，PIC / S 建议“难以去除的产品 (如 API 生产中柏油或粘性残留)、难以清洁的设备(如流化床干燥器过滤袋)，或安全风险高的产

品(如，生物制剂或在可接受限下难以检测到的高活性产品)，应采用专用设备”(22)。PIC / S 指南也指出：“对于某些致敏性成分，如青霉素、头孢菌素或高活性的类固醇和细胞毒素，限度应低于现有最好的分析方法的检测限。在实际操作中这可能意味着使用专用工厂生产这些产品。”另外，ANVISA 决议-RDC 第 17 号指出“应使用专用厂房用于某些药品如生物制剂(如活的微生物)和高致敏性产品(如青霉素、头孢菌素、碳青霉素和其他 β-内酰胺衍生物)，以减少由于交叉污染带来的严重损害健康的风险”，并进一步要求“生产一些高活性产品，比如部分抗生素、激素、细胞毒性物质应在隔离的区域进行”(40)。最后，还有美国 FDA 关于 β-内酰胺生产线专用的建议草案(41)。

Risk assessments and appropriate controls should be considered in cases where regulatory documentsmay be unclear or overly strict on the requirement for dedication or segregation for manufacturing.
当规范性文件对于专用或隔离生产的要求可能不清楚或过于严格时，应进行风险评估并进行适当控制。

10.13.2 Cleaning Validation Issues

清洁验证问题

Since cross-contamination of the active ingredient from the previous product to the next product isnot an issue for dedicated equipment, cleaning validation related to the active itself is generally notconsidered a requirement. The 1993 U.S. FDA cleaning validation guidance states that “When thecleaning process is used only between batches of the same product (or different lots of the same intermediate in a bulk process) the firm need only meet a criteria of, “visibly clean” for the equipment.Such between batch cleaning processes do not require validation”(20). Since “between batches ofthe same product” may refer to dedicated equipment and/or a campaign between products, it can beinterpreted that cleaning validation is not required for these scenarios. However, cleaning validationshould be considered for dedicated equipment if carryover of the cleaning agent or the contributionof bioburden or degradation byproducts to the next manufactured batch is a concern. In its ComplianceGuidance Manual 7356_002, U.S. FDA clarified their position by stating that “lack of demonstrationof effectiveness of cleaning” for dedicated equipment warrants a warning letter (42). It makesgood sense for manufacturers to conduct risk assessments for all cleaning scenarios to determine theneed for cleaning validation to comply with product quality (including residues and lot integrity) andregulatory expectations. Principles for determining acceptance criteria for cleaning agent, bioburden,endotoxin, and degradation products for cleaning validation of dedicated equipment are essentiallythe same as for nondedicated equipment. It is considered to be best practice to document effectivenessof a cleaning process for dedicated equipment even if “visually clean” is the only criteria.
对于专用设备而言，不存在前一产品的活性成分转移至下一个产品中的问题，因此不需要对活性成分本身进行清洁验证。1993 年美国 FDA 清洁验证指南指出,“当清洗过程只用于相同的产品(或不同批次的同一中间体)时，只需要满足一设备“目视洁净”这一个条件。这样的批间清洗过程不需要进行验证”(20)。因为“相同的产品批次之间”可能指的是专用设备和/或阶段性生产，可以认为这些生产方式不需要进行清洁验证。然而，如果清洁剂残留或生物负载或降解副产物影响下一产品质量时，应考虑进行专用设备的清洁验证。美国 FDA 在符合性指导手册 7356 _002 中阐明了自己的立场，专用设备“缺乏清洗的有效性的证明”将导致一封警告信（42）。制造商最好对所有清洁方案进行风险评估来确定是否需要清洁验证，以符合产品质量(包括残留和批的完整性)和法规监管的期望。专用设备的清洁剂、生物负载、内毒素、降解产物的可接受标准确定原则基本上与非用设备相同。即使“目视洁净”是唯一标准，最好还是应记录专用设备清洁工艺的有效性。