Points to Consider for Biotechnology Cleaning Validation

Technical Report No. 49

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1.0 Introduction 介绍

Cleaning validation plays an important role in reducing the possibility of product contamination from biopharmaceutical m a n u f a c t ur i n g equipment. It demonstrates that the cleaning process adequately and consistently removes product residues, process residues and environmental contaminants f r o m the cleaned eq u i p m e n t / s y s t e m , so that this eq u i p m e n t / s y s t e m can be safely used for t h e m a n u f a c t ur e of defined subsequent products (which may be the same or a different product). As used in this Technical Report, "product" may be a drug product, bulk active, intermediate, o r another type of f o rmu l a t i on .If "drug product" is intended, that terminology will be utilized. While cleaning validation for biotechnology m a n u f a c t ur i n g has many of the same elements as for o t h e r pharmaceutical manufacturing, there are enough differences such that a separate Technical Report focusing on biotechnology cleaning validation is appropriate.

清洁验证在生物制药生产设备降低产品污染方面扮演了一个重要的角色。清洁验证证明清洁工艺能够充分的并始终如一的从清洗的设备 / 系统上去除产品残留、 工艺残留和环境污染，以保证该设备 / 系统可以安全的应用到后来产品（可能是同一种产品或是不同的产品）的生产中。在本技术报告中，"产品"可以是药品，活性原料，中间体，或其他类型的构成。

如果"制药产品"是预期的，该术语也将会用到。生物技术生产的清洁验证有很多和其他产品生产相同的因素，但在单独的技术报告中仍然有很多的不同之处，本报告关注于生物技术清洁验证。

Previous PDA documents on cleaning validation, including the 1998 PDA Technical Report No.29 , Points to Consider for Cleaning Validation and the 1996 monograph Cleaning and Cleaning Validation: A Biotechnology Perspective provide valuable insights for biotechnology manufacturers.(1,2) However, this report presents more updated i n f o rm a t i on that is aligned with life cycle approaches to validation and the International Conference on Harmonisation (ICH) guidelines Q8(R2), Pharmaceutical De v elopment , Q9, Quality Risk Management, and ICH Q10, Pharmaceutical Quality System. (3-6) This report also aims to present information in a way that readers can easily utilize to assist in creating a cleaning validation program for their equipment and f acilities .

以前关于清洁验证的 PDA 文件，包括了 1998 年 PDA 技术报告 29 ，清洁验证考虑要点 和 1996 年各论 清洁和清洁验证：一个生物技术视角 ，对生物技术的生产提供了很有价值的深刻见解。然后，这些报告都需要进行更多的更新来紧跟生命周期方法的验证和 ICH 指南 Q8(R2)， 制药开发 ，Q9 ， 质量风险管理 ，和 ICH Q10， 制药质量体系 。这些报告的目标是给读者提供可以利用的信息来帮助设备和设施的清洁和清洁验证计划的建立。

The Biotechnology Cleaning Validation Task Force was composed of European and North American professionals f r o m biotechnology m a n u f a c t ur e r s , c l e a n i n g chemical s u pp li e r s ,regulatory agencies and consulting companies. This report also underwent a global, technical peer review to ensure concepts, terminology, and practices presented are reflective of soundscience and can be used globally.

由欧盟和北美的生物技术、清洁化学品供应商、监管机构和咨询公司的专家组成了生物技术清洁验证专案小组。该报告经历了一个全球的，技术同行业评审来保证理念，术语，和规范反映了科学的声音，并且可以全球应用。

Note: F o r e a s e of u s e , t h i s T e c hn i c a l Report i n c l u de s a li s t of acronyms u s ed throughout the49 © Inc. 5 d o c um e n t . Refer to Section 16.0.

注意： 为了易于应用，该技术报告包含了一个缩略语清单，在 16.0 章提供。

1.1 Purpose/ s cope 目的 / 范围

The focus of this Technical Report is on biotechnology m a n u f a c t ur i n g . Biotechnologym a n u f a c t ur i n g includes bacterial and cell culture f e rm e n t a t i on . While some might excludeplasma fractionation and egg-based va cc i n e m a n u f a c t ur i n g f r o m the s t r i c t de fi n i t i on ofbiotechnology, m a n y of the p r a c t i c e s and guidance in this report are applicable to plasmafractionation and egg-based vaccine m a n u f a c t ur i n g . T h e r e f o r e , examples given will be forbiotechnology m a n u f a c t ur i n g . We have also included a li f e cycle cleaning validationapproach, including de s i g n / de v e l o p m e n t of the cleaning process, process qualification (theprotocols runs), and ongoing validation maintenance. These practices and the associated guidance in this Technical Report are based on technical considerations and should be applicable in all regulatory environments.

本技术报告关注了生物技术生产。生物技术生产包含了细菌和细胞培养发酵。可能有一些说明将血浆和鸡蛋为成分的疫苗生产定义为需要更严格的生物技术，在本报告中的一些规范和指南包含了血浆和鸡蛋为成分的疫苗。因此，给出的案例将会支持生物技术生产。我们同样包含了生命周期清洁验证方法，包含了清洁工艺的设计/开发，工艺确认（方案），和持续的验证维护。在本报告中基于技术问题考虑这些规范和关联的指南，并且适用于所有的监管环境。

The intent of this Technical Report is not to provide a detailed plan or detailed road map for a biotechnology m a n u f a c t ur e r to pe r f o rm cleaning validation. Rather, as the title suggests,it presents “points to consider” as one designs a cleaning validation program forbiotechnology m a n u f a c t ur i n g based on an understanding of on e ’ s m a n u f a c t ur i n g andcleaning processes. In cleaning validation, there are generally multiple ways to accomplish thesame goal of a compliant, scientifically sound and practical cleaning validation program.Where options are given, the rationales for such options are also generally given. TheBiotechnology Cleaning Validation Task Force that developed this document hopes that itwill be used in that spirit. Based on an understanding of the unique nature of any individualsituation, different approaches or additional issues should also be considered.

该报告并不打算提供关于生物技术生产清洁验证的执行一个详细的计划或是详细的路径。更合适的说法是，按照标题建议的，它体现了一种“考虑要点”，就像基于对一种生产和工艺的理解来进行的对生物技术生产清洁验证计划的设计。在清洁验证中， 一般都会有多种方法完成一个目标， 系统的、 彻底的来执行清洁验证计划。生物技术清洁验证专家小组也是怀着同样的心情开发了这些文件。基于对独一无二的性质和特定的情况，不同的方法或额外的问题都将会被考虑。

This report should be considered a resource to help guide the development or evaluation of a cleaning validationprogram. It is not intended to establish mandatory standards for cleaning validation. It is intended to be as i n g l e - s o ur c e overview for biotechnology m a n u f a c t ur e r s that complements existing guidance and referencedocuments, listed in Section 13.0 . The reader should also be aware that a specific topic may be discussed in severalsections of this Technical Report. T h e r e f o r e , a m o r e complete perspective may be obtained by considering allrelevant sections about a certain topic.

本技术报告将会确定一种资源来帮助开发或评估一个清洁验证方案。但是其并不打算做一个清洁验证的强制标准。在 13.0 章进行了说明，它计划做一个生物技术生产唯一来源，补充目前的指南和参考文献。读者可以意识到一个特定的专题将会在本报告中进行多次讨论，因此，一个更多的完整的观点将会通过所有相关章节的全面考虑才会确定。

2.0 Glossary of Terms 术语表

a cceptable daily Intake 可接受日剂量

An amount of a substance administered o r consumed on a daily basis that is considered a safe level
每日可摄取的一个在安全基线以内的一个药物摄取的剂量
A nalyte 分析物
A substance (usually a residue) for which an analysis is being performed
用于分析的一个物质（通常是残留）
Blank 空白
An analytical sample taken to establish the background value for an analytical m e a s ur e m e n t which may be subtracted f r o m an experimental value to determine the “true” value
一个分析样品通过一个分析方法用来建立一种背景值，这种空白可能是取自一个实验值来确定这个真正要检测的值.
Campaign 阶段性生产
The processing of multiple lots or batches of the same product serially in the same equipment
在相同的设备中的一系列工艺批次中进行的批处理
Changeover 更换品种
The steps taken for switching multi-product equipment from the manufacture of one product to the manufacture of a different product
可用于多产品生产的设备从一种产品的生产更换为另外一种产品的生产
Clean 清洁
Having product residues, process residues and environmental contaminants removed to an acceptable level
将产品的残留、工艺残留和环境污染物降到一个可接受的水平
Cleaning Process 清洁程序
A process that is used to remove any product, process related material and environmental contaminant introduced into equipment as part of the manufacturing stream
用来清除任何产品、与工艺相关的物料和工艺流对设备带来的污染
Cleaning V alidation 清洁验证
The documented evidence with a high degree of assurance that a cleaning process will result in products meeting their predetermined quality attributes
用文件来证明清洁工艺将会使产品满足预期的质量属性
Cleaning V erification 清洁确证
A on e - t i m e sampling and testing to ensure t h a t specified equipment has been properly cleaned following a specific cleaning event
一次性的取样和测试来确保特定设备已经按照特定的清洁程序来进行了恰当的清洁
Coupon 试样
A small, generally flat portion of a de fi n ed material of construction (such as stainless steel or PTFE), typically used for laboratory cleaning evaluations a n d / o r for laboratory sampling recovery studies
一种小的，一般是确定材质的平板的一部分（比如不锈钢或者 PTEE），特别是用来实验室清洁评估和/或实验室取样回收率研究
D egradation 降解
The breakdown (usually chemical) of material during m a n u f a c t ur e (including during and a f t e r the cleaning process)
在生产过程（包括清洁工艺中和后）中原材料的降解（通常为化学品）
dry e quipment 干设备
No visible water pool evident in the equipment or line when viewed under appropriate

lighting conditions
在合适的光照环境下在设备或生产线上没有可见的水
equipment T rain 设备链
The sequence of equipment through which a product is produced or processed
产品被生产或者加工的设备使用顺序
Grouping strategy 分组策略
A strategy of establishing the similarity of cleaning processes, usually based on
similar products or similar equipment, and validating the cleaning process based primarily on validation data for a representative of the group
建立清洁工艺的验证，通常是基于相似的产品或者相似的设备，清洁工艺的验证是
基于一个代表性的验证数据
LD 50
The “dose” of a material which results in 50%
mortality in an animal test
半数致死量
在动物试验中，指能杀死一半试验总体的剂量。
L imit 限度
A value for a residue above which a cleaning validation protocol would f ail
一个清洁验证方案将会失效的一个残留值
Normal d ose 正常剂量
The therapeutic dose of a product as given on the approved product labeling
对于一个已批准的产品标记的治疗剂量
Recovery s tudy 回收率研究
A laboratory study combining the sampling method and analytical method to determine the
quantitative recovery of a specific residue for a defined surface
对于一个已定义的表面采用的特定的结合取样方法和分析方法的残留回收率实验室研究方法

3.0 Cleaning Process design and development 清洁程序的设计与开发

3.1 Introduction
The cleaning process requires design and development prior toimplementation in a manufacturing plant to ensure the cleaning process and equipment are acceptable for use. Additionally, the concept of “Design Space,” recently introduced as an approach to the development of pharmaceutical processes, is discussed and applied to the development of cleaning processes.
3.1 介绍
清洗程序需要在正式生产前进行设计和开发， 以证明清洁程序及设备可接受标准。 另外， “设计空间”的概念，近期作为一种开发制药程序的方法被引进，也可用于讨论和应用于清洁程序的开发。
The operational parameters that describe the cleaning process (such as cleaning agent, concentration, contact time, temperature, soil characteristics and soil condition), as well as specifics about the cleaning equipment, automated cleaning pathways, the sequence of cleaning steps, and flow rates during each step, should be determined prior to implementation.
清洁程序的操作参数（如清洁剂，浓度，接触时间，污染物质的特性，污染条件） ，还包括清洗设备的特性，自动化的清洁路径，清洁环境的顺序，每个的流速，在投入使用前，需要确定。
Generally, the establishment of acceptable conditions (or confirmation of acceptable conditions for new soils being introduced to the manufacturing plant) follows a standard progression of activities – beginningwith

identification of control variables, cleaning measurements, and performance criteria. Laboratory (scale-down) experimentation, analogous to process characterization, and specific equipment requirements provide the necessary data to establish cleaning parameter control ranges

一般来说，可接受标准的制定（或者一个新厂房的污染的可接受标准）根据标准活动的进展-从控制变量开始，清洗的测试，性能标准，实验室研究（规模降低），以此类推，程序特性，和特殊设备的要求，提供建立清洁参数的控制范围。

This section describes the application of operational parameters and measurements, the design of laboratory scale experiments, the selection of appropriate test soils, and the scale-up for cleaning the manufacturing equipment.

此章节描述操作参数和测量的应用，实验室规模测试的设计，合适污染测试方法的选择及放大至生产设备清洁。

3.2 Cleaning Process Controls (Inputs) and measurements (outputs)

3.2 清洁程序控制（输入）及测试（输出）

3.2.1 Cleaning Cycle design

Cleaning processes are comprised of 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 biotechnology product are outlined in Table

3.2.1 清洁程序设计

清洁程序由多个步骤组成，每一个单独的功能步骤及每一组参数，均需要控制在确定的范围之内，以保证污染物（和清洁剂）能够有效的去除。生物制药的典型的清洁周期在下表中进行了描述。

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, the presence of an acid cleaning step the concentration of cleaning agents, contact time of cleaning agents on equipment, feed pressure or flow rate, cleaning temperature, and required length or volume of rinse steps.

3.2.1 不同类型的工艺设备的清洁程序可能存在不同，不同之处可能包括使用情况及清洁剂的种类，酸洗时，清洁剂的浓度，清洁剂与设备的接触时间，清洗液体的压力及流速，清洗温度，冲洗时间及水量。

表 3.2.1 清洁程序步骤（例）

步骤 功能 描述

预洗 去除可溶及非粘附性残留物 在正式清洁前减少污物负荷， 一般在室温下进行以避免残留蛋白的变性

碱洗 去除可溶和已经干了的残留物，用清洁剂通过降解，加热和或湿润的方式溶解污物污物及生物污染去除的主要步骤， 通常在高温下进行。 包括碱性清洁剂或碱性氢氧化物。可以考虑污物的成分水洗 去除碱性清洁剂和悬浮或可溶污物如果在酸洗前进行，不可做为最终清洗酸洗 中和残留的碱性物质，并对易溶于酸的污物进行清洗可不考虑污物的成分最终水洗 清除所有清洁剂和产品残留 通常是在高温下进行

3.2.2 Physical-Chemical aspects

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 (Time, Action, Concentration and Temperature). 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 should be established as part of the cleaning development effort (soil type and condition are additional inputs that are discussed in Section 3.5).

3.2.2 物理-化学方面

清洁程序的每部主要包含 4 个清洁输入参数，这四个参数通常简称为 TACT(时间，动作，浓度及温度)，这四个参数是互相联系的，且会对清洁周期中的每一阶段的成功的存在直接关系，例如，比如通过对清洁剂的加热以提高去污能力。做为清洁参数的变量需要确定，清洁参数的可接受范围作为清洁程序开发工作（污

染物类型及情况 i 见 3.5 章）的一部分进行建立。

Time is defined as the length of time for the cycle step. There are two typical methods for defining and measuring time during a cycle step, direct and indirect. Using the direct method, a cycle step counter that is part of the control system 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 finalwater rinse, it is also common to add additional requirements, such as a specified conductivity level.

时间被定义为清洗步骤的时间的长短。在一个清洗步骤中，可以采用两种方式来进行定义和测量：直接法与间接法。直接法时，可使用做为控制系统中的计时器测量时间。也可以通过间接法测量时间，例如，在冲洗时，有时通过测量体积来代替测量时间，因为通过体积和流速可以确定时间。于最终冲洗水，普遍会增加测试要求，如电导率。

Action is the mechanism used to deliver the cleaning agent. This mechanism may be characterized as soak, scrubbing, impingement or turbulent flow. Agitation enhances the chemical actions of the cleaning agents and helps to increase the effectiveness of the cleaning process. 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 type of cleaning action should be identified for each cleaning process. The velocity (flow rate) of the cleaning and rinse fluids traveling through the equipment is an operational parameter that should be specified and verified at each step 8 © 2010 Parenteral Drug Association, Inc. Technical Report No. 49in the cleaning process. Spray devices have minimum and maximum flow rate requirements, and piping should be flushed at a speed sufficient to assure adequate flooding and turbulence.

动作被定义为清洁剂的流体动作。如浸泡，洗涤，冲击，湍流。搅动能够提高清洁剂的有效性和清洁工艺的效果。典型的手工清洗包括浸泡和擦洗，以达到清洁效果。自动清洁程序通常采用冲击刘和/或湍流作为清洁动作。清洁程序需明确清洁动作。流速是清洁剂和清洗水在流经设备时的重要参数，应该在清洁工艺的每个步骤中规定流速并进行确认。喷淋装备要具有最大和最小流量的要求。管道的冲洗流速要确保形成湍流。

Cleaning agent concentrations directly affect the success of the cleaning process. Cleaning chemicals areavailable in concentrate forms that are diluted and used in cleaning cycles. Effectiveness of the cleaners may be related to their concentration. Too little cleaning agent might result in failure to remove the soil from equipment, and too much detergent can result in difficulty in removing cleaning agent residues, requiring excessive rinsing. In general, the greatest effectiveness of alkaline cleaners is achieved atelevated temperatures with agitation or turbulence overextended periods of time. Although there is somerisk of denaturing residual protein onto the surfaces of the equipment at high temperatures, thereby makingit more difficult to clean, it is typically minimized by performing an appropriate pre-rinse at ambienttemperature prior to the caustic chemical wash. Chemicals are also costly, both in their purchase and disposal, thus determining the correct concentration of cleaning agent required to ensure cleanability is

important. The addition of a cleaning agent to an automated system must be designed for reproducibility. Regardless of the method of addition, confirmation 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 cleaning agents is by conductivity.

清洁剂的浓度直接影响清洁程序是否能够成功。化学清洗计可以是浓缩型的，稀释后使用。清洁效果与清洁剂的浓度有关系。清洁剂使用太少，可能达不到清洁效果，使用太多，来自清洁剂的残留可能难以去除，并需要使用大量的冲洗。通常，对于碱性清洁剂达到最佳清洁效果的方法可以是在搅拌状态下提高温度或延长湍流冲洗周期的时间。虽然这样操作可能导致高温下变形蛋白质在设备表面的残留，导致更难得清洁。此类残留可以在化学清洗前，通过室温下的预清洗，最大程度的减少。化学清洗剂在采购和处置方面，均会产生不小的资金投入，因此确定正确的浓度以保证清洁效果是极为重要的。清洁剂添加的自动系统，必

须具有可重现性。不管采用何种添加方式，确认清洁剂浓度有助于证实该方式的一致性。对于自动清洁程序，电导率测试是最容易测试强碱或强酸清洁剂浓度的方式。

A process should be in place to detect anomalies in detergent concentration based on the mechanism bywhich chemical makeup 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.

应能够通过清洁剂的化学组成在线测试出清洁剂浓度的异常变化，例如，一些清洁剂添加系统以体积进行控制并采用电导率测试作为确认方法。当电导率超出预设值时，就会报警。允许的范围需来自清洁程序开发的数据。

Selection of the cleaning agent should consider various aspects, including soil type, ease of removal, and need for chelating agents.

清洁剂的选择需进行多方面考虑，包括污物类型，去除的难易程度，是否需要螯合剂。

The optimal temperature ranges will vary for the different steps of the cleaning process. Initial water rinses are typically performed at ambient temperatures to minimize denaturing effects on proteins and maximize the dilution effects. Cleaning agents are typically heated to increase their effectiveness. Final rinse water steps may be performed at high temperatures to increase both the drying rate and the solubility of any process or cleaning agent residues.

温度：清洁程序中不同步骤的最佳温度范围会有所不同。初始清洁典型的温度为室温，目的是最大程度的去除变性或降解产物和最大程度的稀释产物。清洁剂经过加热以提高效果。最终清洗水可通过高温以加快干燥速率和提高任何工艺及清洁剂残留的溶解性。

3.3 measurements used to determine Cleaning effectiveness

Cleaning effectiveness may be determined by the inspection and analytical methods described in Section6.0. They include visual inspection, analytical technique for measuring removal of manufactured product,cleaning agent, bioburden and endotoxin. Depending on the purpose and the design/development phase,these may be on-line measurements and/or may be off-line measurements of rinse or swab samples.

3.3 清洁有效性的检测

清洁效果可能通过检查和分析分析方法进行确定，见第 6 章，包括对产品，清洁剂，内毒素，微生物的去除效果的目视检查及分析方法检验。依据目的及设计/开发的阶段，检查方法可能包括在线检验或通过棉签或淋洗水取样进行的离线检验。

3.4 equipment and Plant design Considerations

3.4 设备与厂房设计的注意事项

3.4.1 Piping

Piping of the equipment being cleaned and of the CIP skid should be sloped continuously to ensure maximum drainability 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 is not achieved, one part of the loop may become a functional deadleg.9 Technical Report No. 49 © 2010 Parenteral Drug Association, Inc.The pressure drop in the piping also needs to be considered. The CIP skids are often located remotely from the process area, and the length of the distribution piping results in a total pressure drop that can be significant. The greatest challenge is sizing the distribution piping when the supply flow rate set points in the system vary by more than twofold.

3.4.1 管道

设备和 CIP 系统需要清洁的管道需要具有一定的坡度，以确保最大的排水能力，如果在供给和/或回路中采用了主管道，必须确保任何回路都要具有足够的流速。如果达不到足够的流速，回路中的部分管道可能成为死角管道中的压力损失也需要考虑，CIP 系统一般原理生产区，分配管道的长度会对压力损失产生明显影响。

3.4.2 automated vs. manual systems

Use of automation provides consistent and robust control and monitoring of CIP cycles and parameters(such as time, flow rate or pressure, cleaning agent concentration, and temperature). Manual systems require more detailed operating instructions and increased operator attention during use.

3.4.2 自动清洁与手工清洁

自动清洗能够对一致有力的控制和 CIP 周期及参数（如时间，流量及压力，清洁剂浓度，温度）的监控。手工清洁则需要更详细的操作说明，在清洁时，操作人员需提高注意力。

3.4.3 Centralized CIP vs. discrete Cleaning of Isolated equipment Centralized CIP systems can provide a single location for handling cleaning agents and can reducing the plant requirements for cleaning-related equipment (pumps and tanks) and instrumentation. However, centralized systems often require more complex piping designs and may complicate desires to segregate parts of the process (e.g., upstream and downstream operations or pre- and post-virus removal steps in mammalian cell processes). Some process equipment (e.g., reusable membrane systems and chromatography columns) may require special cleaning agents that are different than those used for the rest of the process equipment. For these systems, discrete CIP or CIP systems (including portable CIP systems) that are integrated into the process skids may be desirable.

3.4.3 集中清洗与单独设备独立清洗的比较

集中 CIP 系统能够提供一个单独的。 位置， 用于清洁剂的处理， 并能够减少车间对清洁相关设备 （泵，储罐）和仪器仪表的额要求。然而，集中清洗系统一般需要更复杂的管道设计和工艺分隔（如上、下游工艺的操作或者哺乳细胞的预-除病毒） 。一些工艺设备（重复使用的膜系统和色谱柱）可能使用与其他工艺设备不同的专用的清洁剂，对于这些系统，将独立 CIP（包括便携式的 CIP 系统 ）整合进工艺模块中是更为合理的。

The design of centralized CIP systems should consider the potential for carryove o product residues between process steps, between products being manufactured concurrently in multi-product 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 (e.g., upstream through product clarification steps or one process train in a multi-train plant).

集中 CIP 系统的设计应该考虑产品残留转移的潜在情况，如不同工艺步骤之间；多产品车间同时生产不同产品；产品更换之后。为应对产品残留转移的潜在情况，集中 CIP 系统通常专门用于生产车间的某一部分（例如，上游产品澄清， ）

3.4.4 Clean out of Place (CoP)

Small parts, containers, and other portable process equipment that are difficult to clean in place are often disassembled and cleaned in COP stations, washers or baths. Where COP is used, care must be taken in handling the parts after cleaning and in identifying parts for correct reassembly. COP may be performed in automated washers or baths or by manual cleaning.

3.4.4 离线清洁（COP）

对于难于在线清洁的小部件，容器具和另外一些便携的工艺设备，一般在 COP 清洗站，清洗器及清洗池进行拆卸和清洁。 当使用 COP 方式进行清洁时， 必须注意清洁后部件的处理及重新组装的正确性。COP 可以采用自动清洗机，或清洗池，或手工清洗。

3.5 soil evaluation and Categorization

3.5 污物评价与分类

3.5.1 污物分类

生物制品生产时，接触工艺设备表面的物质有很多种，包括：发酵和细胞培养基，细胞及其代谢产物，比如蛋白质和核酸；有机和无机酸，盐；工艺添加剂：如抗生素，表面活性剂，乙二醇，糖类，或动物水解产物和清洁剂如洗涤剂，酸，主要成分。

.5.1 soil Categories

There are a large variety of substances that contact process equipment surfaces during the manufacture of biopharmaceutical products. They include: fermentation and cell culture media; cells and cellular products, such asproteins and nucleic acids; organic and inorganic acids, bases and salts; process additives, such as antibiotics, surfactants, glycols, polyamines, sugars, plant or animal hydrolysates; and cleaning agents such as detergents, acids and bases.

清洁程序和清洁验证的设计和测试必须考虑各种潜在的污物。在清洁程序的开发及验证过程中，通过对污物的分类并选择具有代表性的污物进展测试和追溯，可以简化清洁程序及清洁验证的工作。工艺污物的分类示例见表 3.5.1

表格 3.5.1 工艺污物的分类（例）

类型 代表性污物 使用的工艺设备

发酵/细胞培养污物 无条件（未使用的）发酵液/
培养基
培养基配制设备
培养基储存与培养罐
有条件(发酵后产物， 包含细
胞)培养基
接种液配制设备
种子反应器（发酵器）
生产反应器(发酵器)
细胞扩大和澄清设备
有条件(发酵后产物， 不含细
胞)培养基
澄清后产品生产和储存设备
收获上清液设备

下游工艺和制剂/灌装污物 包含产品的盐水溶液 纯化设备
浓缩和缓冲液更换设备
包含产品的溶液和制剂成分
（辅料及表面活性剂）
制剂设备
终端除菌过滤设备
灌装设备

缓冲液配制污染 不含产品的盐水溶液 缓冲液配制设备
缓冲液过滤设备和储存罐

清洁剂污物 清洁剂，包括表面活性剂和
酸/碱
工艺设备

一个工艺中代表性污物的最终确定依据污物的理化性质的相似性，多数情况下，类别的可以合并，用于开发活动的代表性污物的数量可进一步减少。

3.5.2 soil Removal

Soils may be removed by physical and/or chemical means. Physical removal may be accomplished by the diffusion of soils away from the surface (static soaking) or by convection, whereby energy from cleaning solution flow is used to transport soils into the fluid stream. Physical removal is dependent on soil size and its degree of adhesion

to the equipment surface.

3.5.2 污物的去除

污物的去除可以通过物理和/或化学手段，物理方法可采用使污物与表面分离（静态浸泡）或对流方式，通过清洁剂流动的能量，使污物进入流体中。物理去除方法依赖于污物种类及及其与设备表面的黏附能力。

Chemical cleaning mechanisms include solubility, emulsification, wetting, chelation, dispersion, hydrolysis and oxidation. Cleaning agents are generally chosen for their ability to removeprocess soils by one or more of these mechanisms. In some cases, multiple cleaning steps may be used in

order to take advantage of different chemical cleaning mechanisms. For instance, alkaline detergent for solubilization and emulsification may be followed by a sodium hypochlorite solution for the oxidation of protein soils. It should always be kept in mind that the more aggressive the cleaning solvents are (e.g., sodium hypochlorite solution), the more corrosion might occur. The right choice of materials

for cleaning purposes is part of the engineering 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。清洁剂的选择依据以上一种或几种作用机制。有时，为用到不同清洁剂的去污特性，可以采取多步清洁的方法。例如，在使用碱液进行溶解和乳化后，可使用次氯酸钠溶液对蛋白质污物进行氧化。应始终 I 牢记，使用的清洁剂越强烈（如高浓度的次氯酸钠） ，越可能对设备造成腐蚀。应该在设计阶段，选择正确的清洁剂。

Factors affecting “cleanability” also include the surface type, the surface finish, the surface geometry,11 Technical Report No. 49 © 2010 Parenteral Drug Association, Inc.the soil type and the soil level. Process surfaces typically encountered in biopharmaceutical manufacturing equipment are listed in Table 3.5.2.

“可清洁性”的影响因素还包括表面的表面类型， 表面光洁度， 表面几何结构， 污物类型， 污物程度。生物制药具有代表性的工艺表面见表 3.5.2

3.5.2 生物制药生产工艺中的表面材料

哈斯特洛伊耐腐蚀镍基合金名称是为海恩斯国际注册

Surface finish also affects

the removal of soils. Rough surfaces provide more area for soil contact and may contain cracks and crevices that are difficult for the cleaning agent to penetrate. Therefore, the interior surfaces of stainless steel process equipment are typically treated (e.g., electropolishing) to smooth and polish rough surfaces.

材质 描述

不锈钢、哈斯特洛伊耐腐蚀镍基合金，其他合金、反应器、储罐、管道、其他大型设备

玻璃、陶瓷 细颈瓶、烧杯、量筒

聚乙烯 广口玻璃瓶

聚丙烯 广口玻璃瓶

碳氟化合物 垫片、软管、管道、小型容器

PETG 塑料 培养容器

聚碳酸酯 小型容器

硅树脂 管道、垫片、O 型圈

氟橡胶 垫片、O 型圈

EPDM（三元乙丙橡胶） 垫片、O 型圈

表面光洁度会影响污物的去除，粗糙的表面为污物的提供更大的接触表面，并可能存在裂纹和裂纹和缝隙，使得清洁剂难以渗入。所以工艺设备的不锈钢表面应进行抛光处理。

The easy with which a soil is releasedfro the equipmentsurface by one of the mechanisms described abovedetermines its cleanability. Soil response to a particular cleaning mechanism may influence the choice ofcleaning agent and cleaning conditions. Attachment to surfaces can be by a combination of van der Waalsforces, electrostatic effects and other forces. The time that the soil resides on the equipment can alsoinfluence the

difficulty of soil removal. Fresh soils are generally easier to remove than soils that have beenallowed to dry on the surface. The planned time between soiling and cleaning must be considered whendesigning the cleaning studies to simulate the dirty hold time with coupons.

采用上述去污机制中的任何一种，将污物带离设备表面的难易程度，决定了该污物的可清洁性。应依据污物对各别清洁机制的响应程度，进行清洁剂和清洁条件的选择。污物对表面的黏附力由范德华力，静电和其他因素力组成。污物残留在设备表面的接触时间，也能够对污物的去除难度产生影响。通常，刚出现的污物比已经干了的污物容易清洁。使用后至清洁前的时限在清洁程序设计时进行考虑，可以模拟污物在相关表面样片上的污染时间。

High soil levels can complicate removal by saturating the cleaning solvent or by depleting surfactants orother components of the cleaner (e.g., oxidizers or emulsifiers). This may limit the minimum cleaningvolumes and should be considered in cleaning cycle design when high soil levels are anticipated.

当污染水平较高时，清洁程序将会更为复杂。可能会使清洁剂饱和，或者耗尽表面活性剂的其组分（如氧化剂或乳化剂） 。这可能对清洁剂的最低用量产生影响，所以当预料到会有大量污物时，在清洁程序开发时，应予以考虑。

3.5.3 Cleaning Comparability Based on soil and surface

Laboratory testing often includes screening a matrix of soils and relevant process surfaces. Screeningexperiments are designed to test soil removal capability using representative soils (Table 3.5.1) andcoupons of relevant surface materials (Table 3.5.2). Cleaning conditions can be selected based on theresults for the soil-surface combination encountered in the production equipment.

3.5.3 基于污物及表面的清洁可比较性

实验室测试通常包括污物与相关表面组合进行筛选。通过代表性污物和相关表面样片，测试去除污物的能力。通过实际生产中污物-表面的组合，进行清洁条件的选择。

3.5.4 soil selection for laboratory evaluations

Care should be taken in the choice of soils and soil conditions used for the 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.

3.5.4 污物选择

在通过实验室评估选择清洁剂时，应谨慎选择污物和污染条件。所选择的污物应该是包括污物的理化性质在内（干燥的，烤干的）的日常生产设备上的代表性污物。

Solutions or suspensions of soils selected for experimentation are generally coated on

coupons representing the process contact surfaces and are dried to simulate the soil condition on theprocess equipment prior to testing for removal with cleaning agents. The representative soils generally49 © Inc. 17should include conditioned culture media and the product solution. Other relevant soils may also beincluded, as mentioned above and outlined in Table 3.5.1. The number of representative soils will varywith an organization’s experience and history as well knowledge about the content and cleanability of thevarious process steps

实验时通常将污物溶液或悬浮液涂在具有代表性的工艺接触表面的样片上，在使用清洁剂清洁前，模拟实际污染条件进行干燥。污物的选择通常需要包含培养基和产品溶液。也需要包含表 3.5.1 中提到的其他污物。代表性污物的数量会因为经验，历史知识。

3.5.4 soil selection for laboratory evaluations

Care should be taken in the choice of soils and soil conditions used for the 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.

Solutions or suspensions of soils selected for experimentation are generally coated on coupons

representing the process contact surfaces and are dried to simulate the soil condition on the processequipment

prior to testing for removal with cleaning agents. The representative soils generally shouldinclude conditioned culture media and the product solution. Other relevant soils may also be included, asmentioned above and outlined in Table 3.5.1. The number of representative soils will vary with anorganization's experience and history as well knowledge about the content and cleanability of the variousprocess steps.

3.5.4 实验室评价的污染物选择

在实验室评价过程中挑选清洁剂时，应当注意污染物和污染物条件的选择。污染物应能代表生产车间中设备的污染物，包括污染物的化学和物理（干，烤）性质。实验选取的污染物溶液或混悬液通常涂抹于代表工艺接触面的实验品上，并且在清洁剂去除测试前干燥，以模拟工艺设备的条件。代表污染物一般应包括使用过的培养基和产品溶液。其他相关的污染物可能也包括在内，如上述表 3.5.1 所述及。具有代表性的污染物数量随公司的经验和历史，以及不同工艺步骤的内容和可清洁性而变化。

3.6 Performing Cleaning development experiments

Biotechnology processes generally involve product contact with a variety of materials (Table 3.5.2).Laboratory evaluation of the interaction between product and surfaces can be performed using test coupons made of the surface of interest under simulated cleaning conditions. Based on the process details, appropriate materials of construction with the appropriate surface finish characteristics should be selected for use in lab-scale cleaning experiments. To minimize the number of experiments, it may be sufficient to include only those surfaces that are expected to be the most difficult to clean (based on prior knowledge and risk assessment tools). Stainless steel coupons are the most common choice, as they represent a majority of equipment surfaces in a production facility. Non-electropolished stainless steel coupons with a representative or worse surface finish compared to vessel surfaces may be preferred for lab evaluations.

3.6 进行清洁开发实验

生物技术过程一般会涉及到各种产品接触的材料（表 3.5.2） 。实验室对产品和表面之间相互作用的评估，可以在模拟的清洁条件下使用测试样品在相关表面上完成。基于工艺细节，在实验室规模的清洁实验应使用适当表面光洁度特征组成的适宜材料。为了尽量减少实验次数，只用那些最难清洁的表面（基于已有知识并经风险评估）进行实验是足够的。不锈钢实验材料是最常见的选择，因为它们代表了生产设施中多数设备的表面。相比于罐子表面，具代表性的非电抛不锈钢试样或最差抛光表面，可能更适合用于实验室评估。

Preparation of coupons typically involves the use of a cleaning regimen in order to ensure that all couponsare uniformly cleaned at the start of the experiment. This also helps to ensure that any foreign material deposited on the coupon surface during the fabrication process is removed to minimize any interference with the process soils or cleaning agent. The coupons are then completely dried before spotting them with soils, which may be the cell culture/fermentation fluid, harvested cell culture fluid, bulk drug active, and/or the final drug product formulation. It is important that the spotting of liquid onto each coupon be kept consistent to minimize experimental variability. The coupons are then dried for a fixed time to simulate the soiled equipment surfaces at the time of cleaning before they are subjected to the lab-scale cleaning process. That fixed time is generally the desired dirty hold time or a longer time.

制备试样通常涉及到使用清洁处理，以确保所有试样在实验开始时都是清洁的。这也有助于确保在装配过程中任何沉积在试样表面上的外来物质被去除，以最大程度减少与工艺污染物或清洁剂的干扰。然后试样在喷洒污染物之前进行干燥，污染物可能是细胞培养/发酵液、收获的细胞培养液、原料药活性物和/或最终制剂产品。重要的是，喷洒到每个试样上的污染物量保持一致，以尽量减少实验差异。然后试样干燥固定时间，模拟弄污的设备表面在受实验室规模的清洁工艺清洁前的保存时间。该固定时间就是期望的脏的保存时间或更长。

The purpose of the experiment could be to make one or more determinations related to cleanability: comparison of the various materials of construction for a given soil, comparison of different process streams for a given

surface, comparison of different cleaning conditions (such as concentration of cleaning agent and temperature), comparison of 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 lab represents the performance in the pilot plant or larger scale process. Key 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 lab, 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. Evaluation of performance for cleaning design space studies can utilize the various analytical methods listed in Section 6.0.

这项实验的目的是搞清楚可清洁性相关的一个或多个课题：给定污染物时各种组成材料的比较，给定表面时不同工艺料液的比较，不同清洁条件的比较（如清洁剂浓度和温度），不同产品对同一工艺步骤和表面的比较，或者联合应用这些因素。分析这些研究结果，以创造清洁“设计空间”。在任何情况下，重要的是，该实验室中的清洁工艺性能代表了中试水平或大规模工艺的性能。关键操作参数，如温度、时间、动作和浓度，应受控制并与制造工厂使用的相似。如果在实验室中模拟实际工艺条件困难，应采用“最差条件”的情况。该实验室的研究也可以用来挑战清洁过程，用修改清洁工艺不同变量的方法，来进一步探索设计空间。对清洁设计空间研究的性能评价可以利用各种分析方法，见第 6.0 节。

3.6.1 Parameter selection

A variety of parameters can impact the performance of a cleaning regimen. These include the nature and strength of the interactions between the product and the surface; the 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, e.g., stagnant, laminar or turbulent, and pressure; and properties of the liquid (ionic strength, pH, components, viscosity, density, etc.). All of theseexcept the cleaning action are independent of the equipment. The 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 that need to be evaluated, the more the number of experiments that are required to understand the impact of the parameters and their interactions. On the other hand, if too few parameters are 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 ignored. Use of a risk analysis tool, such as Failure Mode and Effects Analysis (FMEA), may assist in prioritizing the various operational parameters for further examination (See Section 10.0 on Risk Management). Single

parameter studies that vary one parameter at a time can be designed to identify the parameters that have significant impact on the performance. One such study, conducted at bench scale, reported the concentration and temperature of the cleaning solution to be the parameters with predominant effects. (7) As discussed in the following section, single parameter studies can then be followed by Design of Experiments (DOE) to investigate the interactions between these parameters. Alternatively, if only a few parameters need to be examined, just performing a DOE to measure both the main effects and the interactions may be more resource and time efficient.

3.6.1 参数的选择

许多参数可以影响清洁措施的性能。这包括产品和表面之间相互作用的性质和程度；清洁剂和污染物之间相互作用的性质；时间（脏的保存时间，每个清洁周期的时长）；清洁剂和浓度；温度；清洁动作（流动特性，例如，停滞，层流或紊流，和压力）；以及液体特性（离子强度，pH 值，成分，粘度，密度等）。除了清洁动作，所有这些都是独立于设备的。实验研究中参数的选择应依据情形不同而进行考察。需要进行评估的参数越多，所需要的实验数量越多，以了解参数的影响及其相互作用。另一方面，如果选取的参数太少，在确定重要操作参数和它们的范围时很可能做出错误的结论，因为重要的影响可能被忽略。运用风险分析工具，如失败模式与影响分析（FMEA），可有助于各种操作参数排序，以进一步的检查（见第 10.0

风险管理） 。在一个时间变动一个参数的单参数研究，可以用来鉴别对性能产生重大影响的参数。据报告一个这样的研究，在实验室规模进行，清洁液的浓度和温度为主要影响参数。（7） 正如在下一节讨论的，单参数研究可以用实验设计（DOE）方式来探索这些参数之间的相互作用。另外，如果只有少数几个参数需要进行研究，只执行一个 DOE 来衡量主要的影响和相互作用可能具有资源和时间效率。

3.6.2 Parameter Interactions

The use of DOE-style experiments helps to determine the effect of varying individual parameters on cleanability, as well as provides an indication of their interaction. Statistical tools including regression analysis, leverage plots, response surface analysis and interaction profiles can be used to study both main and interaction effects. Relationships and interactions between such parameters as the temperature of the cleaning solution and the concentration of the cleaning agent may be determined. Such DOE analyses 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. Using existing knowledge and a risk-based approach, cleaning experiments can be reduced or eliminated, for example, for transfer of a manufacturing process from one facility to another.

3.6.2 参数的相互作用

使用 DOE 模式的实验有助于确定不同的参数对可清洁性的影响， 以及为它们的相互作用提供一个指示。统计工具，包括回归分析、条形图、响应面分析和相互作用凸面可以用来研究主要的和相互作用的效果。这些参数之间的关系和相互作用，如清洁溶液温度和清洁剂浓度就可以确定。这种 DOE 分析可用于构建清洁工艺的多参数设计空间， 并建立操作参数的范围， 提供可接受的清洁工艺性能。利用现有知识和基于风险的方法，清洁实验可以减少或消除，例如，从一个工厂到另一个工厂的生产工艺转移。

3.7 Cleaning Process scale-up

Following the selection of cleaning agents and cleaning conditions (such as temperature, contact time,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 larger scale manufacturing equipment. Determination of soil and cleaning agent residue removal is generally performed prior to formal cleaning validation. Adjustments to cleaning conditions may be made during the scale-up process based on plant experience and laboratory development studies.

3.7 清洁工艺扩大

随着从工厂的历史数据（如果有）和实验室的开发工作中选择好清洁剂和清洁条件（如温度、接触时间、清洁剂的浓度和工艺流体力学） ，清洁工艺可以在更大规模的工艺设备上实施。确定污染物和清洁剂残留物的去除方式通常是在正式清洁验证以前进行。在工艺放大阶段可以基于工厂经验和实验室开发研究的基础进行清洁条件的调整。

3.7.1 setting Process Controls

It is both prudent and consistent with current CGMP to establish control ranges for the cleaning process operational and performance parameters. Operational parameters for CIP include: Dirty hold time for equipment (time between use and initiation of cleaning) Flow rate and/or delivery pressure of the cleaning stream (proof of flow for any parallel flow paths) Cleaning agent concentration Duration of each step in the cleaning process (by time or volume) Temperature of cleaning agents and rinses Air flow verification during any water removal or drying steps Instrumentation for each of these parameters should be included in the system design. Alert and action levels can be set for each parameter in order to maintain proper operation. Alert levels may be set based on expected variability of the equipment and instrumentation in the CIP system. Action levels should be set at values that permit adjustment to the equipment to avoid jeopardizing acceptable operation. Both alert and action levels should be within the acceptable ranges for each parameter. It is also reasonable to establish check times, such that an alarm notification will occur if parameters do not reach their set points (e.g., volume flow,

conductivity) within the specified time. Performance parameters should also be evaluated during scale-up. Performance parameters may include: Final rinse water conductivity Final rinse water TOC Final rinse water bioburden Final rinse water endotoxin

3.7.1 设置过程控制

建立清洁工艺操作和性能参数的控制范围应该是审慎的并和 CGMP 规范一致。CIP 操作参数包括：

•需清洁设备的保持时间（即使用后和清洁起始之间的时间）

•清洁液的供水流量和/或压力（够所有平行路径的流量）

•清洁剂的浓度

•清洁过程每一步骤的时长（时间或体积）

•清洁剂和冲洗的温度

•任何去除水或干燥步骤的空气流量确认

系统设计中应包括为所有这些参数设置仪表。可为每个参数设置警戒限和行动限，以维持正确的运行。警戒级别依据 CIP 系统中设备和仪器可以预期的波动性进行设置。行动限的设置值应允许设备的调整，以避免超出范围的操作。每个参数的警戒限和行动限应在可接受的范围内。建立检查时间也是合理的，如果参数在规定的时间内没有达到他们的设定点（例如体积流量，电导率），这样会出现一个报警通知。

性能参数在放大时也应该进行评估。性能参数可能包括：

•最终冲洗水的电导率

•最终冲洗水 TOC

•最终冲洗水生物负载

•最终冲洗水内毒素

3.7.2 Introduction of New soils to a Validated Cleaning system

Once cleaning processes are successfully operating in the manufacturing plant, they are monitored to ensure soil removal remains effective. 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. Generally, the cleaning effectiveness of the existing system for new soils can be tested by performing laboratory experiments using coupons of relevant materials (see Section 3.6 on Lab Development). These experiments can be designed to test both the effectiveness of the proposed cleaning regimen and the relative difficulty of cleaning the new soils compared to soils that have already been introduced to the plant. If the new soils are easier to clean than the most difficult 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 any of the present soils, some modifications to the current cleaning process may be

required, and cleaning validation is an expectation. However, if the new soil is easier to clean, then the number of confirmatory runs needed (if any) is determined based on a risk assessment.

Each organization should have its own system for maintaining effective cleaning after the introduction of new products or raw materials.

3.7.2 验证过的清洁系统引进新污染物

一旦清洁工艺成功运用于工厂，应对其监测，以确保污染物去除一直有效。当新产品或显着不同的原材料引入该车间，应有一个系统确保清洁工艺将继续有效。一般来说，现有系统对新污染物的清理效力，可以在实验室中使用相关材料的样品（见 3.6 章实验室开发）进行测试。这些实验可以设计成既可以测试推荐清洁方案的有效性，也可以比较新污染物与车间现存污染物的相对清洁难度。如果新的污染物比目前最难清洁的污染物更易于清洁，向现有

的清洁程序引入新材料应有信心。如果新的污染物比目前任何的污染物都更难以清洁，可能需要修改现有的清洁程序，而且希望进行清洁验证。但是，如果新的污染物更容易清洁，那么确认性的运行次数应根据风险评估决定。每个组织应该有自己的系统，确保在新的产品或原料引入后维持清洁有效性。

3.8 applying the “design space” Concept to Cleaning Processes

“Design Space” is the multi-dimensional combination and interaction of input variables and process parameters that have been demonstrated to provide assurance of quality. The design space concept has been introduced by the ICH (4) to describe an approach to the development and control of pharmaceutical manufacturing processes. An analogous approach can be applied to cleaning processes. The cleaning design space for a manufacturing facility is defined through a risk- and science-based approach relying on cleaning process knowledge, product/equipment knowledge, regulations and quality practices (requirements). Similar to manufacturing process development, control and validation, cleaning process operational parameters (inputs) can be controlled to ensure predictable and acceptable performance as evidenced by appropriate measurements (outputs). The cleaning design space is represented by the range of each of the operational parameters that results in acceptable performance of the cleaning process. Steps in defining the design space for a cleaning process may be slightly different from steps taken to

define design space for a manufacturing process, in that the design space for a manufacturing process is unique to that process (a fermentation, for example). However, many biotechnology manufacturers may want to design one cleaning process for a specific equipment train that is used, regardless of the manufactured product. This may be accomplished by identifying the “worst-case” soils and defining the design space around cleaning process performance using these soils.

3.8 对清洁工艺运用“ 设计空间” 概念

“设计空间”是能提供质量保证的输入变量和工艺参数多层面的结合与相互作用。 设计空间概念由 ICH（4）引入，用以描述药品生产过程开发和控制的方法。类似的方法可以适用于清洁过程。生产设施的清洁设计空间定义是一种基于风险和科学的方法， 并依靠清洁工艺知识、 产品/设备的知识、法规和质量实践（要求） 。与生产工艺开发、控制和验证类似，清洁工艺操作参数（输入）应可控制，以确保可预见的和可以接受的性能，并有适当数据（输出）证明。清洁设计空间由每个操作参数的范围表征，并导致清洁过程的性能可接受。

清洁过程确定设计空间的步骤可能会略微不同于制造工艺设计空间的确定步骤，主要在于制造工艺的设计空间是具独特的工艺特征的（例如发酵） 。然而，尽管生产的产品不同，许多生物技术制造商可能希望设计一个清洁工艺，用于一系列独特的设备。这个愿望依靠鉴别出“最差情况”的污染物并用其围绕清洁工艺性能确定设计空间，就可以实现。

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,probability of occurrence and 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 repeated if parameters are not kept within their predetermined ranges. The criticality of cleaning process operational parameters is based on laboratory studies that document the influence of each parameter on cleaning effectiveness. Cleaning effectiveness is influenced by the following factors: soil type or family dirty hold time equipment and contact surface type and finish cleaning technology and functional specifications for the cleaning process

This information is used to drive the design requirements for the cleaning method. Cleaning validation supports the worst case range of testing. Field conditions such as the lowest flow rate, least concentration of cleaning agent, minimal contact time, minimal process temperature, and longest dirty hold time are conditions that are considered when developing an effective cleaning process. The assumption is that any cleaning process that is performed within the space defined by these conditions will be effective, reliable and consistent.

应开发规范以支持清洁系统的设计、安装和操作。应识别风险和并评价其对安全性和清洁效果的影响（例如，严重程度，发生的可能性和发现概率） 。参数可根据其关键水平进行分类，最关键的参数应密切监控，以便即使参数不在其预定的范围内，清洁操作也可重复进行。清洁过程中操作参数的关键性建立在实验室

研究的基础上，每个参数对清洁效果的影响以文件形式记录。
清洁效果是受以下因素影响：
•污染物类型或体系
•污染保持时间
•设备和接触面的类型及抛光
•清洁技术和清洁过程功能规范
这一信息是用来推进清洁方法的设计要求。清洁验证支持最坏情况下的测试范围。现场情况诸如最低流量、最低浓度的清洁剂、最短的接触时间、最低的工艺温度，以及最长污染物保持时间，当开发有效的清洁工艺时应考虑这些条件。该假设是，任何在这些条件确定的空间内进行的清洁过程，都是有效的、可靠的和一致的。
A soil evaluation (characterization) study is performed prior to the introduction of any new process into manufacturing. These studies support the design space for the range of soils that will be cleaned from the process equipment. The characterization study is conducted with material that is representative of the process or a soil that represents the worst-case condition. For example, it is typical to use harvest material for this purpose, as it is the most complex and concentrated form of bioprocess soil. The soil type selected for a characterization study is dependent upon the impact to the manufacturing process. If a soil does not
react as expected following exposure to a cleaning agent, alternate cleaning solutions should be evaluated. Cleaning operational parameters (inputs) should be monitored to assure compliance with the established design space. Operational parameters may be set within the design space. Setting operational parameters with tighter ranges than allowed by the design space provides some flexibility in addressing deviations of operational parameters outside the control ranges.
向制造过程引入新工艺之前应进行污染物评价（表征）研究。这些研究应支持在工艺设备中清洁的污染物设计空间。进行表征研究所使用的材料应能代表工艺或为最差条件情况下的污染物。例如，通常使用收获材料用于此目的，因为它是生物工艺污染物最复杂、最集中的形式。进行表征研究所选择的污染物类型也取决于其对制造过程的影响。如果污染物没有跟随后暴露的污染物进行预期的反应，应评估替代的清洁方案。清洁操作参数（输入）应进行监测，以确保与建立的设计空间一致。操作参数设置应比设计空间允许的范围更严格，这样当操作参数超出控制范围时，为偏差的处理提供了一定的灵活性。

4.0 Acceptance Limits

Cleaning validation is performed to demonstrate the effectiveness and consistency of a cleaning procedure. The rationale for selecting limits for product residues, cleaning agents and microbial contamination, as well as any other process components, should be logically based on the materials that impact the manufacturing process and the safety and purity of the product. The acceptable limits for cleaning manufacturing systems and components should be “practical, achievable and verifiable.” (8) Limits for cleaning validation generally contain some measure related to the active protein (or other major component of interest), some measure related to the cleaning agent, some measure related to bioburden levels, some measure related to endotoxin levels, and a requirement that the equipment be visually clean. In addition, if there are any specific toxicity concerns related to the active protein or other process components (for example, cytotoxicity, allergenicity, or reproductive hazards), the manufacturer’s toxicology or pharmacology groups may determine if a modification of limits is required, or whether the use of dedicated equipment is needed.
In the discussion that follows, issues for limits are considered based on the nature of the residue and on the stage of manufacturing (e.g., bulk active vs. formulation/fill). Manufacturing stages include bulk active manufacturing (all steps resulting in the bulk active drug substance) and formulation/ fill (formulation of

the bulk active into a finished drug product and primary packaging of that drug product). Bulk manufacturing is further divided into upstream process steps (all process steps through harvesting) and downstream process steps (purification and following steps).

4.0 可接受限度

清洁验证的目的是为了证明清洁程序的高效性与一致性。选择产品残留、清洁剂、微生物污染，以及其他任何工艺成分的限度，逻辑上应该基于物料对生产流程和产品的安全性和纯度的影响而定。清洁生产系统和成分的可接受限度应该“切合实际、可达到、可证实”。

清洁验证的限度一般包含与活性蛋白 （或者其他的主要物质成分） 相关分析、 与清洁剂相关的分析、与生物负载水平相关的分析、与内毒素水平相关的分析，以及设备目检清洁要求。另外，如果存在任何与活性蛋白或者其他工艺组分相关的特别毒性物质（例如细胞毒性、变应原性、或者生殖危害物） ，那么生产商的毒理学或生理学团队就需要确定是否有必要改变限度，或者是否需要使用专用的设备。在接下来的讨论中，限度的考虑应该基于自然残留和生产的各个阶段（例如，原液 vs.配制/分装） 。生产阶段包括主要原液生产（所有的步骤是为了获取活性药物）和配制/分装（将原液加入到成品的制剂以及药品物质的初级包装） 。原液的生产进一步分为上游生产步骤（收获药物前的所有步骤）和下游生产步骤（药物纯化以及后续步骤） 。

4.1 key Issues in limits for actives

Biotechnology cleaning processes often involve a change of the active molecule itself, which is commonly a protein. Proteins typically are degraded to some extent by the cleaning processes commonly used in biotechnology manufacturing. The most important mechanism for degradation is summarized below.

In alkaline solutions, such as hot, aqueous solutions containing sodium or potassium hydroxide, proteins may hydrolyze to soluble oligomers or free amino acids. Ester groups on actives may be hydrolyzed to an alcohol and a fatty acid. A common example of this is saponification of fats and oils to glycerol and fatty acid anions.

Sodiumhypochloriteissometimesusedinbiotechnologycleaning.Asacleaningagent,itisparticularly effective in removing denatured protein residues from surfaces. It is a reactive oxidizer which will degrade proteins in a more random manner to smaller fragments. A general concern with sodium hypochlorite use is its

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possible deleterious effect on stainless steel components. Therefore, it is critical that the rinse cycle following the use of sodium hypochlorite is adequate enough to remove any residual chloride ion before adding the subsequent acid wash.

Proteins will hydrolyze at a high pH. The parameters of time and temperature have a significant influence on protein hydrolysis. Therefore, the higher the temperature and pH, the more extensive protein hydrolysis will occur. Because the protein is typically degraded into smaller fragments and those fragments tend to be more polar, they are likely to be more water soluble and more readily removed from equipment surfaces during the washing and rinsing processes. A second effect after protein exposure to high pH solutions is a possible irreversible, significant decrease of biological activity due to hydrolysis.

4.1 活性物限度的关键问题

生物技术的清洁过程经常涉及到活性分子本身的改变，因为这些活性物质通常是蛋白质。在生物制品制造通常应用的清洁过程中，蛋白质都会在一定程度上发生降解。下面就总结一下最主要的降解机制。在碱性溶液中，尤其是高温，溶液中含有氢氧化钠和氢氧化钾，蛋白质就会水解成可溶的寡聚物或者自由氨基酸。活性物质上的酯旨基团会水解为一个醇和一个脂肪酸，一个最为普遍的例子就是将脂肪和油脂转化为甘油和脂肪酸的皂化反应。次氯酸钠有时会用于生物技术清洁， 作为一种清洁剂， 它能非常有效地从表面去除变性蛋白质残留。

它是一种活泼的氧化剂，它能够使蛋白质更随机地降解为更小的片段。使用次氯酸钠时通常关注其对不锈钢成分的危害作用。 因此， 关键的是， 使用次氯酸钠后的漂洗循环能将氯离子残留冲洗干净，然后再进行酸清洁。在高 pH 下蛋白会水解，控制时间和温度参数都会在很大程度上影响蛋白质的水解。因此，pH 和温度越高， 蛋白就越容易发生水解。 因为蛋白通常降解为更为小的片段， 这些小片段趋向于高度极化，他们更加易于溶于水，也更加容易通过清洁、漂洗的过程从设备表面去除。蛋白质暴露于高 pH 的第二个效果就是，水解导致其生物学活性的下降可能是一个不可逆的、显著的过程。

Degradation of the active can be demonstrated in a laboratory study by exposing the active to the cleaning solution under simulated cleaning conditions (or less stringent conditions) and performing analytical and/or biochemical tests on the resultant mixture.

For these reasons, in most cases biotechnology manufacturers do not directly set limits for and directly measure the active in cleaning validation. Because of the degradation of the active, no active protein should remain after completion of the cleaning process. It is for that reason that analytical methods like TOC (see Section 6.0) are used for the detection of protein residues (or their fragments). If a nonspecific method like TOC is used for the correlation to residues of the active, it should be noted that the “real” value of protein residues after cleaning may be significantly lower, as TOC measures all sources of organic carbon (and not just residues from the active protein).

活性物的降解可以在实验室中验证，通过将活性物质暴露在模拟清洁条件（或者强度更低的条件）的清洁溶液中，然后对生成的混合物进行分析和/或者生物化学的测试。基于这些原因，在大多数情况下生物技术制造商在清洁验证流程中并不直接设置活性限度，或者直

接检测活性。由于活性物质的降解，在清洁过程完成后，应该不会有活性物质的残留。正是出于这个原因，人们用像 TOC{总有机碳（Total organic carbon）}的分析方法（见第 6.0 节）检测蛋白质的残留物（或片段）。如像 TOC 的非特异性的方法被用于活性物质残留的检测等相关使用， 应该指出，清洁后真正的蛋白质残留是非常低的，因为 TOC 检测的是所有的有机碳源（并不仅仅是来源于活性蛋白的残余） 。

4.1.1 establishing limits for actives in Formulation and Final Fill

In biotechnology formulation/fill manufacturing, limits for protein actives are typically set using a carryover calculation (often called MAC, or Maximum Allowable Carryover) in the same way as for small molecule cleaning validation. Though the product is degraded (as discussed above), the calculations are based on active product. This is assumed to represent a worst-case approach if the cleaning method used in formulation/fill results in degradation of the protein active to fragments. Such calculations may be revised based on degradation considerations.

This method only applies when the therapeutic daily dose is known. For products dosed chronically, a typical calculation allows no more than 1/1000 of the minimum daily therapeutic dose of an active in the maximum daily dose of the subsequent manufactured product; the factor of 1/1000 may be modified depending on the specifics of the situation. In addition, if that calculation allows more than 10 ppm of the active protein in the subsequent drug product, a limit of 10 ppm active protein in the next drug product may be utilized. Similar criteria are included as examples in the both the U.S. FDA

(8) and PIC/S guidance documents. (9)

Limits per surface area can then be calculated based on the minimum batch size of the next drug product and the shared surface area. Limits in swab and/or rinse samples can then be calculated using the sampling parameters.

When this method is used for setting limits, the limit for the active is calculated. It can then be converted to appropriate units for the analytical procedure to be utilized. For example, if the analytical procedure is TOC, the limit calculated for the active is converted to TOC based on the TOC content (percentage) of the active.

An example carryover calculation for formulation/fill is given as Example 1 in Section 15.0 of the Appendix.

It should be noted that limits based on carryover calculations are one example of a “science-based” method of setting limits. Some companies choose to set limits based on more stringent criteria, such as the WFI TOC specification of 500 ppb TOC. Such an approach is acceptable, but should only be used if it can be demonstrated that the WFI TOC specification is more stringent than the TOC result, as determined by a carryover calculation.

4.1.1 在制剂和最终分装中建立活性物限度

在生物技术产品的制剂和分装生产中，蛋白质活性限度的设定是用污染（传递）量计算（通常称为 MAC，或最大可允许的传递量），跟小分子清洁验证使用同样的方法。虽然产品降解（如上所述），计算是基于活性产品的量。 如果在制剂/分装所用的清洁方法导致了活性蛋白降解为小分子片段， 该方法就代表了最差的情况。考虑到降解作用，这个计算可以进行修正。只有当每日治疗剂量是已知的，才能应用这种方法。对于长期使用的产品，一个典型的方法是，在随后制造最大活性日治疗剂量的产品中，允许其携带不超过最小活性日治疗剂量的 1/1000；1/1000 的因子可能根据特殊情况而修订。此外，如果计算允许在随后的药物产品中活性蛋白残留量超过 10ppm，可以使用在下一批次的药物产品中，10 ppm 活性药物蛋白的限度。类似的标准在包括美国 FDA（8）和 PIC / S 的指导文件中是有例子的。

然后单位面积的限度可以基于下一个最小批量的药物生产所共用的设备面积上计算出来。擦拭或冲洗样品中的限度可以通过采样的参数计算出来。当使用这个方法设定限度时，活性物的限制可以计算出来。 然后它可以转换为分析方法适当的单位而被利用。例如，如果分析方法是 TOC，活性物质的限度可以通过转换为 TOC，即基于 TOC 在活性物质的含量（百分比）而计算出来。在文章的附录的第 15 个章节中有一个关于制剂/分装污染量计算的例子。

应该指出的是，基于污染量（传递量）计算的限度是设置限度的 “科学根据的”方法之一。一些公司选择基于更严厉的标准设定限度，例如用 WFI TOC 值 500ppb 作为标准。虽然这种方式是可以接受的，但是只有证明 WFI TOC 标准要比污染量计算的 TOC 结果更加严格，才可以使用这种方法。

4.1.2 establishing limits for actives in Bulk manufacture

Carryover calculations used for formulation/fill are typically not applicable for bulk manufacture. The primary reason is that if the carryover calculation is based on the entire equipment manufacturing train surface area, limits are extremely low and are not measurable by available analytical techniques, unless the active is not degraded during the cleaning process. As previously discussed, the active protein is, in almost all cases, degraded by the cleaning process. Therefore, even though typical specific assays for the active can measure the active at very low levels, those assays are not useable when the active is degraded. As noted above, the residues of the active are generally measured “indirectly” by measuring a property like TOC (for purposes of this report, TOC will be used as an example of such analytical methods, although assays like Total Protein could also be used). Typical quantitation limits for TOC for cleaning validation purposes are on the order of 100-500 ppb carbon, which is equivalent to about 200-1,000 ppb protein for proteins containing about 50% carbon. Therefore TOC cannot be used as an analytical method if limits are based on a carryover calculation using the surface area of the entire equipment train.

Some companies choose to use a carryover calculation for a limited surface area, such as for the last manufacturing vessel or for all of the manufacturing equipment after the last purification process. Such a modification may result in a carryover limit, which possibly could be measured by TOC. One rationale for such an approach can be found in ICH Q7, Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients; Section 12.7 of the guide says that early processing steps do not require validation if subsequent processing steps remove those residues. (10) The various processing steps after fermentation and processing, including chromatographic purification and ultrafiltration, can be expected to remove

those residues of the active from earlier cleaning steps, since those residues are typically smaller fragments. This generally has not been demonstrated for a specific active but is a reasonable supposition based on an understanding of degradation and the various purification processes utilized in a given manufacturing process. Inactivation of active protein can be considered in carryover calculations with rationales. This results in a conservative limit, because it is assumed that the degraded fragments have significantly less pharmacologic effect and/or safety concern compared to the native protein.

4.1.2 在原液生产中建立的活性物限度

用于制剂/分装的污染量计算通常不适用于原液的生产。主要的原因是如果污染量计算的方法是基于整个生产线的设备表面积，限度是极低的，除非药物活性成分在清洁过程中不会降解，否则是不能用现行分析技术测量的。正如前面讨论的，活性蛋白在大多数情况下，都会在清洁过程中被降解。因此，即使典型的特异性方法可以在很低水平上测量活性物质，但是当活性分子降解后这些方法是不能使用的。如上所述，活性物的残留一般都是像 TOC 一样通过 “间接”测量某一特性（为了这个报告的目的，TOC 将作为此类分析方法的例子，尽管也可以用总蛋白测量之类的方法）。通常清洁验证 TOC 的定量限度大约为 100-500 ppb 碳，与含碳量为 50%的约 200-1000 ppb 蛋白质的数值等效。因此说如果限度是基于整个设备链的表面积而计算污染量的，那么 TOC 是不能用作分析方法的。一些公司选择使用一些限制区域的表面积计算污染量，例如使用最后一个生产罐或用最后一步纯化工艺后的所有生产设备。这样的修订也许会导致计算的污染量，可以用 TOC 测定。这种方法的原理可以在 ICH Q7（药物活性成分的 GMP 指南）中找到；在指南的 12.7 章节中提到如果在随后的生产步骤中去除这些残留物，在早期的生产步骤中不需要验证。 （10）发酵和处理后的各种工艺步骤，包括层析纯化及超滤等，预期可以去除早期清洁过程中所留下的残留物，因为这些残留物通常是小分子片段。这一点对于一个特定的活性物还没有被证实，而是根据对蛋白质降解的理解以及生产工艺中所使用的各个纯化工序的了解，所做的一个合理假定。在污染量计算的依据中，应考虑活性蛋白的灭活。 这将导致一个保守的限度， 因为它假定降解碎片的药理学作用和/或安全考虑是远远低于天然蛋白质的。

Because of these measurement issues, and because of the degradation issues, a more common technique for setting limits for residues of the active is based on process capability. This is not a true process capability study, but is based on what has been and can be achieved by conventional cleaning procedures in biotechnology manufacturing. These limits are typically based on the TOC values of any sample, whether rinse or swab. As a general rule, the limits may be more stringent following the purification process. TOC limits upstream are typically less stringent, because the product cleaned fromtheequipmentsurfaceshasmoreextraneousmaterials(suchascellularmaterials).Typicalvalues established as acceptance criteria by manufacturers are 1-2 ppm TOC for downstream processes and 5-10 ppm TOC for upstream processes. As in other cleaning validation protocols, it should be noted that typical values achieved are significantly below established limits.

Exceptions to this practice are for product-dedicated materials like ultrafilter membranes and chromatography resins. These are part of the downstream processing, but limits may be set higher. This higher level is acceptable when these items are dedicated to the manufacture of only one product.

An example carryover calculation for bulk active manufacture (assumes the entire manufacturing train is the shared surface area) is given as Example 2 in Section 15.0 of the Appendix. The purpose of that illustration is to demonstrate the low (and unmeasurable) TOC values that are achieved in such calculations.

由于这些测量问题,也由于降解的问题，一个更普遍的设定活性物残留限度的技术是基于工艺能力。这不是一个真正的工艺能力研究，而是基于在生物产品制造中已有的和传统的清洁操作程序来实现的。这些限度通常基于所有样品的 TOC 值，不论是冲洗或擦拭。作为一般规则，那些纯化工艺后的限度应更加严格。上游工艺的 TOC 限度通常会严格性差一些，因为设备表面清洁的产品会有更多外来材料的（例如细胞物质）。

制造商所建立的可接受标准通常为下游工艺 TOC 1-2ppm 和上游工艺 TOC5-10ppm。就像其他清洁验证方案一样，应该注意，通常获得的数值应显著低于既定的限度。但是对于如超滤膜和色谱树脂这些产品专用材料来说是可以有例外的。这些都是下游工艺的一部分，但是可以设定更高的限度值。当这些对象只是专门用于制造一种产品时，更高水平的限度是可以接受的。关于原液生产的污染量计算方法例子（假定整个生产线的表面共用）在附录的第 15.0 节中的第二个例子有所体现。那个例证的目的是证明低（不可计量的）的 TOC 值通过计算是可以达到的。

4.1.3 limits Based on Toxicity data

An alternative to establishing limits for the active for either formulation/fill (Section 4.1.1) or bulk manufacture (4.1.2) is to establish limits based on toxicity calculations. These toxicity calculations for the active are similar to toxicity calculations for cleaning agents covered in Section 4.2.1. Toxicity calculations typically involve the use of the short-term toxicity data for the active, ultimately to arrive at an ADI (Acceptable Daily Intake). Calculations should preferably be based on toxicity data by the same route of administration (such as intravenous studies if the drug product is given by injection). If the data are based on oral toxicity, additional safety factors may be required for the cleaning of injectables. As a general observation, such calculations for actives based on safety considerations generally result in higher limits as compared to calculations based on dosing. Furthermore, if the active protein is degraded, the more

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relevant toxicity data is not the toxicity of the native protein, but the toxicity of the degraded fragments, which is often assumed to be less of a safety concern (although toxicity studies on degraded fragments are typically not performed).

4.1.3 基于毒理学的限度

一种为制剂/分装（章节 4.1.1）或者原液生产（4.1.2）而建立活性物限度的替代方法，是基于毒理学计算而建立的限度。这些活性物的毒理学计算与在第 4.2.1 章节中所提到的清洁剂毒理学计算是类似的。毒理学计算通常涉及活性物质短期的毒理学数据，最后到达一个 ADI（允许的日摄入量） 。基于同一种用药途径（如果是注射给药的产品应通过静脉注射来研究）的毒理学数据计算会更好。如果数据是基于口服的毒理学，对注射药的清洁应要求增加安全系数。作为一个总的看法，这种基对安全考虑而进行的计算，与基于剂量的计算相比，通常会导致较高的限度。此外，如果活性蛋白降解，更多的相关毒理学数据不是天然蛋白质的毒理学，而是降解碎片的毒理学，通常认为后者安全问题更少（虽然通常不会进行降解碎片的毒性研究） 。

4.2 limits for Cleaning agents

Limits for cleaning agents will also depend on the stage of manufacturing (formulation/fill vs. bulk active manufacture). Typical cleaning processes for biotechnology involve either a caustic wash followed by a phosphoric acid step, or an alkaline detergent followed by an acidic detergent. Each of these situations will be handled separately.

4.2 清洁剂的限度

清洁剂的限度也取决于生产的各个阶段（制剂/分装与原液生产） 。典型的生物制药清洁程序包括强碱清洗以及下一步的磷酸物的清洗，或者是碱性清洁剂以及随后的酸性清洁剂。这些过程都是分开处理的。

4.2.1 limits for Commodity Chemicals

If only commodity chemicals such as sodium hydroxide and phosphoric acid are used for cleaning, it is common practice to set limits for these indirectly as a conductivity value. Preferably, an acceptable level of sodium hydroxide or phosphoric acid is established based on toxicity carryover calculations or based on the effects on process parameters. The conductivity limit is then set at a level equivalent to that concentration at a specified temperature. It is typically the case that the conductivity limit established in

this way is well above the conductivity limit for WFI at the same temperature. Therefore, limits are based on either WFI specifications or on a slightly higher value (such as 5 µS/cm). The rationale for this is that it is more stringent than the "scientific" calculation allows. Furthermore, in many cases, phosphate ions and/or sodium ions may be part of any subsequently manufactured product. Therefore, carryover of small amounts is not significant. It should also be noted that calculations based on toxicity of the commodity chemicals are extreme, since sodium hydroxide is not carried over into a final product as sodium hydroxide, and phosphoric acid is not carried over into final product as phosphoric acid. If such chemicals were carried over intact at high concentrations, process checks (such as a significant change in pH) would also cause a non-conformance. Thus, the purpose is not to confirm compliance with WFI specifications, but rather to confirm low amounts of a cleaning agent. The rationale for allowing a conductivity limit slightly higher than the WFI limit is that the WFI limit applies to water in the recirculating WFI loop. As soon as the water is taken out of that loop and passed through clean equipment (particularly through spray devices where it can pick up carbon dioxide from the air), there is no expectation that it will necessarily meet the WFI conductivity limit.

4.2.1 市售化学试剂的限度

如果只有市售化学试剂如氢氧化钠和磷酸用于清洁，那么通常的做法是用电导率的值为其设定间接的限度。更好的做法是，氢氧化钠或者磷酸的可接受水平建立在毒理学的污染量计算或者是工艺参数的效果之上。然后电导率限度的设定水平就等同于在特定温度下的那个浓度。这种情况下用这种方法设置电导率的限度，通常要好于在相同温度下注射用水的电导率限度。因此，限度是基于注射用水的标准或者是稍高于这个标准（例如 5 µ S/cm） 。这种做法的原因是它要比"科学"计算的限定值更加严格。此外，在许多情况下，磷离子/或钠离子可能是随后制造出来产品的一部分。因此，少量的污染量并不明显。还应指出的是，基于市售化学试剂的毒性计算是比较极端的，因为氢氧化钠并不会以氢氧化钠的形式污染到最终的产品中，磷酸也不会以磷酸的形式污染到最终产品的。如果这些化学物质以高浓度完整地污染下来，通过工艺检查（这样会引起 PH 的显著变化）也会发现这种不符合性。因此，目标并不要求与注射用水的标准一致，而是确认一个很低的清洁剂含量。而允许电导率限度略高于注射用水限度的原因是，注射用水的限度要求只是适用于管路中的循环注射用水。一旦从循环管路中取出水并通过清洁设备（尤其是通过喷淋装置时它可以从空气中摄取二氧化碳） ，不要期望它一定会满足 WFI 的电导率限度。

4.2.2 limits for Formulated Cleaning agents

For formulation/fill manufacturing, limits for residues of formulated cleaning agents (which may contain a variety of organic components in addition to inorganic hydroxide) are typically set based on a carryover calculation using the short-term toxicity (LD 50) data for that formulated cleaner. Such toxicity information may be supplied by the cleaning agent manufacturer or may be calculated using worst-case assumptions based on an analysis of the formulation components. A typical calculation is given in Example 3 of Section 15.0 of the Appendix. For the determination of the limit in the next drug product, a default value for the formulated cleaning agent may also be used if it is more stringent than the carryover calculation. That default value is typically 10 ppm formulated cleaning agent. Note that the only difference between a carryover calculation for the active and a carryover calculation for the formulated cleaning agent is how the limit in the subsequent product is calculated – one uses a fraction of a dose and one uses a fraction of the LD 50 . Once that calculation is performed, subsequent calculations for cleaning agents use the same formulas as for actives to determine the limit per swab or the limit per analytical sample.

For manufacturing of bulk actives, some of the same issues discussed for limits of actives also apply to cleaning agents. That is, a carryover calculation considering the total shared surface area results in extremely low limits, typically not measurable. However, the formulated detergents typically used may be removed by various purification processes (such as ultrafiltration or size exclusion chromatography) based

on molecular weight. As with limits for actives, toxicity calculations may be applicable for downstream processes following the purification steps or for the last downstream process vessel.

4.2.2 处方清洁剂的限度

对于制剂/分装制造，处方清洁剂（可能在无机氢氧化物中添加很多有机组分）残留量的限度通常是依据其短期毒性（LD50）数据而计算污染量的。这种毒性资料可提供的清洁剂制造商或可使用的计算制订成分分析的基础上最坏情况的假设。这种毒理学的资料可由制造商提供或使用基于处方成分分析得出的最差情况而计算。在附录的 15.0 章节中给出的第三个例子是一个典型的计算。为了确定下一个药物产品中的限度值，如果处方清洁剂的默认值比污染量计算的值更加严格，也可以采用。处方清洁剂的默认值一般为 10ppm。请注意活性物污染量计算与处方清洁剂污染量计算的差异在于对后续产品的污染限度计算方法不同，一个使用的是剂量比率，而另一个用的是半致死率 LD50 比率。一旦完成计算，随后的清洁剂计算使用与活性物同样的公式，来确定每个拭子或每个分析样品的限度。对于原液生产，为活性物限度而讨论的一些问题也同样适用于清洁剂。也就是说，考虑到整个共享面积的污染量计算值是极低的，通常难以测量。但是，使用的处方洗涤剂通常在分离提纯等过程中可根据分子量去除（例如超滤或者是分子排阻色谱法） 。就像活性成分的限度一样，毒性计算可能适用于下游纯化后的步骤或下游工艺的最后一个容器。

4.3 Bioburden limits

In considering bioburden limits following cleaning, it is not expected that the cleaning process itself results in sterile equipment. However, even if the process equipment is steamed in place or autoclaved prior to manufacture of the next product, it is typically the practice to evaluate bioburden to establish that the subsequent process is not overly challenged. Achievement of typical bioburden limits for non-sterile manufacturing (1-2 CFU/cm 2 for surface sampling methods) is considered more than adequate. For rinse sampling, some companies will utilize typical WFI values (10 CFU/100 mL), while others will utilize a value of either 100 CFU/100 mL or 1,000 CFU/100 mL. The rationale for the higher limit is that the equipment will be subsequently sterilized. Furthermore, the WFI value is the value for the WFI in the recirculating loop; once it is removed from that loop and placed in clean equipment, there is not necessarily an expectation that it will still meet the WFI value.

4.3 微生物限度

考虑到清洁后微生物的限度，不要预期清洁过程本身会导致设备的无菌结果。然而，即使如果设备进行在位灭菌或者是在下一产品生产前灭菌，通常的做法是评估微生物负载来确保随后的生产工艺不会过度挑战。只要达到一般的非无菌生产微生物限度标准（1-2CFU/cm2 表面取样方法）就已经是足够的。对于冲洗取样，一些公司将利用典型 WFI 的值（10 CFU/100 毫升） ，而其他公司将利用 100CFU/100 毫升或 1,000 CFU/100 毫升的值。设定较高的限度原因是随后设备将进行灭菌。此外，WFI 的值是在管路中循环的注射用水值，一旦它从循环管路中取出并加到设备中时，并不要期望它能必然符合原有的注射用水值。

4.4 endotoxin limits

Endotoxin carryover to the final product is more of a concern after the various endotoxin removal steps. In those cases, endotoxin is typically measured only in the final rinse water, and limits are set at the typical WFI limit of 0.25 EU/mL. Prior to the endotoxin removal steps for cell culture processes, it can be expected that rinse samples should meet the WFI limit. For bacterial fermentation with E. coli (a gram-negative bacterium which will produce large amounts of endotoxin in the washing step), meeting the WFI limits following cleaning at the fermentation and harvesting steps may not be achievable. For that reason, some companies may not set endotoxin limits for cleaning for those steps, while others will set endotoxin limits but at a higher value, such as 5-25 EU/mL. Achieving such values indicates a measure of control in the cleaning process, and any possible carryover at those levels should be

addressed by subsequent endotoxin removal process steps.

4.4 内毒素限度

在内毒素经各个去除步骤后，内毒素对最终产品的污染量是更值得关注的。在这种情况下，内毒素通常只在最后的冲洗水测定，限度设定通常是注射用水标准 0.25EU/ml。在细胞培养过程的内毒素去除步骤之前，冲洗水取样预期应该符合注射用水限度。对于用大肠杆菌进行的细菌发酵（革兰氏阴性细菌， 在冲洗过程中能够生产大量的内毒素） ， 在发酵和收获步骤后的清洗符合注射用水限度，是不可能完成的，这种情形下，其它公司在更高的水平设置内毒素限度，例如 5-25 EU/mL。实现这一水平表明清洁工艺得到控制，任何在这种水平上的可能污染量应在随后的内毒素清除工序中评价。

4.5 Visual Clean Criterion

The visual appearance of production surfaces is a direct measurement that verifies removal of residuals. Visual appearance is not a quantitative method but is very useful to directly verify that production surfaces are clean. Visual appearance is easy to perform provided there is ready access to the critical surfaces. It verifies the cleanliness of a significant area of production equipment. Literature indicates that low levels of residues (if present) are visible and can be detected. As used in biotechnology manufacturing, a visual clean criterion is typically used with swab and/or rinse testing for residues for cleaning validation protocols.

4.5 视觉清洁标准

产品表面的外观目测是核实残留物去除的一种直接衡量手段。外观目测也不是一种定量的方法，但是对于直接检查产品表面清洁非常有用。只要有路径可以到达关键的表面，外观目测很容易完成。它能确认生产设备重要区域的洁净程度。 文献表明少量的残留 （如果存在） 是可见的和可被察觉的。如同在生物制药中所使用的， 目测清洁标准能典型地用做清洁验证方案中的擦拭和/或冲液中残留物的测试。

4.6 modifying limits

Manufacturers may establish action and/or alert levels on validated processes as part of routine monitoring. Those values are typically more stringent than the pass/fail limits in the validation protocol. Based on process capability showing consistently low values and the ability to maintain those values, manufacturers may perform a risk assessment and consider the use of more stringent limits for future validation protocols.

4.6 修改限度

制造商可能会设立行动和/或警戒限度， 作为日常工艺验证监测的一部分。 这些值通常比验证方案中的合格/失败限度更加严格。 依据工艺能力显示连续的低水平和维持这些水平的能力， 制造商可以进行风险评估并考虑为将来的验证方案采用更加严格的限度。

5.0 Sampling Methods 取样方法

It is essential to a cleaning validation program that the appropriate sampling techniques are utilized. Sampling must be conducted with techniques appropriate for the equipment surfaces and for the nature of the study, including the analytical methods used. This section discusses types of sampling methods, sampling recovery validation studies, and the training and qualification of samplers.

在清洁消毒验证中采用适当的取样技术是必要的。取样过程中涉及的技术方法应与设备表面和研究本质相适应，包括使用的分析方法。这一部分讨论了取样方法的类型，验证取样回收研究以及取样人员的培训及资质。

5.1 Sampling Method Selection

取样方法选择

Selection of a sampling method depends on the nature of the equipment and the nature of the residue

being measured. Sampling methods discussed here are direct surface sampling, swabbing, rinse water sampling and placebo sampling. It should be noted that while regulatory documents refer to swabbing as "direct" sampling and to rinse water sampling as "indirect" sampling, it is preferable and more descriptive to refer to those sampling methods as "swab sampling" and "rinse sampling," and reserve the term "direct sampling" for techniques such as the use of visual inspection.
取样方法的选择取决于设备性质以及检测残留物的性质。此处讨论的取样方法是直接表面取样，擦拭取样，冲洗水取样以及空白对照取样。 值得注意的是法规文件中指出擦拭被认为是 "直接" 取样，冲洗水取样被认为是"间接"取样，所指的取样方法如"擦拭取样"和"冲洗水取样"是更可取并且更好被描述的，技术上保留"直接取样"的术语，比如使用目测检查。

5.1.1 Direct Sampling Methods 直接取样方法
Direct sampling methods (as used in this document) include visual inspection.
直接取样方法（本文中使用的）包括目测检查。
It is a well-accepted practice that a cleaning process should remove visible residues from the production process off of 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.
清洁过程中应除去设备表面上来自于生产工艺可见残留，这一点是被广泛认可的。设备的目测检查具有局限性，因为一些设备表面（比如管道）通常是不易观察的。像镜子或者内视镜之类的光学仪器的使用作为辅助照明能够帮助进行目测检查。
Remote inspection techniques (with fiber-optic probes and a LCD viewing screen) are utilized when visual inspection by a trained inspector is difficult to perform because of access to equipment surfaces, or when one prefers to supplement an "unaided" visual inspection procedure.
当由经过培训的人员由于要接触设备表面而难以进行目检时或者是补充 "未受协助" 的目检程序时，远程检查技术（纤维光学探头以及 LCD 观察屏）被应用。
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. Typical benefits of these scopes are that they: can fit into confined spaces not accessible to operators; are very maneuverable; have additional lighting attached; and may come with optional magnification and/or zooming capabilities. The major drawback of these scopes is the complexity of use, controlling lighting/brightness, and that the operator still has to make the determination if the area viewed is visually clean.
管道内窥镜，纤维内窥镜以及光纤视镜允许对难以达到的区域进行目检。管道内窥镜用于观察管道内部和水槽焊接点。这些范围的典型好处是：适用于操作人员接触不到的密闭空间；易操作，具有辅助照明并且具有选择性放大和/或提升的能力。 这些范围的最大缺点是使用复杂， 控制照明/亮度，并且操作人员需要判断该区域是否能够清晰可见。
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, with 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 the actual amount of residue present, since operators will typically zoom in on a particular area when taking a picture.
远程可视相机允许操作人员在屏幕上观察远程区域。相机与范围具有大部分相同的优势和劣势，而更多的优势是操作人员能够代表性的记录视频或者拍照。多个操作人员能够同时观察到屏幕显示了什么。记录视频以及允许多个观察者观察屏幕的可能性可以帮助支持厂区目检培训程序。来自相机的打印的图片可能扭

曲残留的实际数量，因为操作人员将在特殊区域内聚焦，当拍照时。
All these techniques, like visual inspection, require an adequate training program.
所有这些的技术，像是目检，要求具有充足的培训程序。
5.1.2 Rinse Sampling
冲洗取样
Rinse sampling involves sampling the equipment by flowing water over all relevant equipment surfaces to remove residues, which are then measured in the rinse water. The most common rinse sampling technique is to take a grab sample from the final rinse water during the final rinse of the cleaning process. Another option is to fill the entire equipment with water after the cleaning procedure is completed. Then, a bulk sample is taken and analyzed. A third option is to utilize a separate CIP sampling rinse of defined volume following the completion of the final process rinse.
冲洗取样涉及对设备取样通过流水冲洗所有相关设备表面移除残留，残留将在冲洗水中进行测量。大部分冲洗取样技术是在清洁过程中的最终冲洗中通过从最终冲洗水中提取随机样品。另一个选择是在完成清洁程序后，用水填满整个设备。然后，取大部分样品进行分析。第三个选择是使用单独的 CIP 取样冲洗定量，在最终冲洗完成后。
Advantages and disadvantages of both methods for CIP rinsing are shown in Table 5.1.2.
CIP 冲洗的两种方法的优势和劣势见表格 5.1.2
Table 5.1.2 Comparison of CIP Grab Sampling versus Separate CIP Sampling Rinse
表格 5.1.2 CIP 简单取样与单独 CIP 取样冲洗的比较

Grab Sampling from CIP Final Rinse 来自 CIP 最终冲洗的简单取样	Separate CIP Sampling Rinse 单独的 CIP 取样冲洗
Advantages 优势	
Represents the normal cleaning process 代表了正常的清洁过程	
Allows on-line testing 允许在线检测	
Requires no additional amounts of rinse water 不要求附加的冲洗水	
Equipment can be used for further processing without additional steps 不需要附加步骤，设备用于进一步的过程	
Results can easily be used for carryover calculations 结果易用于遗留计算	
Represents what is left on surfaces after the completion of the cleaning process 代表了完成清洁过程后什么留在了表面	
More likely to result in an acceptable result if done correctly 如果正确完成，更有可能产生 可接受的结果	
Disadvantages 劣势	
Sample represents a worst-case carryover to the next batch (but can demonstrate robustness of the cleaning process) 样品代表了对下一批次的最差情况的遗留（但是能够显示清洁过程的稳定性）	
Utilizes an additional step 使用附加步骤	
Requires additional amounts of rinse water 要求附加的冲洗水量	
Contamination is possible due to the method of water addition 由于补充水	
Assumptions need to be made about sampling for carryover calculations 制定假设关于遗留计算 的 取样的方法引入污染	

Online testing not practical 在线检测不实际

A special case of rinse sampling is the sampling of small parts. Those parts may be sampled by swabbing, but there are two options for rinse sampling. One type of rinse sampling is extraction of the small parts. In an extraction procedure, the extraction solution (typically water for biotechnology residues) is placed in a clean vessel. The small part is then placed in the extraction solution and agitated or sonicated for a fixed time. The sampling solution is then analyzed for potential residues. A second type of rinse sampling for small parts is typically used for items with an orifice, such as filling needles. In this procedure, a fixed volume of sampling solution (again, typically water) is passed through the lumen and collected in a clean collection vessel. The sampling solution is agitated for uniformity, and then analyzed for the potential residues. Because the surface area and sampling volume are precisely known, limits can be accurately calculated for such situations.

冲洗水取样的一个特殊情况就是小部件取样。冲洗取样的一种方法就是小部件提取。提取过程中，提取液（生物技术残留的典型水）被放置在清洁的容器中。之后小部件被放置在提取液中并且在固定的时间进行摇动或者超声处理。之后对样品溶液进行分析可能存在的残留。对于小部件冲洗取样的第二种方法典型的用于具有孔口的部件， 比如灌装针头。 在这个程序中， 定量的样品溶液 （再次，代表性的水）通过内腔并在洁净的收取容器中收集。匀速摇动样品溶液，之后对可能存在的残留进行分析。因为表面区域和取样量是精确已知的，对于这种情况，能够精确计算限度。

5.1.3 Swab Sampling 擦拭取样

Swab sampling involves wiping a surface with a fibrous material (most commonly). During the wiping procedure, the residue on the surface may be transferred to the fibrous material. The fibrous material is then placed in a solvent to transfer the residue to the solvent. The solvent is then analyzed for the residue by an acceptable analytical technique. The most common fibrous material is some kind of textile (knitted, woven or nonwoven) attached to a plastic handle.

擦拭取样涉及使用纤维材料擦拭表面（最一般的） 。擦拭过程中，表面的残留被转移至纤维材料上。随后纤维材料被放置在溶剂中，将残留转移至溶剂中。之后采用可接受的分析技术对溶剂进行残留分析。最常见的纤维材料是带有塑料手柄的一些纺织物（针织的，梭织的或者无纺布的） 。

In most cases the swabs are wetted with a solvent prior to sampling the surface. For TOC and conductivity, the solvent is almost always water. For sampling the same site, companies may choose to sample the same surface area with multiple swabs in order to provide a higher percent recovery of residue from the surface. In such cases, the additional swab(s) utilized may be either dry swab(s) or swab(s) wetted with the same solvent.

大部分情况下，在对表面取样前棉签是湿的并且带有溶剂。对于 TOC 和电导的方法，溶剂大部分情况下总是水。对于同样位置的取样，公司可能选择取样同样的表面积进行多次擦拭，以提供表面更高的残留回收率。在这些情况下，使用的附加擦拭可以是干擦或者具有同样溶剂的湿擦。

5.1.4 Comparison of Swab and Rinse Sampling 擦拭和冲洗取样的比较

Both swab sampling and rinse sampling are listed as acceptable sampling techniques in most regulatory documents. (8,9,11) Both methods have their advantages and disadvantages, as shown in Table 5.1.4

在大部分的法规文件中，作为可接受的取样技术，擦拭取样和冲洗水取样都被列出。 （8.9.11） 。两种方法都具有其各自的优势和劣势，见表格 5.1.4.

Table 5.1.4 Comparison of Swab Sampling and Rinse Sampling

表格 5.1.4 擦拭取样和冲洗水取样的比较

Swab sampling

擦拭取样

Rinse sampling

冲洗水取样

Advantages

优势

Enables the analysis of residues found on the specific surfaces. Includes the recovery of proteins that are denatured and/or adhered to the surface. 基于特定的表面进行残留的分析。包括变性和/ 或粘附于表面的蛋白质的回收。

Allows for sampling of areas that are more difficult to clean (i.e., worst cases). 对于难以清洁的区域进行取样（即，最差情况）

During rinsing, the entire product-contacting surface is wetted. One analysis result represents the sum of all removed residues for the flow path. 冲洗过程中， 产品接触的全部表面都是湿的。一个分析结果代表了冲洗过程中所有移除残留的总和。

The sampling procedure does not contaminate the equipment. Re-cleaning is not required after sampling. 取样过程不会对设备产生污染。取样后不需要再次清洁。

This method allows for conclusions on the cleanliness of areas that are not accessible for swabbing. 这种方法允许对不能进行擦拭的区域的清洁度作出结论。

Disadvantages

劣势

Only discrete sampling areas can be analyzed, and these must represent the entire equipment; sampling must include worst-case locations. 只有离散采样区域能够被分析，这些必须代表整体设备 ，取样必须包括最差情况位置。

The sampling itself can potentially contaminate the equipment. Re-cleaning may be required after sampling. 取样本身能够对设备产生潜在污染。取样后要求进行再次清洁。

Some areas are not accessible for swabbing (e.g., piping systems). 一些区域是不能进行擦拭的。（如管道系统）

Only water soluble residues can bedetected. 只有水溶性的残留能够被监测。

Those areas that are hard to clean cannot be identified. 难易清洁的区域不能被识别。

Does not deal with residues that preferentially transfer from one part of the equipment to the next product.不能够处理从设备一部分优先转移至下一个产品的残留。

May dilute out the residue to be undetectable by the analyticalmethod. 通过分析方法可能会稀释残留而不能检测。

In cases where the equipment surface is difficult to access for swabbing (e.g., piping), swabbing is not anoption. It should be appropriately justified that the cleaning procedure is considered effective if swab testing will not be performed. The following situations will justify a decision to not swab a surface:

在设备表面难以进行擦拭取样的情况下（如，管道） ，擦拭方法就不是一个选择。如果擦拭检测不能够进行，应适当说明清洁程序被认为有效的。下列情况将说明不进行表面擦拭：

- Equipment not accessible for swabbing is constructed of the same materials as equipment that allows swabbing.不能够进行擦拭的设备与能够进行擦拭的设备具有相同的材质。
- Difficult to access equipment surfaces are exposed to the same residues and conditions as equipment surfaces that allow swabbing.难以接触的设备表面暴露在与能够进行表面擦拭的设备相同的残留和条件下。
- Difficult to access equipment surfaces are cleaned with the same cleaning procedure (i.e., the samecleaning agents and the same temperature) as equipment that allows swabbing.采用与能够进行擦拭的设备相同的清洁程序对难以接触的设备表面进行清洁。 （即，同样的清洁剂和同样的温度）
- The mechanical forces during cleaning in piping systems (e.g., turbulent flow) are higher compared totank cleaning using spray balls.管道系统中清洁过程的机械力与使用喷淋球清洁的罐体相比更大。
- In contrast to tanks, the piping system is completely filled with flowing liquid during cleaning.与罐体相比，清洁

过程中管道系统完全充满了流动的液体。

• Rinse sampling appropriately addresses the issue of cross-contamination from those surfaces.冲洗取样适当的解决了表面交叉污染的问题。

5.2 Placebo Sampling 空白对照取样

In biotechnology, placebo sampling generally does not include actual product placebo; instead, it includes only WFI or the aqueous processing buffer without any product. In this sampling process, the equipment is cleaned. Following cleaning, a manufacturing process is performed (to the extent feasible) using only WFI or buffer. Following processing, the WFI or buffer is evaluated as any other cleaning validation sample, typically for TOC (or Total Protein), conductivity, bioburden and endotoxin, as measures of possible contamination of a manufactured product with those residues. Placebo runs can be done for both bulk and formulation/fill manufacturing to demonstrate actual carryover to the processed material.

在生物工程中，空白对照取样通常不包括实际产品的空白对照，相反的，只包括注射用水或者没有任何产品的水性处理缓冲液。在取样过程中，设备被清洁。随着清洁只用注射用水或者缓冲液进行生产加工过程。随着加工，注射用水或者缓冲液被认为是任何其他的清洁确认样品，尤其是对 TOC（或总蛋白），电导率，生物载荷以及内毒素，作为具有这些残留的生产产品可能存在的污染的测量。对于散装和制剂/灌装生产进行的空白对照显示了真实的到处理过材料的遗留。

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

Sampling for bioburden involves rinse water sampling, swabbing or contact plates. Rinse water sampling for bioburden must involve the use of sterile sample containers. A careful sampling technique is required for any microbial method to avoid external contamination of the sample.生物载荷的取样涉及冲洗水取样，擦拭或者接触碟。生物载荷的冲洗水取样必须包括无菌取样容器的使用。一个细致的取样技术对任何微生物方法都是被要求的，以避免取样的外部污染。

Sampling for endotoxin is almost always a rinse water sample.内毒素取样总是采用冲洗水取样。

There is nothing unique to biotechnology about the use of these sampling techniques for microbialevaluation.关于微生物评估的这些取样技术，对于生物技术不是唯一的。

5.4 Sampling Recovery Studies 取样回收研究

Sampling recovery studies are generally required to adequately demonstrate that a residue, if present on equipment surfaces, can be adequately measured or quantified by the combination of the analytical method and the sampling procedure. These studies provide a scientific basis for utilizing those sampling and analytical methods to measure residues. Three types of sampling recoveries are discussed below: swab sampling recovery, rinse sampling recovery, and “visual examination” recovery.取样回收研究一般都是要求的，充分显示如果存在在设备表面，残留能够通过分析方法的结合和取样程序进行监测和定量。这些研究为使用检测残留的取样和分析方法提供了科学依据。下面讨论了三种取样回收：擦拭取样回收，冲洗水取样回收以及“目检”回收。

For swab and rinse sampling, recovery studies may be performed as part of the analytical method validation, or they may be performed as separate studies, once it is determined that the analyticalmethod can appropriately measure residues in solutions. Sampling recovery studies are laboratory studies involving coupons of sampled equipment of different materials of construction (such as stainless steel, glass, PTFE and silicone) spiked with residues to be measured.对于擦拭和冲洗水取样，回收研究作为分析方法验证的一部分进行，或者可以作为单独的研究进行，一旦决定分析方法能够在溶液中检测出残留。取样回收研究是实验室研究，包括不同材质的被取样设备的取样片（如，不锈钢，玻璃，PTFE 和硅胶），带有残留以检测。

5.4.1 General Considerations 总则

Recovery studies may not be required for certain residues which are known to be readily water soluble and are used well below the solubility limit, such as sodium hydroxide or phosphoric acid used as cleaning agents.回收研

究对于已知是水溶的并且低于溶解限度的某些残留是不需要的，如，作为清洁剂的氢氧化钠或者磷酸。
In performing recovery studies for swabbing and rinse sampling, the amount of material spiked onto coupons should represent an amount equal to what could be present at the residue limit, as this represents a worst case.在进行擦拭和冲洗水取样回收研究中，带有材质的取样片的数量应代表等同于代表残留限度的数量，这也代表了最差条件。
The residue spiked should be the same residue present at the end of the cleaning process. For biotechnology protein actives, this is actually degraded protein fragment. However, it is common practice to spike the native protein active, as this is simpler and represents a worst case. For bulk biotechnology manufacturing, some manufacturers only perform recovery with the bulk active, whereas others will also utilize an early stage harvest product to represent early stage residues.标记的残留应是与警戒过程结束时出现的一样的残留。对于生物技术蛋白活性物，实际是降解的蛋白质碎片。但是惯例做法是标记主体蛋白活性物质，因为这样更简单并且代表了最差条件。对于大部分生物技术生产，一些生产生只对原料药进行回收，其他的将使用早期阶段的产品代表早期阶段的残留。
Recovery values should be established for all surfaces sampled. For swab and rinse sampling, this may be accomplished by performing recovery studies on all surfaces. An alternative is to perform one residue study 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 or family approach for recovery studies. Equivalence for establishing the group or family may be established based on published studies or in-house data. Another approach used by some companies is to exclude formal recovery studies for sampled surfaces constituting less than a small percentage (such as 1% or 2%) of the total equipment surface area; in such cases, the recovery value used for that excluded surface is the lowest recovery of any other surface type for which a formal sampling recovery study was performed, or the minimum acceptable recovery percentage required by the company’s procedures.对于所有取样的表面都应建立回收值。对于擦拭和冲洗水取样，在进行所有表面的回收研究时完成。可替换的选择就是在表面上进行一个残留研究，通过记录的证据，等同于（术语是回收率）其他没有进行正式回收研究的表面。对于回收研究，这是本质的分组或者家族方法。建立分组或家族等值是基于发布的研究或内部的数据。一些公司使用的另一个方法是排除整个设备表面少于小的百分比（如 1%或 2%）取样表面组成的正式回收研究，在这样的情况下，用于排除表面的回收值是任何其他表面种类的最低回收，为此进行正式的取样回收研究或者根据公司程序要求最低可接受回收百分比。
Swab recovery studies are typically performed on a nominal coupon square surface area of either 25 cm 2 or 100 cm 2 . In sampling manufacturing equipment for a protocol, it is not always possible to swab a 10 cm X 10 cm area (it might be necessary to swab a 5 cm X 20 cm area). Furthermore, it might not be practical to swab exactly 100 cm2 (an area of 60 cm2 or 128 cm2 may be required because of the specific equipment geometry). In such cases, the recovery percentage based on sampling 10 cm X 10 cm may be applied to each of those cases. If such an approach is used, a range of acceptable surface area (such as 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 nominal value, the residue limit for that sample should be adjusted based on the actual surface area swabbed.
擦拭回收研究被进行是在平方面积为 25cm 2 或者 100cm 2 。方案中取样生产设备中， 擦拭 10cm×10cm 的区域并不总是可能的 （必要时擦拭 5cm×20cm 的区域） 。此外，精确的擦拭 100cm 2 实际上是不可能的（可能要求 60cm 2 或者 128cm 2 ，由于设备特定几何结构） 。在这种情况下，针对这些情况基于取样 10cm×10cm 应用回收百分比。如果采用这种方法，可接受表面积范围（如，实际取样区域的 25%到 150%）应该建立。但是，如果方案中设备表面的取样区域与实际有区别，样品的残留限度应基于实际的擦拭面积进行调整。

5.4.2 Swab Recovery 擦拭回收

For swab recovery studies, coupons are spiked with solutions of the target residue, allowed to dry, and sampled with the swabbing procedure to be utilized in the cleaning validation protocol. The swab is desorbed in a suitable solvent, and the amount of residue is measured in that solvent sample. The amount recovered is compared to the amount spiked on the coupon, and the result is expressed as percent recovery. Because swabbing is a manual procedure, typically each person performing a recovery study performs three replicates. It is preferable to have at least two persons 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 defined as the lowest average recovery of any one analyst. An acceptable swab recovery depends on how that swab recovery is being used. If the recovery is performed to qualify the sampling method without correction of either a limit or an analytical result, a recovery of 70% or more is typically required. If the recovery percentage is used to correct a residue limit or an analytical result, a recovery of 50% or more is typically required. An upper limit for percent recovery should be established.

对于擦拭回收研究，取样片使用目标残留溶剂标记，干燥，在清洁验证方案中使用擦拭程序进行取样。在适当的溶剂中擦拭被解吸，在实际样品中测量残留的数量。回收量与取样片上标记的数量进行比较，以回收百分比的形式表示结果。因为擦拭是手工程序，每个人重复

进行三次回收研究。最好是至少两个人对每个残留结合和表面种类进行擦拭回收研究。研究所建立的回收百分比可以以不同的方式定义，但是代表性的被定义为任何一个分析者的最低平均回收率。一个可接受的擦拭回收率取决于如何使用擦拭回收率。如果进行的回收率以证明取样方法不具有限度或者分析结果的修正， 要求至少 70%的回收率。 如果回收百分比被用于修正残留限度或分析结果，要求至少 50%的回收率。应建立回收百分比的上限。

At a minimum, recovery values are generally performed at the residue limit on the surface (in µg/cm 2 , for example). While it is possible to perform recoveries at different spiked levels, in general, there is little value to such additional spiked levels because of the variability of the sampling procedure. It is preferable to 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.

最低限度，回收值通常是表面的残留限度（如，µ g/cm 2 ） 。在不同标记水平进行回收是可能的，通常，对于这种附加标记水平几乎没有值，由于取样程序的可变性。最好在一个残留限度进行附加的重复而不是在附加水平上进行重复研究。 在一个标记水平的回收结果的可接受变化是近似于 15-30%RSD。

5.4.3 Rinse Recovery 冲洗回收

Rinse recovery studies address the validity of rinse sampling for that residue. They demonstrate that if the residue were on a surface, that residue would be effectively removed and could be analyzed in the rinse solution. Rinse recovery studies address the U.S. FDA's "dirty pot" and "baby/bath water" analogies. (8) Rinse recovery studies, like swab recovery studies, are performed on coupons that have been spiked with solutions of the target residue and then allowed to dry. For swab recoveries, it is necessary to perform the exact swabbing procedure to be used in the cleaning validation protocol. For rinse sampling, in contrast, the exact rinsing procedure cannot be duplicated in the laboratory. However, it is possible to simulate the rinsing procedure in the laboratory. Where possible, the conditions of the simulated rinse should be the same as the equipment rinsing situation. This includes the selection of rinsing solvent (typically water), as well as the temperature of the rinsing solvent. In other cases, the rinsing conditions should be selected as the same or worst case as compared to the equipment rinsing situation. For example, the ratio of solvent to sampled surface area should be the same or lower in the recovery study compared to the equipment-rinsing situation。

冲洗回收研究解决了残留冲洗取样的正确性。说明了如果表面有残留，残留将被有效移除并在冲洗液中进

行分析。冲洗回收研究解决了美国“脏罐”和“婴儿/浴缸水”的类比（8） 。冲洗回收研究像擦拭回收研究一样，在标有目标残留溶液的取样片上进行并允许干燥。对于擦拭取样，在清洁验证方案中使用准确的擦拭程序是必要的。对于冲洗取样，相反的，精确地冲洗程序在实验室中是不能够被复制的。 但是， 在实验室中模拟冲洗程序是可以实现的。 如果可能，模拟冲洗的条件应该与设备冲洗的情况相同。这包括冲洗溶剂的选择（典型的是水） ，以及冲洗溶剂的温度。在其他的情况下，应选择与设备冲洗条件相同或者最差情况的冲洗条件。比如，取样表面的溶剂比在回收研究中应与设备冲洗条件相同或者低于设备冲洗条件。

One method of simulating the rinse process is to suspend a spiked coupon above a clean collection vessel and cascade the rinse solution across the surface into the collection vessel. Another method is to spike 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 of the final rinse. The rinse solution is either pipetted or decanted from the beaker and analyzed. A third option, used in cases where a beaker of suitable material of construction is not available, is to place a spiked coupon in the bottom of a beaker and perform a simulated rinse, as in the second situation.

模拟冲洗过程的一种方法是在清洁的收集容器之上悬挂标记的取样片并倾倒冲洗溶液到表面至收集容器中。另一种方法是标记适当材质的烧杯底部，允许残留干燥，加入冲洗溶液至烧杯，温和搅拌一段时间，近似于最终冲洗的时间。冲洗溶液从烧杯中由移液管吸出或者倒出并进行分析。第三种选择，这种情况下使用材质的烧杯是不合适的，在烧杯底部放入标记的取样片，模拟冲洗，后续如第二种方法。

Since rinse sampling is not significantly operator dependent, three replicates by one operator are adequate to determine percent recovery. Acceptable percent recoveries are typically established at the same levels and conditions as for swab recovery studies.因为冲洗取样不典型的依赖于操作者，一个操作人员重复三次以确定回收百分比是充足的。可接受的回收百分比建立在擦拭回收研究同样的水平和条件下。

5.4.4 “Recovery” in Visual Inspection 目检中的“回收”

This process is actually the determination of a quantitative “visual detection limit” where visual examination is the sole sampling/analytical method and “visually clean” is used as the sole acceptance criterion for the given residue in the absence of swab or rinse sampling for that residue. (12,13) If visual examination is used to supplement swab or rinse sampling, such determination of a visual detection limit is not required. A visual detection limit under specified viewing conditions can be determined by spiking coupons of the equipment surface materials with solutions of the residue at different levels (in µg/cm 2) and by having a panel of trained observers determine the lowest level at which residues are clearly visible across the spiked surface. The significance of such a visual detection limit is that if equipment surfaces are determined to be visually clean under the same (or more stringent) viewing conditions in a cleaning validation protocol, the level of the residue is below the visual detection limit. Appropriate viewing conditions include distance, lighting and angle. The visual limit depends on the nature of the residue as well as the nature of the surface (for example, stainless steel vs. PTFE) and the visual acuity of the inspector. Typical values reported in the literature for a visual detection limit are 1-4 µ g/cm 2 . (14)这个过程实际上是确定定量的“目检限度” ，在此，目检是唯一的取样/分析方法并且“目检清洁”被用作给定残留唯一可接受的标准，当对残留缺少擦拭或冲洗取样时（12,13） 。如果目检用来补充擦拭或者冲洗取样， 则不需要确定目检限度。 特定观察条件下的目检限度可通过在不同水平下 （以 µ g/cm 2 ）带有残留溶液的设备表面材质标记取样片确定并且通过受训观察人员小组确定在标记表面清楚观察到残留的最低水平。这种目检限度的意义是如果设备表面被确定目检清洁在清洁验证方案中同样（或更严格）观察条件下，擦流水平是低于目检限度的。适当的观察条件包括距离，亮度和角度。目检限度取决于残留的特性以及表面的特性（比如，不锈钢表面 vs.PTFE）以及检察人员的视觉灵敏度。文献中目检限度报告的标准值是 1-4 µ g/cm 2 .。(14)

5.4.5 Recovery for Bioburden and Endotoxin Sampling 生物载荷和内毒素取样的回收

Recovery studies to determine percentage recovery from surfaces are not appropriate and are not required for microbiological sampling or for endotoxin sampling for the following reasons

回收研究确定表面回收百分比是不恰当的并且对于微生物取样或者内毒素取样是不要求的，原因如下：

1. The question of enumeration in microbiological tests—"colony forming units" are typically counted, as opposed to individual organisms.微生物检测计算的问题——"菌落形成单位"是可计数的，而个体微生物是不能计数的。

2. Vegetative organisms will die or lose viability when dried on a coupon in a standard sampling recovery procedure.植物微生物将死亡或者失去生存能力当在标准取样回收程序中对取样片干燥时。

3. It is unclear which species should be used for a recovery study.那个菌种用于回收研究是不清晰的。

4. The limits set for bioburden typically are significantly below what could possibly cause either product quality issues or process performance (e.g., SIP) issues; therefore, even though recovery may be low (<50%), product quality and/or process performance are not impacted by excluding a recovery factor. 微生物限度的设置显著的低于能够引起产品质量问题或工艺性能（如，SIP）的可能，因此，即使回收可能是低的（＜50%），产品质量或工艺性质不能受到影响通过排除回收因子。

5.5 Training and Qualification of Samplers 取样人员的培训和资质

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 prospective sampler can appropriately sample.培训包括的步骤是帮助预期取样人员学习取样/检查的技术。这章的目的是，"取样"和"取样人"也包括目测评估的"检查"和"检查人"。资质确认包括证明的过程，预期的取样人员能够恰当的完成取样。

Training always precedes qualification. At a minimum, the trainee should read the sampling procedure, and a trained sampler should demonstrate the correct procedure. During the reading and demonstration, the trained sampler provides commentary on the rationale for certain practices or aspects of the sampling procedure.Demonstration of technique may also utilize a visual indicator on the swabbed surface, which assists the trainee in seeing consequences of poor technique. The last step in training is demonstration of the correct procedure by the prospective sampler.培训总是在确认资质确认前。至少，受训人员应了解取样程序并且经过培训的取样人员应说明正确的程序。在了解和说明的过程中，经过培训的取样人员对取样程序中的某些实践或细节给予合理解释。技术说明也可以使用目测指示剂在擦拭的表面上，以帮助受训者观察结果。培训的最后一步是由预期取样人员对正确的程序进行说明。

Qualification processes used for sampling will depend on the type of sampling performed. Qualification may involve merely demonstration of the correct technique (that is, the last step of the training process), or it may involve a "test" which challenges the trainee's ability to perform the activity correctly (e.g., perform a visual inspection using an array of coupons, including some that are soiled and others that are not, or perform a swab sampling for a known soil residue level on coupons). Either type of qualification may be repeated on a regular basis, or upon any retraining of a sampler.取样资质确认的过程将取决于取样的种类。资质确认只包括正确技术的说明（也就是培训过程的最后一步）或者，还包括一个"测试"，挑战受训者正确进行活动的能力（如，使用一些取样片进行目检，包括一些是脏污的其他的不是，或者在取样片上对已知的脏污残留进行擦拭取样）。任何一种资质确认都可以定期重复或者根据取样人员在培训情况进行重复。

5.5.1 Key Issues for Training for Swab Sampling 擦拭取样培训的关键问题

It is preferred to have a separate swab sampling SOP for training prospective samplers. This helps prevent "procedure creep" which might occur if the swabbing procedure text is just repeated in every protocol. It

also helps ensure that the same sampling procedure is used in recovery studies as in protocol execution, and thus simplifies training.对于培训预期取样人员最好有一份单独的擦拭取样 SOP。这将避免可能出现的“程序变形” ，如果擦拭程序内容在每一个方案中重复出现。这也将有助于保证在回收研究中使用同样的取样程序，如同方案中执行的并简化培训。

Four keys to consistency in swab sampling training are:

擦拭培训中一致性的 4 个关键点：

1. Consistency of wetting the swab head 湿润擦拭头的一致性
2. Consistency of the swabbing motion (including overlapping strokes)擦拭动作的一致性 （包括重叠的笔划）
3. Consistency in applying pressure 使用压力的一致性
4. Consistency in swabbing of the correct surface area 适当表面擦拭的一致性

It is assumed, of course, that the correct swab, the correct number of swabs, and the correct wetting solution (if any) for the swab are utilized. A fifth key factor for swab sampling involving TOC is emphasis on preventing external contamination of the swab due to the ubiquitous presence of organic carbon. It can be beneficial to emphasize “aseptic technique” used in microbiological sampling in training swab samplers, particularly when the sampling involves TOC analysis. In contrast to aseptic techniques used in microbiological sampling, however, the negative consequences (that is, artificially high TOC values) of using isopropanol on gloves or on adjacent surfaces prior to sampling should be emphasized.假设使用的正确的擦拭，擦拭的正确数量以及正确的润湿溶液，那么第五个擦拭取样的关键因素包括 TOC，强调避免擦拭的外部污染， 由于到处存在的有机碳。 在培训擦拭取样人员时微生物取样中强调采用 “无菌技术”是有好处的，尤其是取样涉及 TOC 分析。相对于微生物取样中使用的无菌技术，手套上或者在取样前在邻近的表面使用异丙醇的负面结果（即，人为的提高了 TOC 值）应强调。

Since swab sampling is not unlike manual cleaning processes, in that it is highly dependant on a person for consistency, consideration should be given to retraining and/or requalifying swab samplers on an established basis. Retraining may involve the same process as for initial training, or may involve only portions of that initial training. Requalification generally involves a repeat of the initial qualification process. The need for retraining and/or requalification should also be addressed as part of change control for the swabbing procedure and as remedial action when swab sampling “operator error” is suspected in the investigation of a non-conforming result.因为擦拭取样不想人工清洁过程，更高的取决于人员的一致性，应考虑在已建立的基础上对擦拭取样人员进行再培训和/或再确认。再培训可能包括与初始培训同样的过程，或者只包括原始培训的一部分。再确认通常包括对初始确认的重复。再培训和/或再确认的需求应作为擦拭程序变更控制的一部分进行处理并且作为补救措施，当调查不合格结果时，怀疑发生擦拭取样“操作失误”。

5.5.2 Key Issues for Training for Rinse Sampling 冲洗取样培训的关键问题

It is preferred to have a separate rinse sampling SOP for training prospective samplers. For CIP systems, the rinse sampling procedure may be the same procedure that is used for sampling water systems, appropriately modified to cover sampling of process equipment.对于培训预期的取样人员最好有单独的冲洗取样 SOP。对于 CIP 系统，冲洗取样程序可能与水系统取样是相同的程序，适当的修正以覆盖工艺设备的取样。

The major concern for accuracy in rinse samples is to prevent contamination of the rinse sample due to the sampling port and the environment around the sampling port. This includes adequately flushing or cleaning the port prior to taking a sample, as well as avoiding sample contamination due to the use of isopropanol on gloves or the use of isopropanol to clean the port (prior to sampling). As in swab sampling training, it can be beneficial to emphasize the “aseptic technique” used in microbiological sampling in training rinse samplers, particularly when the sampling involves TOC analysis. In training rinse samplers to

take a sample for the final rinse of a CIP cycle, timing of the sampling process is critical. Typically the very last portion of the rinse is sampled; but, it may be acceptable to sample before 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).冲洗取样中精确度的最大问题是避免对冲洗样品产生污染，由于取样口和取样口周围的环境。这包括充分的冲洗或者清洁取样点，在取样之前，以及避免由于在手套上使用异丙醇或者使用异丙醇清洁取样口（在取样之前）而对样品产生污染。正如在擦拭取样培训中，在培训冲洗取样人员过程中强调微生物取样中使用“无菌技术”是有好处的，尤其取样涉及 TOC 分析。在培训冲洗水取样人员从 CIP 循环系统的最终冲洗水取样时，取样的时间是至关重要的。一般的是冲洗水的最后一部分用来取样，但是，如果取样能够代表最差条件，在此之前进行取样也是可接受的。然而，一旦冲洗过程完成，就没有办法返回和收集冲洗水样品。 （除非进行一个单独的冲洗水取样）

Since the consistency of rinse sampling is less operator dependent, the need for retraining and requalification should also be addressed as part of change control for the rinse sampling procedure, as well as when rinse sampling “operator error” is suspected in the investigation of a non-conforming result.
由于冲洗水取样的一致性较少的依赖于操作人员，再培训和再确认的需求作为冲洗水取样程序变更控制的一部分进行处理，并在不合格结果调查中疑似取样操作失误时进行。

5.5.3 Training for Visual Inspection 目检培训

Training for visual inspection depends on whether the visual inspection is part of a protocol execution or whether the visual inspection is the laboratory “limit of detection” determination. In either case, it is preferred to have a visual inspection SOP, so that training can be for that SOP. Visual inspectors for either type of visual examination should have appropriate vision tests 目检的培训取决于目检是否作为执行程序的一部分或者目检是否是实验室“检测限度”的决定。在任何一种情况下，最好有目检的 SOP，以便根据 SOP 进行培训。任何目检的检察人员都应有适当的视力测试。

For training of visual inspectors in a protocol execution, key issues are:
执行方案中关于目检人员的培训，关键点是：

- Access to sites for viewing 进入地点查看
- Appropriate lighting 适当的光源
- Ability to discern the difference between residues on the surface and surface imperfections 识别表面残留和表面缺陷之间差异的能力

An important element of visual inspection training is knowing when to call for further analysis to determine the nature of the residue. For example, if what appears to be rouge is seen on the equipment, the presence of that residue should be noted. Determining whether that residue causes a failure in the cleaning process is a separate decision. The procedure for visual inspection for laboratory “limit of detection” determination is generally different from that of visual inspection during protocol execution, because the objective is different. The objective is to determine at what level a certain residue can be consistently seen across a spiked surface in order to correlate a visual detectability limit with a level of known residue(s) below that spiked level. This procedure may be in a separate SOP, or may be incorporated in an overall SOP for visual inspection. In addition to the same elements that are included in training for protocol execution, a key for training in this procedure, which involves viewing spiked coupons, is a careful distinction between a visually clean surface, a partially soiled surface (in which residue is apparent only over a portion of the spiked area), and a “fully” soiled surface.目检培训的一个重要元素是知道什么时候要求进一步的分析以确定残留的性质。比如，如果设备上发现变红，应注意残留的存在。确定是否是残留导致清洁过程失败是一个单独的决定。实验室“检测限度”确定的目检程序通常与执行方案中的目检不同，因为目的是不同的。目的决定了在什么水平上某一种残留能够始终被观察到跨过标记的表面以关联已知残留水平的目检检测限度低于标记水平。这个程序可以在单独的 SOP 中，或者整合到目检的 SOP

中。除了包括在执行方案培训中的相同元素外，这个程序中培训的关键，涉及观察标记的取样片，是仔细区别目测清洁的表面，部分脏污的表面（标记区域的一部分有明显的残留）以及完全脏污的表面。

6.0 Analytical Methods

分析方法

It is essential to a cleaning validation program that the appropriate analytical methods are utilized.

一个清洁验证程序使用适当的分析方法是非常必要的。

Analytical methods must be appropriate in that they can adequately detect the residue(s) of concern.

分析方法必须适当，能充分检测到相关残留物。

It is also important to understand what can be concluded from the analytical result (e.g., was the product not removed or was the cleaning agent not removed?).

对能从分析结果中推断出什么的理解也是非常重要的（比如：产品没有被去除或清洗剂没有被去除？） 。

The results of testing will determine if the cleaning validation cycle is acceptable or if it needs to be redeveloped.

检测结果将决定清洁验证周期是否接受或者是否需要重新开发。

Thus, it is important to have confidence in the results.

因此，对结果的信任是非常重要的。

This section discusses how to select the appropriate assay methods, detailed information on the applicability and use of nonspecific assays and microbial test methods,and assay method validation.

本部分讨论怎样选择合适的分析方法及其适用性的详细信息，非特定分析和微生物测试方法的使用，和分析方法验证。本部分套乱怎样选择合适的含量分析方法，实用性的详细信息，非特定含量方法和微生物测试方法以及含量方法验证。

6.1 Specific Analytical Methods

6.1 特定分析方法

Specific analytical methods are those which measure a certain residue in the presence of expected interferences.

特定分析方法是指用于测量存在预期干扰时某个残留的方法。

In a cleaning process for biotechnology products where the specific analyte is the active protein, such interferences may include degradation products and related substances, excipients, cleaning agents and cleaning agent by-products.

在生物技术产品的清洗过程中，特定分析物是活性蛋白，这样干扰可能包括降解产品和相关物质，辅料，清洗剂和产品清洗剂。

Examples of specific methods include HPLC, ELISA,SDS PAGE, and PCR.

特定方法的例子包括 HPLC,ELISA,SDSPAGE,和 PCR

Each of these methods requires the use of an appropriate reference standard.

这些方法每个都需要使用一个适当参考标准。

In contrast, nonspecific analytical methods measure a general property, such as conductivity or TOC,which could be due to a variety of analytes or sources.

相对而言， 非特定分析方法测量通用属性， 比如： 电导率或者 TOC， 因为分析物或者来源的多样性。

Selection of an analytical method will depend on the nature of the residue as it exists after the cleaning process.

一个分析方法的选择将取决于清洁过后残留物的性质。

Only if a protein (or other organic active) is not degraded during the cleaning process (surviving high temperatures and pH extremes in an aqueous environment, for example) does it make sense to use a specific analytical method for that active.

只有当一种蛋白质（或者其他有机活性物质）在清洁过程中不能被降解（例如：在高温和极端 PH 的水环境下残存），使用那种物质的特定分析方法才有意义。

The advantage of using a specific analytical method in this situation is that it gives a precise measure of the major residue of concern – the active itself.

在这种情况下使用特定分析方法的优势是它可以给出主要相关残留--活性物本身的精确测量。

If a specific analytical method for an active protein were utilized following a cleaning process which has been demonstrated to denature (degrade) that active protein, it is likely that residues of the active protein would be non-detectable (i.e., not measurable) by that specific analytical method.

如果一个活性蛋白质的特定分析方法在紧接着的清洁过程中被使用，这个清洁过程用来证明降解（变性）这个活性蛋白质。这个活性蛋白残留通过这个特定分析方法将很可能检测不到（不能被检测）。

Residues of that protein would be various degraded fragments.

那个蛋白质的残留可能讲解成多种片段。

If the native protein were actually detected using a specific method for that protein, it is likely that there had been a serious problem with the cleaning process, such as a clogged spray device causing a lack of coverage of that portion of the equipment surface.

如果天然的蛋白质真的用特定方法被检测到，那么清洁过程很有可能有一系列的问题，比如堵塞喷淋设备引起的设备表面喷淋覆盖不全面。

In such a case, failure would also most likely be detected by a nonspecific method and/or by visual examination.

在这种情况下，失败也可以通过非特定方法或目视检察被检测到。

Consequently, if a specific assay method is used, a nonspecific assay method is also required, unless studies prove that the product is not degraded by the cleaning process.

因此，如果一个特定的含量分析方法被使用，一个非特定的分析方法也是需要的，除非研究证明清洗过程中产品没有被分解。

In biotechnology cleaning validation, specific analytical techniques such as HPLC are more likely to be used for detergents, because the surfactants or other functional materials in the detergents are not likely to degrade in the cleaning process.

在生物技术清洁验证中，特定分析技术比如 HPLC 更倾向用于清洗剂的检测，因为表面活性剂或者清洁剂中的功能材料在清洁过程中不可能分解。

However, it should be noted that nonspecific methods can also be used for detergents and other cleaning agents.

无论怎样，必须注意非特定方法也可以用于洗涤剂或者其他清洁剂

6.2 Impact of Inactivation/Degradation of the Active

6.2 活性物质的降解/ 灭活的影响

Product inactivation means that the active protein is modified in some way such that it is no longer active and may no longer be measurable by specific analytical methods for that native protein.

产品灭活意味着活性蛋白被某些方式改变，这样这些蛋白不再有活性和不再被这种天然蛋白质的特定分析方法测量到。

This modification usually involves degradation of the active protein into smaller fragments, but may also involve a process in which larger molecules are formed.

这个改变通常包括活性蛋白降解成小片段，但也可以包括蛋白大分子的形成过程。

A key issue for process equipment cleaning in biotechnology manufacturing is the degradation or deactivation of the active protein during the cleaning process.

在生物技术产品生产中，工艺设备清洁的一个关键问题是活性蛋白在清洁过程中的降解或者钝化。

This is a result of cleaning processes in biotechnology utilizing hot, aqueous,alkaline and acidic cleaning solutions.
这是生物技术产品的清洗过程使用热，水，碱和酸的清洗溶剂的结果。
Under such conditions, it is well recognized that protein actives will degrade.
在这种条件下，将要降解的蛋白质活性物是容易被识别的。
This degradation affects several issues in the cleaning and cleaning validation process.
这个降解物在清洁和清洁验证过程中的影响是多方面的。
Because of the degradation, the residues of the active protein (which are actually now residues of the degraded active protein) are more readily rinsed away during the rinsing step of the cleaning process.
因为降解，活性蛋白的残留（实际上是活性蛋白降解物的残留）很容易在清洁过程中的淋洗这步时被淋洗掉。
This is because the degraded fragments typically have a lower molecular weight and are potentially more polar, both conditions leading to greater water solubility.
这是因为降解的片段通常分子量小和极性更大，两种条件都导致更好的水溶解性。
A second consequence of the degradation is that it no longer is scientifically justified to have an analytical method which is specific for the native protein.
降解的第二个结果是使用一个特定的天然蛋白质分析方法不再是科学合理的。
For this reason, a nonspecific method such as TOC or Total Protein is typically used to measure residues of the degraded active (as well as other organic molecules) in a
cleaning validation protocol.
基于这个原因，在清洁验证方案中，一个非特定方法（如：TOC 和总蛋白）通常被用于测量降解活性物质（其他有机分子也一样）的残留。
A third consequence is that limits in bulk biotechnology manufacturing are typically not appropriately established based on a “fraction of a dose” calculation of the native protein, since the residues are degraded fragments.
还有一个结果是生物原料生产中的限度通常不能基于天然蛋白“剂量分数”的计算建立，因为残留是降解片段。
Since residues being sampled are residues of the degraded protein, it may also make more scientific sense to perform sampling recovery studies based on recovery of the degraded fragments.
因为残留取样是降解蛋白的残留，所以执行基于降解片段回收率的取样回收研究是更加科学有意义的。
However, assuming an increase in solubility for degraded proteins, sampling recovery studies on the native protein will typically be a worst case as compared to recovery of degraded fragments.
假如降解蛋白的溶解性增加，天然蛋白的取样回收研究与降解片段的回收相比，其通常作为最差情况。
While it is assumed in almost all cases that the active proteins or other large organic molecules produced in biotechnology manufacturing are readily degraded in hot, aqueous alkaline conditions, it is desirable to demonstrate this with a laboratory study.
几乎所有情况下，活性蛋白或者大型有机分子在生物生产中，在热，水，碱条件下非常容易降解，这只是个假设，因此需要在实验室中证明。
In such a simple “beaker” study, the bulk active protein is exposed to the conditions of the cleaning process, including cleaning agent concentration,temperature and time.
在这样一个简单的“烧杯”研究，活性蛋白原料暴露在清洗过程的条件下，包括清洗剂浓度，温度和时间。
At the end of that exposure time, the pH is neutralized, and the temperature is reduced.
在暴露时间的最后，PH 是中性的，温度是降低的。
The resultant solution is then analyzed for the active protein by the specific analytical

procedure (such as ELISA, HPLC or a bioactivity assay).
最终溶液被特定分析程序分析其活性蛋白质（例如：ELISA,HPLC 或者生物活性含量）
In such a procedure, the ratio of protein to cleaning solution should represent the same ratio present during cleaning, or a worst-case ratio (a worst-case is a higher ratio of protein to cleaning solution).
在这个过程中，清洁溶液的蛋白质比例应等于清洁过程中蛋白质的比例，或者最差情况蛋白质的比例（最差情况是一个更高蛋白比例的清洁溶液） 。
The assay methodology for such studies must be appropriate and valid.
这个研究的含量方法学必须是合适的和经验证的。
Care needs to be exercised in performing such a study to ensure that the chemicals in the cleaning solution do not interfere with the analytical procedure.
为了确保清洁溶液中化学成分不被分析程序干扰，在进行这个研究过程中应特别注意。
This can be addressed by having adequate controls, such as adding the active to a solution of the neutralized cleaning solution at ambient temperature.
这可以用充分控制来解决，如：向日常温度的中性清洗溶液加入活性物质。
If chemicals in the cleaning solution interfere with the specific analytical procedure, another option is to remove them by diafiltration.
如果清洗溶液的化学成分被干扰特定分析程序，另一个选择是通过透析过滤去除它们。
If it is just the surfactants in the cleaning agent that interfere, another option is to perform the degradation study with just the equivalent amount of alkali present in the cleaning solution.
如果它只是清洗剂中的表面活性剂的干扰，另一个选择是用与清洗溶液中等量的碱进行降解研究。
Note that in many cases, cleaning in a biotechnology facility utilizes alkaline cleaning agents followed by an acidic cleaning solution.
注意在许多情况下，生物技术设施的清洁碱清洁剂在使用酸清洁溶液之后使用。
Current evidence suggests that it is the alkaline portion that is most effective in degrading active proteins.
现有的证据证明含碱的部分对降解活性蛋白非常有效。
Companies may choose to perform a degradation study only with the alkaline agent and not pursue degradation studies with the acidic solution unless the alkaline cleaning agent alone is inadequate for degradation.
公司可以选择只使用含碱试剂进行降解研究，不追求使用酸溶液进行降解研究除非单独使用含碱清洁剂对降解不充分。
6.3 Nonspecific Analytical Methods
6.3 非特定分析方法
6.3.1 Total Organic Carbon (TOC)
6.3.1 总有机碳
Most of the compounds used in biotechnology processes are of organic nature.
在生物技术过程中使用的大部分成分是有机物。
TOC can detect organic carbon with a good sensitivity in the sub-ppm range;
TOC 在亚于 PPM 范围内可以非常灵敏的检测有机碳。
however this sensitivity may still not be adequate for highly active substances.
尽管这样的灵敏性可能对于高活性物质来说仍然是不足够的。
The method can be semi-automated with an autosampler and has a short analyzing time.
这种方法可以是半自动的，用一个自动采样器和用很短的分析时间。
In contrast to specific analytical methods, TOC analyzers can detect all organic residues, including complex mixtures of compounds like cell culture media or product degraded by the cleaning process.
相对于特定分析方法而言，TOC 分析仪可以检测所有有机残留，包括复杂的混合成分像细胞培养基或者清

洗过程中产品讲解物。

With TOC, it is not possible to distinguish between a biotechnology product and other organic compounds present in the same sample.

使用 TOC，在相同的样品中是无法区别生物制品和其他有机物成分的。

As a consequence, all organic carbon is assumed to be product, representing a worst-case approach.

因此，所有有机碳被当成产物，这是最差情况的方法

Another aspect is the potential for sample contamination with organic substances during sampling and testing, requiring well- trained personnel and clear sampling instructions.

另一方面，在取样和测试过程中存在有机物取样污染的可能性，需要经过充分培训的人员和明确的取样说明。

Special care should be taken to ensure that the sampling container does not introduce unacceptably high amounts of carbon to the sample.

必须有特别措施确保取样容器不能给样品引入不可接受数量的碳

Different TOC analyzers are commercially available. All instruments oxidize organic carbon and measure the resulting carbon dioxide.

不同的 TOC 分析仪是商业上可行的。所有仪器氧化有机碳和测量产生的二氧化碳。

When selecting a TOC instrument, care should be taken to select an instrument and instrument parameters that are able to completely oxidize the organic carbon present.

当选择一个 TOC 仪器时，必须注意：选择一个仪器和仪器参数，其必须能够完全氧化有机碳。

The TOC method can be used for rinse and swab measurements. If used for final rinse water testing, samples can be analyzed directly.

TOC 方法可以被用于淋洗和擦拭测量。如果被用于最终淋洗水检测，样品必须能够直接被分析。

If used for swab testing, the organic carbon has to be extracted from the swab after sampling.

如果被用于擦拭测试，取样后有机碳必须能够从擦拭棒上被萃取出

It is important to consider some additional topics during TOC swab method development, such as swab material and technique.

在擦拭方法开发过程中考虑一些额外的问题是非常重要的，比如:擦拭材料和技术

Swabs should not significantly contribute carbon to the sample and should not adsorb significant amounts of the residue such that it is not released for analysis.

擦拭对于样品不是重要的碳来源， 不能吸附大量的残留成分， 分析过程中残留成分也不能释放出来。

The sampling technique (e.g., swab size and shape, swabbing pattern, swab container and extraction method) is much more complex in comparison to rinse water testing.

取样技术（如：擦拭面积和形状，擦拭方式，擦拭容器，提取方法）相对于淋洗水测试来说是及其复杂的。

The swabbing technique can have a high influence on residue recovery.

擦拭技术能对残留回收率产生极大的影响

6.3.2 Total Protein

6.3.2 总蛋白质

Several total protein assays of different sensitivity are commercially available. Assays often used are Bradford, Lowry or BCA.

一些不同灵敏度的总蛋白质含量测试方法在商业上是可行的。含量测量方法通常使用 bradford 法,lowry 法或者 BCA 法。

Total protein assays are not product specific, but specific towards a class of molecules.

总蛋白质含量不是产品特定，但是对于分子类型来说是特定的。

Total protein assays can be used if the majority of the residues are proteins.

总蛋白质含量可以被用于检测主要残留是否是蛋白质。
If proteins are just one of many residues present (e.g., cell culture fermentation), the use of an assay with a broader spectrum (e.g., TOC) should be considered.
如果蛋白质不只是许多残留（细胞培养发酵）中的一种，使用宽谱（如 TOC）测量含量可以被考虑。
One advantage of total protein assays is potential commercial availability.
测量总蛋白质含量的一个优势是具有商业上的可行性。
Different companies offer test kits and support during test implementation.
不同的公司提供测试工具和测试应用支持。
Lead times for implementing commercial test kits are typically shorter compared to in-house developed methods.
与内部开发方法相比，使用商业测试工具通常测试时间更短。
In-house methods may be developed to provide enhanced sensitivity.
内部方法可以被开发用来加强灵敏性。
Proteins often degrade (e.g., by hydrolysis during a cleaning cycle if high pH and temperatures are used).
蛋白质经常降解（比如，如果用高 PH 和温度进行清洁，清洁过程中会水解）
During assay implementation, it should be investigated if the assay still can detect protein after exposure to cleaning agents.
在含量测定方法应用过程中，暴露在清洁剂过后如果蛋白质含量仍然能被检测到，必须进行调查。
6.3.3 Conductivity
6.3.3 电导率
Conductivity measurement is a very sensitive method to detect dissociated ionic substances in water samples.
电导率测量是一种检测水样中游离离子物质非常灵敏的方法。
WFI has a conductivity of ≤ 2.4 μ S/cm at 65° C. For cleaning validation purposes,
conductivity readings are expressed in milli-Siemens/cm (mS/cm) for higher concentrations (such as cleaning solutions) and micro-Siemens/cm (μS/cm) for lower concentrations (such as final rinse waters).
注射用水在 65° C 时电导率≤ 2.4 μ S/cm。清洁验证的目标，电导率的读数单位浓度高时（清洁溶液）用 mS/cm 浓度低时（如：最终淋洗水）用(μ S/cm)。
It is often used to measure cleaning agent residues (e.g., caustic agents) and to control automated cleaning processes (e.g., CIP).
电导率经常被用来测量清洁剂残留（如：腐蚀剂）和控制自动清洗程序（如：CIP）
Conductivity instruments can be used for a wide range of concentrations by exchange of conductivity probes.
电导率仪器通过更换电导率探头，可以被用来测量很宽范围的浓度。
Conductivity readings are highly influenced by the sample temperature.
样品温度对电导率的读数有很大影响。
Either temperature adjustment of the sample or automated temperature compensation can be used to standardize the measurements.
调整样品温度或者自动温度补偿可以被用来标准化测量。
Conductivity is a nonspecific method that correlates linearly (within a defined range) to the ion concentration in an aqueous sample.
电导率是一个相关于水样离子浓度的线性非特定方法。
Analytical instruments are robust and can be used on the manufacturing floor by trained personnel.
分析仪器非常耐用，可以在生产现场被经过培训的人员使用。
The high influence of the sample temperature on the instrument reading should be considered to avoid incorrect results.
样品温度对仪器读数的重大影响必须被考虑，避免错误结果。

The method cannot differentiate between different ions.
这个方法不能因为是不同离子而不同。
Therefore, as for TOC, all conductivity results above the water baseline should be attributed to the contaminant in question (e.g., the cleaning agent).
因此，和 TOC 一样，所有电导率在水基准线上的结果应归因于污染（如：清洗剂）所致。
For biotechnology cleaning validation applications, conductivity is normally not used to detect product residues.
由于生物制品清洗验证的应用，电导率是通常不用于检测产品残留。
To allow correlation of conductivity readings with concentrations of cleaning agents, a dilution curve(conductivity vs. concentration) should be established (at a relevant temperature) by conductivity measurements of different dilutions in the relevant range near the acceptance value.
为允许电导率读数与清洗剂浓度的相关性，应该通过在接近可接受值的相关范围，测量不同稀释液的电导率，建立（在相关温度）稀释曲线（电导率 VS 浓度） 。
6.3.4 Visual Inspection
6.3.4 目视检查
Visual inspection is a qualitative method to determine cleanliness on specific equipment surfaces.
目视检查是一种检查设备表面是否清洁的等同方法
Visual inspection has been demonstrated to be a simple and effective direct sampling method in the evaluation of equipment cleanliness.
目视检查已被证实是衡量设备清洁的一种简单有效直接取样方法。
Visual inspection does have multiple weaknesses that are inherent.
目视检查也确实有很多内在的不足。
Extensive training and a detailed documented procedure are required to ensure that “visually clean” from one operator to the next is consistent.
为确保能从一个操作者到下一个操作者都持续的“目视清洁” ，大量的培训和一个详细的有记录的程序在是非常必要的。
What one can visually see will vary with distance, angle, lighting, the nature of the surface and inspector’s visual acuity.
目视结果会随着距离，角度，光线，表面本质和检查者的视觉敏锐度的变化而变化。
Some equipment surfaces (e.g., piping) are usually not accessible for visual inspection.
一些设备表面（如管道）通常不接受目视检查。
The use of optical equipment (e.g., mirrors, remote visual cameras or endoscopes) can help to facilitate visual inspection.
一些光学设备（如：镜子，远程可见摄像，内窥镜）的使用能帮助目视检查
In order to view some equipment areas, wear and tear on the equipment may occur (e.g., the disk stacks in a centrifuge are not designed to be removed and inspected for visual cleanliness after cleaning).
为了能看到某些设备的取样，可能损耗设备（如离心机里的圆盘不能被设计成是可移除的和请接收被目视检查）
In other cases, an operator may be required to enter a confined space for viewing equipment surfaces.
另一种情况，操作者可能需要进入一个限制的空间观察设备表面。
The visual inspection procedure should specify how operators are to deal with visual observations.
目视检查程序应详细记录操作者如何处理目视结果的。
Visual inspection could find four different types of visual observations: residue, surface anomalies, foreign object and water pooling.
目视检查可以找到中不同类的目视结果：残留，表面异常，异物，积水。

Residue is the main concern, which would constitute a visual failure when one is looking at the acceptability of a cleaning cycle.
残留是主要关注的，它可能导致目视失败，当评审清洁周期的可接受性的时候。
A sample of the residue should be collected for further testing, if possible, to assist in the investigation of the cause.
如果有必要，残留的样品应收集起来进行深入测试，有助于原因调查
Typically, surface anomalies and foreign objects are not considered visual inspection failures for cleaning validation purposes, but must be further investigated and corrected, as applicable.
典型的，表面异常和异物不认为以清洁验证为目的的目视检查失败是适当的，但必须进行深入调查和纠正，
Surface anomalies should be noted and a “suitability for use” assessment should be performed to remediate any issue(s) found.
表面异常应记录和应进行一个“适用性”评估去补救任何发现的问题。
Rouge is the most common type of surface anomaly discovered during visual inspection; rouge is generally considered a preventive maintenance problem, not a cleaning process problem.
Rouge 是目视检查中发现的非常普通的表面异物种类；rouge 通常被认为是一个预防性维护问题，不是清洗程序的问题。
Foreign objects and their removal should be noted. How the foreign object came to be in the equipment should also be investigated.
外来异物和其去除应注释。外来异物如何进入设备也应进行调查。
Water pooling should be documented, and the cause should be investigated.
积水应进行记录，其原因应进行调查。
All equipment surfaces that can be readily inspected visually should be visually inspected.
所有设备表面能容易被进行目视检查的应进行目视检查。
Visual inspection may not be performed on the interior of lines and tubing (although outlets may be inspected)on equipment where disassembly of the equipment is not practical or possible, or where inspection of the equipment could potentially be dangerous to the inspector (e.g., entry into a confined space).
目视检查不应用于设备管线和管道内部（虽然出口处可以被检查），拆解设备是不可行或者是不可能的，或者设备检查的地方可能对检查者有潜在的危险。
A visual inspection training program should be developed for visual inspection.
目视检查的目视检查培训程序应开发。
Inspectors typically should be trained and/or requalified on an established basis.
检查者应进行培训或者在建立已培训的基础上再确认
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 detect potential residues of concern.
如果目视检查在相关的区域是不可能进行的，确保其他取样方法（如淋洗取样）能足以检测到潜在的相关残留是非常必要的。
The use of “visually clean” alone (in the absence of other analytical methods such as TOC or conductivity) is not generally used in the biotechnology industry, because all critical surfaces are not readily available for visual examination.
单独使用目视清洁（不使用其他分析方法如 TOC 或者电导率）在生物制药领域是不常用的。因为所有关键表面不溶液被目视检查。
6.4 Microbial Test Methods
The U.S. FDA’s cleaning validation guidance states that “Control of the bioburden through adequate cleaning and storage of equipment is important to ensure that subsequent sterilization or sanitization procedures achieve the

necessary assurance of sterility."
FDA 的清洁验证指南指出"通过对设备的充分清洁和存储来控制生物负载，对保证后续的灭菌或者消毒程序达到必要的无菌保证是非常重要的"
Endotoxin is a concern in that steam sterilization does not destroy or remove endotoxin.
内毒素是重要的，因为蒸汽灭菌不能消灭或者去除内毒素。
Thus, both bioburden and endotoxin are typically monitored and controlled during the manufacturing and cleaning processes.
因此，生物负载和内毒素在生产和清洁过程中，都被代表性的监测和控制。
Typically microbiology sampling is performed during all cleaning validation studies throughout the manufacturing process.
生产过程中的所有清洁验证研究必须进行代表性的生物学取样
6.4.1 Endotoxin
Typically, endotoxin testing is performed for cleaning validation runs.
典型地，清洁验证需进行内毒素测试
Endotoxin testing may not need to be tested in upstream cell culture and initial purification processes where it is proven during process validation that one or more purification steps is able to effectively remove endotoxin that is present.
内毒素测试可不需要在上游细胞培养和初始纯化程序进行测试，上述程序被证明在工艺验证中一个或者更多纯化步骤可以影响内毒素去除效果。
Typically, a three logs or greater reduction of endotoxin in endotoxin removal steps is required to justify decisions not to test for endotoxin upstream.
在内毒素去除步骤，3 个对数单位或者更多内毒素的减少是必须的，这将是不测试上游内毒素决定因素。
Endotoxin methods are typically compendia methods.
内毒素方法是典型的药典方法
6.4.2 Bioburden
Testing of bioburden is typically done through rinse water sampling, although other methods may be used.
淋洗水取样过程应完成生物负载测试，尽管其他方法可能被使用。
The benefit of rinse water sampling for bioburden is that it is convenient.
生物负载的淋洗水取样的优势是它非常方便。
Typically, rinse water sampling is being performed to verify removal of protein and cleaning agent(s), so one additional rinse water sample does not require significantly more work.
淋洗水取样被用来确认蛋白质和清洁剂的去除，所以一个额外的淋洗水样品不需要更多的工作。
Also, bioburden testing of rinse water is typically already a qualified method for testing water systems for bioburden.
淋洗水的生物负载测试是一个典型的，已经确的，测试水系统生物负载的方法。
The biggest weakness of rinse water sampling is that the full range of the acceptance criteria is not able to be utilized, for example,if 100 ml of rinse water is used for testing with an acceptance criterion of 10 CFU/mL.
淋洗水取样最大的缺点是： 大范围的可接受标准不能被应用。 比如： 如果 100ml 淋洗水被用来测试，可接受标准是 10CFU/ml
The typical number of colonies that can be counted is 300 before TNTC (Too Numerous To Count) is achieved;
在获得 TNTC（太多数而不能数）之前，菌群的典型可数数目是 300。
this only allows an acceptance criterion of 3 CFU/mL before failing to meet the acceptance criteria.
在满足可接受标准之前，只能允许 3CFU/ml 的可接受标准。
In most situations this is not an issue; it may result in the need to test smaller sample volumes.

在很多情况下这不是一个问题；这可能导致需要去检测更小容量的样品。
If this situation occurs, it is important to test an adequate amount of rinse to ensure that bioburden is detected.
如果这种情况发生，为保证生物负载被检测，足够数量的淋洗测试是非常重要的
Two methods for measuring directly on surfaces are swab and contact plate method.
测量直接表面的两种方法是擦拭法和接触碟法。
For swab samples, the swab can be desorbed, and a count can be made by a pour plate method.
擦拭样品，擦拭可以被吸附，可以被冲洗碟方法计数。
Contact plates are directly incubated and enumerated.
接触碟是直接培养和计数。
The biggest concern with contact plates and swab procedures is potentially exposing product contact surfaces to an unknown media or buffer solution from swabs;
接触碟和擦拭程序最大相关的是潜在暴露产品与未知培养基或者擦拭的缓冲溶液接触表面。
Thus, acceptable removal of this media or buffer solution should be demonstrated before manufacturing can occur.
因此，这些培养基或者缓冲溶液的可接受移除应该在生产之前证明。
Another concern is that contact plates require flat surfaces.
另一个关注点是接触碟需要平整的表面。
6.5 Analytical Method Validation
6.5 分析方法验证
This section focuses on analytical method validation for “chemical” residues.
这部分关注化学残留的分析方法验证
Typically, endotoxin methods are compendia methods and do not require formal validation but require a confirmation for their application of use or suitability.
内毒素方法是药典方法，不需要正式的验证，但需要使用或者适用性确认。
Microbiological methods that are approved microbiology laboratory methods do not require additional method validation.
被微生物学实验室方法批准的微生物方法不需要额外的方法验证。
6.5.1 General Principles
6.5.1 基本原则
Since one key part of cleaning validation is setting residue limits and then measuring (using an analytical method) the actual residues left on surfaces after cleaning, it is critical that the analytical method be appropriately validated.
因为清洁验证主要的一部分是设定残留限度，然后测量(使用分析方法)清洁后表面的实际残留。分析方法被适当的验证是非常关键的。
Method validation is typically accomplished using the criteria in ICH Q2(R1),
Validation of Analytical Procedures: Text and Methodology. (16)
方法验证是典型地完成，使用 ICHQ2(R1)分析方法验证程序：内容和方法学的标准。
However, the types of assays listed in ICH Q2 do not explicitly cover cleaning validation methods.
不管怎样，ICH Q2 上所列的内容类型，没有明确涵盖清洁验证方法。
Some companies will essentially validate analytical methods much like an “assay” in ICH Q2, establishing accuracy, precision specificity, linearity and range, with the added determination of LOD/LOQ.
一些公司将验证分析方法，如同 ICH Q2 的内容一样，建立精确度，精密度，专属性，线性和范围，另外还有 LOD/LOQ 的测定。
LOD/LOQ must be below the acceptance limit for the sample and ideally is significantly below the

acceptance limit so that the robustness of the cleaning process can be established.
LOD/LOQ 必须低于样品接受标准限度，完美低于可接受标准限度以至于清洁程序的耐用性被建立。
In addition to the ICH Q2 parameters, sample stability as a function of storage conditions (time, temperature, vial, etc.) may be evaluated if there is a significant interval between sampling and analysis.
除 ICH Q2 的参数之外， 样品稳定性作为存储条件 （时间， 温度， 瓶子等） 的一个功能因素要被评估，如果取样和分析之间有一个重要间隔。
In cases where a nonspecific method (such as TOC) is utilized, it is not necessary to compensate for the lack of specificity by “other supporting analytical procedures” (as suggested in ICH Q2).
为防止一个非特定方法（如 TOC）被应用，补偿缺少专属性的“其他支持分析程序”是非常有必要的。
The reason for this is that for cleaning validation purposes, the limit value is not a target (as it is for a potency assay); rather the limit is a value not to be exceeded.
这样做的原因是满足清洁验证的目的，限度值不是一个对象或者说限度是一个不被超越的值。
As long as other organic substances contribute positively to the TOC value, and as long as all measured carbon is attributed to the target residue, such complementary methods suggested by ICH Q2 are not required.
由于其他有机物对 TOC 值影响很大， 和所有被测量的碳影响目标残留， 这个 ICH Q2 推荐的互补的方法是不需要的。
Furthermore, it is not required to correlate TOC results with a specific analytical method, except to the extent that accuracy in method validation is established using a known standard that establishes the concentration or activity by a specific analytical method.
此外， 不需要关联 TOC 结果和特定分析方法， 除非在分析方法验证中使用一个已知标准扩展精确度，这个标准通过特定分析方法建立了浓度或者活力。
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 preestablished limit for the residue (otherwise itwould not be possible to claim that residues were below the predetermined limit values).
检测限和定量限不是 ICH Q2 中含量测定部分的要求， 这些值等于或者低于残留的预设限度是非常关键的（否则将不能说残留低于预定检测限度值。 ）
However, it is not necessary to drive detection or quantitation limits as low as possible; having detection or quantitation limits around 10% of the residue limit in the analytical sample is ideal (but not always possible) to establish the robustness of the cleaning process.
不管怎样，使检测和定量限尽量低是非常必要的；为建立清洁程序的耐用性，使检测和定量限在分析样品中残留限度 10%的范围内是理想的（不是永远可行） 。
Assay capability should take into account both the target/limit and the process capability and provide relevant measurements for both.
含量能力需同时考虑目标/限度和工艺能力，并提供这两个方面的相关测量
When performing carryover calculations (as is typically done for the formulation/fill side of biotechnology manufacturing) it should be ensured that the analytical methods that will be used for cleaning validationare sensitive enough to meet the acceptance criteria.
当执行残留计算（通常作为处方/生物制品生产灌装面）时，应该保证被用于清洁验证的分析方法足够灵敏以至于满足可接受标准。
To provide reliable results for carryover calculations, the results should be equal to or above the LOQ.
为残留计算提供可信任的结果，这个结果应等于或高于 LOQ
Results between the LOQ and the LOD typically show a higher-than-acceptable variation of the resultsobtained and are typically reported as less than LOQ.
在 LOD 和 LOD 之间的结果通常认为高于可接受获得结果的变化，并被报告为低于 LOQ

For companies that use a pass/fail analytical method for meeting cleaning validation limits, analyticalmethod validation is less extensive.
由于公司使用一个通过/失败的分析方法来满足清洁验证限度，分析方法验证缺少广泛性。
In such a procedure, the only conclusion of the analytical procedure is whether the experimental sampleis less than or equal to the pass/fail value, or above that pass/fail value.
在这样一个程序，分析过程的唯一一个结论是：实验样品是否小于衡量通过/失败值，或者高于通过/失败值。
Accuracy and precision are typically performed only at the residue limit, but linearity and range are notperformed.
精确度和精密度通常只在残留限中执行，但是线性和范围不执行。
Note that in this case, the pass/fail value selected should take into consideration any applicable correctionfactor due to the sampling method, recovering less than 100% from the surface.
Note that in this case，通过/失败值的选择，由于取样方法应该考虑任何应用纠正因素，表面回收率应少于100%
Pass/fail analytical procedures are more likely to be part of a cleaning verification mode, used in the manufacture of early clinical trial materials.
通过/失败分析程序更多像是清洁确认模式的一部分，被用在早期临床试验物料的生产中。
Analytical method validation protocols may only include validation of the residue in solutions.
分析方法验证方案可以仅包括溶液中的残留验证。
They may also include sampling recovery studies, although those sampling recovery studies may be performed as separate studies apart from the analytical method validation.
也可以包含取样回收率研究， 虽然这些取样回收率研究可以当做独立研究， 从分析方法验证中分开。
Acceptability of the variability of results for parameters such as accuracy and precision for methods at typical residue levels are generally much broader than in a typical potency assay.
参数结果可变性的可接受性，如在通常残留水平上，方法的精确度和精密度在通常宽于通常含量限度。
RSD requirements of 15-20% are typical.
RSD 在 15-20%之间是有代表性的
6.5.2 Compendia Methods
6.5.2 药典方法
Compendia methods do not require separate analytical method validation, provided those methods are used within the parameters in the compendia.
药典方法不需要单独的分析方法验证，提供的这些方法被用在药典里面。
For example, a compendia method for endotoxin is generally appropriate for measuring endotoxin in final rinse water samples.
比如，一个内毒素的药典方法是通常适用测量最终淋洗水样的内毒素
When using TOC in rinse water samples (a compendia method), additional work should be done to support the applicability of that method to test samples that could have TOC values above 500 ppb, or where a linear range is to be established.
当在淋洗水样使用 TOC （一个药典方法） 时， 需要做额外的工作去支持该测试样品方法的可应用性，方法可以使 TOC 值大于 500ppb，或者可以建立线性范围。
Just performing system suitability as specified in the various pharmacopeias may not be adequate todemonstrate that the analytical procedure could accurately analyze samples at 1 ppm or 5 ppm.
仅进行系统实用性试验，在许多药典中可能不足够证明分析程序可以精确分析在 1ppm 或者 5ppm 水平的样品.
For that reason, analytical method validation as for any other method should be considered.
基于上述原因，关于任何其他方法的分析方法验证应该被考虑。

An additional reason for formal method validation for TOC in rinse water samples is that the compendiamethods are essentially set up as a pass/fail test, not as a quantitative assay.
另一个正式淋洗水样 TOC 方法验证的原因是：药典方法本质上是作为通过/失败测试建立的，不是作为一个量化内容建立的。
Measurement of TOC in swab samples does not follow a compendia method and must be validated prior to use in cleaning validation or verification studies.
擦拭样品的 TOC 测量不根据药典方法，但必须在清洗验证和确认研究之前验证。
Particular attention should be given to the choice of swab, swabbing technique, and recovery of residue from the swab (see Section 6.3.1).
选择擦拭应特别注意，擦拭技术，和擦拭残留回收率。
6.5.3 Visual Inspection
6.5.3 目视检查
Method validation in this case is actually the determination of a quantitative “visual detection limit” in cases when visual examination is the sole sampling/analytical method and “visually clean” is used as the sole acceptance criterion for the given residue in the absence of swab or rinse sampling for that residue.
在这个例子中方法验证实际上是 “目视检测限” 定量的检测， 以防当目视检查是单独取样/分析方法，和“视觉上的清洁”被用作缺少擦拭取样或者淋洗取样，给定残留的单独可接受标准。
If visual examination is used to supplement swab or rinse sampling, such determination of a visual detection limit is not required.
如果目视检查被用擦拭或者淋洗取样的补充，这样目视检测限度是不必要的。
A visual detection limit under specified viewing conditions can be determined by spiking coupons of the equipment surface materials with solutions of the residue at different levels (in µg/cm2) and by having a panel of trained observers determine the lowest level at which residues are clearly visible across the spiked surface.
可以通过下列两种方式确定特定观察条件下的目视检测限度：在设备表面材料中加入不同水平(in µ g/cm2)的溶液残留于取样片上；或者通过一组经过培训的观察员确定加标表面上可以明显看出残留的最低水平。
The significance of such a visual detection limit is that if equipment surfaces are determined to be visually clean under the same (or more stringent) viewing conditions in a cleaning validation protocol, the level of the residue is below the visual detection limit.
目视检测限的重要性是因为：在清洁验证方案中的相同（或更严格）的视觉条件下，如果设备表面被认为视目干净，残留水平是低于目视检查限度的。
Appropriate viewing conditions include distance, lighting and angle.
合适的视觉条件包括距离，灯光和角度。
The visual limit depends on the nature of the residue as well as the nature of the surface (for example, stainless steel vs. PTFE).
视觉限度取决于残留属性和表面属性（如：不锈钢 VS PTFE 材料）
6.5.4 Bioburden Methods
6.5.4 生物负载方法
Approved and qualified microbiological lab procedures do not require additional method validation foruse in cleaning validation programs.
批准和确认的，在清洁验证程序中使用的微生物实验室程序不需要额外的方法验证
6.5.5 Use of a Contract Laboratory
6.5.5 合同实验室 的使用
Contract laboratories can be used to develop and validate an analytical method for use in cleaning validation.
合同使用室可以被用来开发和验证一个清洁验证中使用的分析方法

The same considerations given to method validation discussed in Section 6.5.1 apply in this situation.
6.5.1 部分讨论的分析方法验证相同条件下可以在种情况下使用。
However, if the method is to then be performed by the biotechnology company, it is mandatory to have a method transfer protocol established and executed so the method can be used “in house,”
无论如何，如果这个方法被生物技术公司使用，必须强制进行方法转移方案建立和执行，故这个方法可以被作为内控使用。
If the method is developed by a contract laboratory and protocol samples are analyzed by that contract laboratory, no transfer protocol is required.
如果方式是合同实验室建立的并且方案样品也是合同实验室分析的，则不需要转移方案。
It is preferable that analytical method validation protocol be reviewed and approved by the biotechnology company prior to execution of that protocol.
生物技术公司可选择在方案执行前审核和批准分析方法验证方案。
If an analytical method has been developed and validated previously by the contract laboratory, the biotechnology company must review that protocol and the final report to determine the acceptability of the method for its (new) intended use.
如果合同实验室完成一个分析方法的开发并事先经过验证，生物技术公司必须审核方案和最终报告，确认方法作为预定用途的可接受性。
If an analytical method has been developed and validated by a biotechnology company and cleaning validation samples are to be analyzed by a contract laboratory, a method transfer protocol must be established to determine that the contract laboratory can suitably analyze samples using that method.
如果分析方法的开发和验证由生物公司进行，清洁验证样品由合同实验室分析，方法转移方案必须建立，以确认合同实验室使用此方法可以合适的分析样品。

7.0 Cleaning Validation Protocols
7.0 清洁验证方案

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 purpose, scope, responsibilities, applicable product(s) and equipment, cleaning SOP, acceptance criteria and a requirement for a final report. Key elements for cleaning validation protocols include residue limits (see Section 4.0), sampling procedures (see Section 5.0) and analytical methods (see Section 6.0). The organization and rationale for cleaning validation protocols for biotechnology manufacturers is fundamentally the same as for other pharmaceutical manufacturers.
清洁验证方案具有与工艺验证方案相同的要素。为使清晰易懂，清洁验证方案的版式通常遵循工艺验证方案所用的版式（若适用） 。共同要素包括目的、范围、职责、试用产品和设备、清洁 SOP、可接受限度及对最终报告的要求。清洁验证方案的关键要素包括残留限度（参见 4.0） 、取样程序（参见 5.0）及分析方法（参见 6.0） 。对于生物制剂厂来说，清洁验证方案的组织规则和基本原理本质上与其它制剂厂相同。
7.1 清洁验证方案
7.1 Cleaning Verification Protocols
Protocols for cleaning verification purposes are the same as for cleaning validation, except that the protocol is specific to one cleaning event. From a compliance perspective, the protocol 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 a verification protocol is typically performed on a unique cleaning event, there may be limited cleaning development before execution of that protocol. Alternatively, companies might use a concept that defines explicit requirements for cleaning verification

in an SOP and documents the specific activities, sample positions, etc., on a form, which will be approved.
清洁确认 方案与清洁验证的目的相同，但这个方案特指一次清洁活动。从合规角度看，这个方案仅仅适用于一次清洁活动（尽管从科学角度看，若重复进行这个清洁活动，数据资料可以显示出类似的性能） 。另一个差异是，因为一个确认方案通常是一次唯一的清洁活动，所以方案中针对清洁的研究可能是有限的。或者，公司可能会这样做，在一个 SOP 中详细规定了清洁确认的要求，并在一个需要批准的表格上规定一些特殊活动，取样位置等。

7.2 基于法规变更的关键问题

7.2 key Issues Based on Regulatory Changes

It is assumed that the validation protocol is not written and approved until the cleaning process has been designed and developed (see Section 3.0). This is particularly important as it relates to a life cycle approach to validation. Two key issues for protocols, each of which is in a state of flux because of regulatory changes, are discussed below.
一般认为，清洁工艺的设计和开发完成后才形成书面的验证方案并被批准（参见 Section3.0） ，因其与验证的生命周期方法相关，所以这一点尤其重要。方案有两个关键问题，其中每一个都会随着法规的变化而变化，讨论如下：

7.2.1 方案中清洁验证的批次数量

7.2.1 Number of Runs in a Protocol

The traditional approach for cleaning validation protocols has been to require an evaluation of a minimum of three consecutive runs of the cleaning processes. By consecutive, it has meant that no cleaning events of that same process are skipped without appropriate rationale.
This practice is in flux because of changes in approach by the U.S. FDA; the Agency no longer suggests a minimum of three runs. (17,18) Rather, the manufacturer must provide a rationale (based on its understanding of the process) for determining the number of runs. Providing such a rationale is not straightforward for cleaning processes, and some companies specify in their master plans that three runs will be required unless there is a written rationale for a different number. It should be noted that as of publication of this Technical Report, the question of the “number of runs” remains a significant issue in terms of applicability to cleaning validation and global harmonization for cleaning Validation.
清洁验证方案的传统方式要求评估至少三个连续批次的清洁过程。连续性是指在没有适当依据的支持下，不得有忽略相同操作过程的清洁事件发生。这一操作惯例会随着 U.S.FDA 清洁方法的改变而不断变化；FDA 不再建议至少三个批次，而是要求生产商需提供关于实施批次数量的证明（基于对清洁过程的理解） 。提供这样一个清洁过程证明并不直观，公司需要在他们的主计划中明确规定进行三次清洁验证，除非另有书面证明证实不同验证次数的合理性。应该指出，至本技术报告发表时，从清洁验证的适用范围及清洁验证的各国协调来
看，这个“数量”问题仍是一个重要的仪题。

7.2.2 最差条件

7.2.2 Worst-Case Process Conditions

The traditional approach for cleaning validation protocols has been to include worst-case process conditions in the three protocol runs. Worst-case process conditions may include maximum dirty hold time, maximum batches in a campaign, use of different operators for manual cleaning, shortest allowed time for manual cleaning steps, lowest allowed temperature for manual cleaning processes, and worst-case circuits for CIP skid selection. Parameters such as temperature, cleaning agent concentration, and process step times for automated cleaning processes are generally controlled in a narrow range such that challenging the cleaning process at the lower or upper end of the specification is not appropriate. In this traditional approach, worst-case process conditions may be addressed in each of the three required validation runs, unless there is adequate data

from the design and development of the cleaning process to support worst-case conditions in fewer runs.
清洁验证方案的传统做法是已在三次清洁验证中包含了最差过程条件。最差条件可能包括最大“dirty hold time”(指生产结束至清洁开始的时间)、批组最大批次、手动清洁中不同操作人员的使用、手动清洁步骤的最短允许时间、 手动清洁过程的最低允许温度及 CIP （在线清洗） SKID 的最差回路。通常将参数如温度、清洁剂浓度及自动清洁程序的过程步骤时间设定在一个狭窄的控制范围内，如此在较低或较高标准上挑战清洁程序是不适当的。在传统方法中，三次验证中的每一批都可能描述最差条件，除非有充分的清洁程序设计与研发资料可以支持较少批次。

8.0 maintenance of Validated state

8.0 验证状态维护

A key part of the validation life cycle for any system is maintenance of the validated state. This section deals with activities after the cleaning process has been designed and developed and after the formal validation protocols have been successfully executed. This is critical for cleaning validation, because a lapse 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, risk-based periodic monitoring and data trending review. Additionally, training and retraining are important areas of control for manual cleaning processes, as they are the primary mechanisms for controlling the cleaning cycle. In each of these three areas, knowledge of the design space (see Section 3.8) should be applied.
验证状态维护是任何系统的验证生命周期的一个关键组成部分。这部分内容是指清洁过程已经设计和开发并且正式验证方案已被成功实施后的活动。维护对清洁验证是至关重要的，
已验证状态的缺失可能会对随后生产的相同或不同产品的质量、安全和纯度带来不良影响。确保已验证状态获得持续维护的主要手段是变更控制、基于风险的定期监控及数据趋势分析。另外，培训和再培训是人工清洁过程的重要控制方式，因为它们是控制清洁周期的主要机制。以上三个方面，均应运用设计空间的知识（参见 3.8 部分） 。

8.1 关键参数控制

8.1 Critical Parameter Control

In controlling a validated cleaning process, it is of utmost importance to understand the critical parameters used to control the cleaning process. Typically these include cleaning agent concentration, temperature, flow rate and times for all processing steps. During the design phase, an appropriate level of understanding of the process and its variability should be obtained to design a cleaning process capable of addressing this inherent variability. Once the process is well defined, there are a variety of control strategies that may be used.
One control strategy is to set minimum and/or maximum values for each of the key parameters during a cleaning cycle. In this model, each of the steps of the cycle has a defined range that must be monitored and maintained during each execution of the cleaning cycle, and each parameter does not vary outside that range. This approach has an advantage in that that it is straightforward to implement and control.
在对一个已验证清洁程序的控制中，明白用于控制清洁过程的关键参数是至关重要的。通常，包括清洁剂浓度、温度、流量及所有清洁步骤的时间。在设计阶段，应对清洁程序及其可变性有适当程度的理解，以设计一个能够解决这个内在可变性的清洁程序。可能会使用各种各样的控制策略来制定清洁程序。控制策略一，在一个清洁周期过程中为每个关键参数设置最小和/或最大值。在这种模式中，清洁周期的每个步骤都有一个明确的范围，在每次清洁周期的实施过程中必须进行监控和维护，且每个参数的变化不能超出规定的范围。这种做法的优势在于它可以直接进行实施和控制。

8.2 周期反馈控制

8.2 Control by Cycle Feedback

Another control strategy is to use analytical feedback to determine cycle step length. For example, the final rinse for a CIP cycle may be continued until the rinse conductivity indicates adequate
completion of the rinsing step. This approach has elements of Process Analytical Technology (PAT) (see Section 11.8) to ensure the cleaning cycle is appropriately controlled. In the example given,
other control parameters, such as temperature and cleaning agent concentration, are maintained
in their appropriate ranges. Furthermore, it must be ensured in the design/development steps that conductivity is adequate to measure process step completion. Based on the initial validation, other analytical results (e.g., TOC) may be deemed more indicative of cycle step completion. However, since the cleaning of biotechnology products is accomplished by highly alkaline and/or acidic cleaning agents, conductivity is usually an appropriate indicator of completion of the rinsing step. If one ensures minimum and maximum values are set for other critical parameters and uses these values in concert with control of the rinse time based on analytical feedback, this approach will yield appropriate control of the cleaning cycle.
另一个控制策略是通过分析反馈确定周期步骤的时长。例如，一个 CIP（在线清洗）周期的最终淋洗应持续至淋洗电导率显示淋洗步骤彻底完成。这种方法包含了 PAT（即过程分析技术，参见 11.8 部分）的内容，可以确保清洁周期已被适当控制。在上面的例子中，其他控制参数如温度、清洁剂浓度在各自适当的设定范围内被维护。此外，在设计/开发阶段，必须确保电导率足以测定过程步骤的完成。依据最初的验证，其他分析结果（例如 TOC）可能会更好的指示周期步骤的完成。然而，因为生物制品的清洁使用了强酸/碱，所以电导率通常是指示淋洗步骤完成的适当指标。 如果可以确保其他关键参数已设置了最大和最小值，并且根据分析反馈使用这些与淋洗时间相一致的值，那么这个方法将会对清洁周期产生适当控制。

8.3 过程报警
8.3 Process alarms
Another key component of applying design space to cleaning processes is alarming of critical
parameters. In an automated CIP cycle, alarms may be based on a variety of parameters, such as
temperature of the wash and rinse solutions, conductivity of the recirculating wash solution, pressure at the spray device, flow though various circuits, and conductivity of the final rinse. There are a variety of approaches to cleaning the equipment on which an alarm occurred. In all cases, the cause of the alarm should be investigated. One strategy is that on specified alarm conditions, the cleaning cycle may be restarted. For example, if inadequate cleaning agent concentration occurred (as indicated by an alarm on the wash cycle conductivity), the cleaning cycle can be restarted from the beginning after appropriate actions are taken to ensure the alarm does not reoccur. This is a conservative approach and ensures a complete cleaning cycle is performed, but care must be taken that alarms are noted and trended to ensure cycle performance is not trending towards being ineffective and to better correct repetitive problems. Alternately, the step in which the alarm occurs may be restarted. This approach strikes a balance between ensuring cycle performance and minimizing cleaning time, as the entire cycle does nothave to be repeated. Automated alarming is generally not done in manual cleaning operations. However, if cleaning agent dilution is confirmed by conductivity, or cleaning agent temperature is confirmed by temperature measurement, measurements outside the specified range can serve as an “alarm.” In addition, for all cleaning processes, visual inspection after cleaning can serve as an “alarm.” In all cases, it must be ensured that cycles performed during validation are not “best case” due to alarm conditions. For example, if equipment is soiled, and during the initial validation of the cleaning cycle alarms occur that result in multiple rinse steps being completed, this cycle is no longer representative or worst case, but best case.
设计空间应用于清洁程序的另一个重要方面是对关键参数进行报警。在自动 CIP 周期中，报警来自多个参数，如清洗液和淋洗液的温度、再循环清洗液的电导率、喷雾装置的压力、多种环路的流动及最终淋洗的电导率。有不同方法清洁出现报警的设备。无论在何种情况下，应调查报警出现的原因。一个策略是在预

先报警的情况下，清洁周期可以被再次启动。例如，如果清洁剂浓度不足（清洗周期电导率报警提示），这个清洁周期可在采取适当行动确保报警不再出现后开始重新启动。这是传统做法，可以确保进行一个完整的清洁周期，但必须记录报警并作出趋势，以确保周期的执行是有效的，并能够更好的改正重复出现的问题。或者说，出现报警的步骤可被再次启动。这种方法可以在确保周期性能和减少清洁时间之间找到平衡。通常，人工清洁操作未使用自动报警。然而，如果清洁剂的稀释液由电导率确定，或者清洁剂温度由温度测量确定，规定范围之外的测量可看作是一个“报警”。此外，对于所有清洁程序来说，清洁后目视检查可看作是一个“报警”。不管在什么情况下，必须确保验证过程中因报警出现的多次循环不是“最好情况”。例如，如果设备有污渍，并且在清洁周期的最初验证阶段因报警出现了多个待完成的淋洗步骤，那么这个循环就不是有代表性

的或是最差情况，而是最好情况。

8.4 变更控制

8.4 Change Control

A robust change control system is critical to ensuring maintenance of the validated state for cleaning processes. The change control system must cover all key parameters and components of the cleaning system to ensure that all changes with a potential to impact maintenance of the validated state are evaluated. This includes not only changes in the cleaning process, but also changes in equipment and changes in the manufacturing process (for example, a change in temperature in a manufacturing process) which might affect the performance of the validated cleaning process. Quality preapproval and robust tracking of changes are key requirements for this system.

The change control system should provide for a review of each change by an interdisciplinary team. This must include a review of current validation for the equipment being changed, and depending on the nature of the change, may result in laboratory, pilot scale and/or commercial scale evaluations. Significantly major changes may result in the decision that the new cleaning process requires separate validation as a new process. There are some important considerations for designing the test plan to verify changes; review of the design space will assist in this evaluation. First, control parameters must stay within their validated ranges or must be revalidated. For example, if the pump on a CIP skid is validated to deliver water between 5 and 10 liters per minute, and the desired change is to increase the flow rate to 12 liters per minute, new validation testing is required to verify that the pump is capable of delivering the desired flow before validation of the cleaning cycle can occur. Second, the acceptance criteria for analytical methods should remain unchanged from the previous validation unless there is a justified reason for the difference. This is to ensure that changes result in maintenance of the validated state rather 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 to confirm validation based on a change. For example, if the effect of the change is only on bioburden, then it may be appropriate to evaluate only bioburden in studies that evaluate the effects of the change. These differences must be justified in the testing plan/protocol.

一个强健的变更控制系统是确保清洁程序的验证状态得到维护的关键。变更控制系统须包含所有清洁系统的关键参数和组件，以确保所有可能影响验证状态维护的变更得到评估。这不仅包括清洁程序的变更，也包括设备变更及生产工艺的变更（例如，生产工艺中温度的变更），即可能影响验证清洁程序性能的变更。质量预批准和强健的变更追踪是变更系统的关键。

在变更控制系统中，每个变更须由一个跨学科专家团队进行评估。评估须包含对变更设备同步验证的评估，依据变更的特性，可能会涉及关于实验室、中试规模和/或商业规模的评估。

很明显重大变更可能会做出这样的计划行动，这个新的清洁程序作为一个新的程序需要进行独立验证。设计清洁验证检测计划有一些重要的考虑因素；设计空间的评估将有助于变更的评估。首先，控制参数必须在它们各自的验证范围内或必须进行再验证。 例如， 如果 CIPskid 上的泵经验证可以以每分钟 5-10 公升

的流量送水，并且理想的变更是使流量增加到每分钟 12 公升， 那么就需要新的验证测试验证，在清洁周期验证前这个泵能够达到理想的流量。第二，分析方法的可接受标准应与之前验证的标准一致，除非有说明这种差异的合理理由。这里要确保是变更产生了验证状态的维护，而非创建一个新的状态，这可能需要重要的测试来确保验证的有效。最后，在多数情况下，减少取样点和/或简化分析方法可能适合依据变更确认验证。例如，变更的影响仅是生物负载，那么在评估变更效果的研究中仅评估生物负载可能是合适的。这些差异必须在测试计划/方案中进行合理说明。

8.5 累计变更的评估

8.5 evaluation of Cumulative Changes

Equally important as a review of each individual change is the review of the cumulative impact of changes on a system. This review must provide evidence that the cleaning cycle meets prescribed requirements. It is possible that many minor changes (each deemed to have no impact on the validated state) could have an impact when considered in total. This review of cumulative changes should take two approaches. First, a documented analysis (i.e., review of the changes and the impact these changes will have on other parts of the process) of the changes should be undertaken on a regular basis. Second, process performance and alarms must be monitored (as discussed above) to ensure continued maintenance of the validated state and system performance.

另一个同样重要的是将每个单独变更的评估看做是所有单个变更对系统的累积影响的评估。评估必须能够证明清洁周期符合规定要求。 当将一些微小变更 （单个不会影响验证状态） 作为整体考虑时，很可能会产生影响。 累积变更的评估应采用两种方式。 首先， 定期对所有变更进行文档化的分析 （即，变更评估及这些变更对程序中其他内容的影响） ；其次，需监控程序性能及报警，正如上面讲述的，以确保对验证状态和系统性能的持续维护。

8.6 Periodic monitoring 周期监控

Another tool for ensuring maintenance of the validated state is a risk-based periodic monitoring program. A periodic monitoring program may provide analytical data to be trended. In most cases involving automated processes, the data are provided by the CIP equipment itself. For example, data may be generated by the CIP skid on wash solution conductivity, final rinse conductivity, temperatures, times and pressure. In other cases, separate sampling may be established for data collection, such as rinse bioburden or TOC. Visual examination after each cleaning process is another type of periodic monitoring. For routine use, however, visual inspection typically does not involve disassembly of equipment solely for the purpose of that inspection.

另一种为确保验证状态维持的是一个基于风险的定期监控程序。定期监控程序可以提供分析数据形成趋势，大部分情况下，数据是由 CIP 设备自己提供的。如，数据可能由 CIP 清洗液电导率也产生，最终淋洗水电导率、温度、时间和压力。其他情况下，可以设立单独的样品数据收集，如清洗液的微生物负荷或 TOC。每次清洁后的目视检查是另一种形式的定期监控。常规用法，目视检查通常不会为了仅为了检查而拆卸设备。

A documented risk-based approach should be used to optimize compliance in an efficient manner. This could include leveraging family approaches, reduced sample sites and reduced analytical methods. When defining these approaches, the inherent risk associated with a given cleaning process and historical experience/data should be considered. For example, when performing the initial validation on a bioreactor, TOC may be measured via a variety of swab and rinse samples. However, with the proper data analysis, it may be appropriate to measure only rinse TOC during periodic monitoring. Historically it was considered acceptable to perform periodic revalidation on cleaning processes in lieu of periodic monitoring. However, this approach yields a much less robust picture of the state of control of the cleaning process

应该使用一个文件化的基于风险方法用于优化合规高效的方式。这可能利用家庭模式，减少取样点和减少分析。当考虑这些方法时，这些固定的清洁过程风险应该基于工艺和历史经验/数据被考虑。如：当低生物反应器进行初次验证时，TOC 可能通过擦拭或者淋洗水取样，然而，通过适当的数据分析，在日常周期监控中，可能 TOC 仅仅用润洗水。过去的经验告诉我我可以执行周期性的再验证清洗过程代替定期监测。然而，这种方法产生一个更具有说服力的清洁过程控制。

8.7 Trending 趋势

Trending of cleaning cycle performance, analytical data from routine monitoring, and alarms are another recommendation to ensure continued cleaning cycle performance. When trending any of these data sets, procedures must be in place to initiate an investigation when adverse trends are observed, even if ineffective cleaning cycles have not occurred. Trending of cleaning cycle performance data is important for identifying potential cleaning cycle issues before they result in ineffective cleaning cycles. For example, a slowly increasing trend in the final rinse conductivity may not be indicative of an ineffective cleaning process. However, such a trend should require an investigation of the cause. In the example given, it may be that the spray device is becoming clogged, in which case it should be cleaned, and appropriate steps should be taken to prevent clogging in the future. On the other hand, it may be a result of a fouled conductivity sensor. Alarm monitoring and trending will indicate cycle failure, though it will not proactively identify potential issues, as is desired. The incidents of all alarms should still be trended to determine if additional process controls are required to reduce the frequency of alarming.

清洗周期的趋势表现,分析数据从日常监视和警报是另一个建议,以确保持续的清洁周期性能。当趋势这些数据集、程序必须到位立案调查发现不良趋势时,即使没有发生无效的清洗周期。趋势的清洗周期性能数据是很重要的对于识别潜在的清洁周期问题才导致无效的清洗周期。例如,缓慢增加的趋势在最后漂洗电导率可能不是无效的清洗过程的说明。然而,这种趋势应该需要调查原因。在给出的例子中,这可能是因为喷雾装置被堵塞,在这种情况下,它应该清洗,应采取适当措施防止堵塞。另一方面,这可能是由于污染电导传感器。报警监测和趋势将指示周期失败,虽然它不会主动识别潜在的问题,是理想的。事件的警报仍应趋势来决定是否需要额外的过程控制来降低频率的担忧。

9.0 Master Planning For Cleaning Validation

9.0 总体规划清洁验证

All validation activities should be planned. The requirements for a cleaning validation program should be defined and documented in a master plan or an equivalent document. While in principle the parts of a cleaning master plan may be the same for all drug manufacturing, certain specifics of the master plan for biopharmaceutical manufacturing will be different because of the significant differences between manufacturing and cleaning for large molecule biopharmaceuticals and for small molecules. 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. This plan would be described in the overall site validation master plan. The cleaning master plan may be all-encompassing. However, an alternate approach is to have a high-level cleaning master plan and then a cleaning execution or project plan, which has more detailed

explanations of the validation requirements. These documents are living documents that should be reviewed and updated on a regular basis. A report to the plan should be written periodically to summarize the major activities executed under the plan during that interval.

所有验证活动应该计划。清洁验证程序的要求

应定义和记录在主计划或一个等价的文档。虽然原则上清洁主计划的部分可能是相同的所有药品生产、生物制药生产主计划的某些细节会有所不同,因为制造和清洁之间的显著差异大分子生物制药和小分子。这个计划应该提供一个描述的职责和活动的计划和执行清洁验证。这最好通过一个特定的清洁验证主计划。这个计划将被描述在整个站点验证主计划。清洗主计划可能包罗万象。然而,另一种方法是有一个高级清洁主计划,然后清洗或项目执行计划,验证需求的更详细的解释。这些文件是生活的文档应定期审查和更新。应该定期书面报告计划总结的主要活动,间隔期间根据计划执行。

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 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.

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所有验证活动应有计划。清洁验证计划的要求应在主计划或类似文件中规定和记录。尽管所有药品生产清洁验证主计划的内容原则上可能是相同，但生物药品清洁验证主计划的特定内容会有所不同，因为对于大分子生物药品和小分子药品生产和清洁存在着显著差异。计划应描述职责、清洁验证计划和清洁验证的实施情况。最好有一个详细的清洁验证主计划，该计划在整个厂区验证主计划中有所描述。清洁验证主计划可能包含所有内容。不过，还一种方法是准备一个概述版的清洁验证主计划，再准备一个清洁验证执行或项目计划，详细说明清洁验证的要求。应当定期审核和更新这些实际存在的文件，定期编写计划报告，总结计划执行过程中的重要活动。

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清洁主计划要描述整体计划、清洁验证所用的基本原理和方法学。计划应概述清洁验证思路和策略来支撑厂区内进行的验证活动。执行清洁验证的详细操作会在单独的方案中陈述。

为确保清洁陈程序符合CGMPs，计划会规定所需工作。按照计划要求，验证工作要记录，为评估清洁程序的适用性提供充分的科学依据，，从而使设备清洁一直符合质量标准。GMP检查期间，为了确定计划是否合适，并且确保计划和每个方案的各项都有遵守，检察官可能会审核主计划、特定验证方案和最终报告

9.1 Elements of a Comprehensive Plan

9.1 完整计划的构成

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

主计划应说明清洁验证程序的每个重要方面。主计划的构成及所需提供的适当细节取决于特定设施的实际操作。有些公司的主计划可能包含了很多详细信息，但其他公司更倾向于在操作规程中描述与主计划一致的详细信息。主计划的构成可能包括，但不限于以下主题：

Purpose of the plan

- Scope of the cleaning program
- Designation of responsibilities
- List of equipment to be validated
- Definitions and glossary of terms
- Prerequisites to cleaning validation (e.g., equipment and utility qualifications)
- Spray device coverage testing
- Use of various cleaning systems (e.g., CIP, COP, mechanicalwashers or manual cleaning)
- Cleaning reagents and mechanisms
- Cleaning cycle development requirements
- Definition of the production cleaning cycle
- Precleaning methods (e.g., presoaking or inactivation of biologics)
- Soiling solutions
- Definition and use of “worst-case conditions” associated with a cleaning process (e.g., flow rates or step durations)
- 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”)
- Use of dedicated or shared equipment; single use (disposable) equipment

- Definition of circumstances in which cleaning verification is preferred or acceptable (e.g., clinical stages)
- Specific approaches for cleaning upstream vs. downstream bulk process equipment
  - Elucidation of approaches for cleaning bulk vs.formulation/fill manufacturing equipment
- Strategies for non-product surfaces,such as lyophilizers
- Use of quality risk management to determine the scope and extent of validation activities
- Establishment of design space based on cleaning parameters and use in ongoing monitoring
- Chromatography and ultrafiltration system requirements
- Use of mock (blank) runs
- Equipment hold study approaches (e.g., dirty hold, clean hold or storage hold)
- Microbial contamination (e.g., bioburden and endotoxin)
- Sampling techniques (e.g., visual inspection, rinse sampling or surface sampling)
- Training/qualification for sampling techniques
- Analytical methods (e.g., validation and recovery requirements)
- Rationale for the use of product-specific assays and nonspecific assays
- Calculations and/or rationales for limits for process residues, microbial contaminants and cleaning agents
- Routine monitoring/validation maintenance
- Change control and revalidation requirements
- References
- Attachments/appendices (e.g., various tables or lists of items within the realm of the plan such as a responsibility matrix or a list of cleaning circuits)

计划目的
- 验证范围
- 指定责任
- 需验证设备清单
- 术语及定义
- 清洁验证前提条件（如设备和公共设施确认）
- 喷洒设备覆盖范围测试
- 各种清洗系统的使用（如CIP、COP、机器清洗或手动清洗）
- 清洗剂和清洗机制
- 清洁周期要求
- 生产清洁周期定义
- 预清洗方法（如预浸渍或生物灭活）
- 脏物清洁方法
- 清洁过程中“最坏情况”定义和使用（如流速或步长）
- 族方法描述、基于相似性的产品组/设备组/系统组，包括基于影响清洗的属性（例如“脏物”中所有组分的溶解性）确定“最坏产品”的方法
- 使用专用或公用设备；一次性使用设备
- 清洁确认倾向或接受的环境定义（如临床研究阶段）
- 清洁上游、下游原料药工艺设备的特定方法

清洁原料药、制剂、灌装生产设备的方法描述
- 非产品表面清洁策略，如冻干机
- 使用质量风险管理确定验证范围和内容

- 基于清洁参数建立设计空间，在持续监测中使用
- 色谱和超滤系统要求
- 模拟（空白）运行的使用
- 设备存放研究的方法（如脏东西保持时间、清洁保持时间或存放时间）
- 微生物污染（如生物负载和内毒素）
- 取样方法（如目测检查、清洗取样或表面取样）
- 取样方法的培训/确认
- 分析方法（如验证和回收率要求）
- 使用产品特定含量分析和非特定含量分析的合理依据
- 工艺残留限度、微生物限度及清洁剂浓度的计算和/或限度制定依据
- 日常监测/验证维护
- 变更控制和再验证要求
- 参考文献
- 附件/附录（如清洁验证计划涉及到的各种表格或项目列表，像职责矩阵、清洁列表等）

9.2 Harmonization of Site Cleaning Programs

生产场地清洁程序的协调

For a product made at more than one site, the cleaning requirements should preferably be the same, where appropriate. For example, if the process equipment scale is different, or the type of cleaning equipment available and/or cleaning process is different (e.g., CIP skid vs. manual), the programs can only be harmonized to a limited degree. The analytical methods used to determine the level of cleanliness should be the same, but 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, since the contractor is also obliged to follow his own master plan. A contract manufacturer may validate their cleaning process using techniques and procedures that differ, but the resulting validation must be compliant and must meet appropriate regulatory expectations. Any critical differences should be addressed up front in the quality agreement with the contractor.

对于不止一个生产场地的产品，适当情况下清洁要求最好一样。例如，如果生产设备大小不同，或现有清洁设备类型及/或清洗程序不同（如在线SKID清洁、手动清洁），清洁程序只能协调至一个限度。用来测定清洁效果的分析方法应该一样，但是可接受标准可能不同，因为任何限度都是基于批量和设备表面面积的。这种情况某种程度上也适用于合同生产商生产相同的产品。

但是，由于合同生产商也必须遵守他们自己的主计划，会有额外的考虑。合同生产商可能用不同的方法和程序验证他们的清洁程序，但是清洁验证的结果必须遵守和符合法规要求。任何关键差异应提前在和合同商的质量协议中说明。

9.3Cleaning Validation Activities as a Function of Clinical Stage

清洁验证在临床阶段的功能

Validation requirements will vary according to the stage of the product. It may not be feasible to do cleaning validation for equipment processing clinical materials, since typically a limited number of lots are being made, and the manufacturing process may not be locked in yet. Therefore, extensive cleaning process design and development required for cleaning validation is not warranted. In these situations, cleaning verification should be done using testing that is equivalent to that used in the validation program. The analytical methods might not be validated to the same extent as for an

analytical method used for a cleaning validation protocol. In these cases, their suitability has to be assessed. The test results are used to release the equipment before the next use.

验证要求会因产品所处阶段而有所变化。对生产临床材料的设备进行清洁验证可能不可行，因为临床材料一般只生产有限的批次，且生产工艺可能还未确定。因此，清洁验证所需大量的清洁程序设计和开发是没有保证的。在这些情况下，应进行清洁确认，所用测试方法和验证程序测试方法相同。对于用于清洁验证方案的分析方法，其验证内容可以不同。这种情况下，必须评估分析方法的适用性。检测结果可用于设备下次使用前放行设备。

In processing clinical materials, cleaning validation may be possible for process support equipment like buffer and media vessels. The support equipment can be qualified using a worst-case soiling solution in a grouping strategy (see Section 11.1). However, in the future, if a new worst-case soiling solution is identified, validation would need to be performed on that new worst case.

Cleaning validation may be considered for late-stage clinicals and is required for commercial manufacturing. It may be acceptable to do cleaning verification for late-stage clinicals, for example, if sufficient lots are not manufactured and cleaned at the same siteusing the same conditions.

在生产临床材料过程中，清洁验证可能适用于工艺支持设备，像缓冲罐和培养基罐。这种支持设备可以通过使用组策略中的最坏情况脏物清洁方法来验证（见11.1章节）。但是，以后如果出现新的最坏情况脏物清洁方法，需要对新的最坏情况进行验证。

清洁验证可能考虑的是后期临床阶段，商业生产所需。后期临床进行清洁确认是可以接受的，例如，如果未生产足够多的批次且在相同条件、相同场地下进行清洁。

10.0 Risk assessment and Management

风险评估和管理

Quality Risk Management (QRM) is a readily applied and logical process that iseffectively used to support the planning and strategy for maintaining a system or a process under continuous quality oversight. The many benefits of a quality risk management process include, but are not limited to:

Improved planning and preparation to prevent potential failures

- Increased understanding of the critical aspects of systems, processes and products
- Improved stakeholder relationships through better communication
- Increased levels of assurance through documentation of the decision-making process
- Reduced risk to patients by modifying processes to eliminate or reduce risk
- Improved detectability of fault conditions
- Optimization and prioritization of qualification efforts and resources
- Selection of test methods and acceptance criteria which are aligned with critical quality attributes of products
- Compliance with regulatory requirements or expectations
- Assistance in maintaining processes in a state of control

质量风险管理（QRM）是一个便于应用且合理的流程，它能有效地支持计划和策略，使系统或工艺维持在连续的质量监督下。质量风险管理有许多优点，但不局限于以下几点：

改进计划、预防潜在失误

- 增进对系统、工艺和产品关键方面的理解
- 通过更好的沟通改善利益双方关系
- 通过对决策流程的记录提高保障水平
- 通过改进工艺消除或减少风险，降低给患者带来的风险
- 提高故障检测性
- 优化验证资源

- 选择检测方法和可接受标准，同产品关键质量属性一致
- 符合法规要求或期望
- 使工艺维持在受控状态

The role of risk management is integral to the design and validation strategy for manufacturing systems. Risk management is a continuous process. Key inputs and data are analyzed and evaluated, and risk mitigation measures are implemented to ensure the outputs of the design are appropriately considered and verified, and that the subject system is demonstrated as fit for purpose. Cleaning and cleaning validation requirements are determined from inputs related to the knowledge of process systems, soils and equipment cleaning aids (e.g., chemical and mechanical features). These requirements are subject to a design review and then verified in accordance with the acceptance criteria that are used to prove that the system requirements have been achieved.

Product knowledge, process knowledge, regulations and quality attributes are used to develop the requirements for cleaning and to define the technologies that will best support the cleaning of manufacturing systems and components. Issues that may impact cleaning include: soil type, cleaning process, equipment design and configuration and availability of utility services. Process knowledge is used to determine CPPs and define CQAs. Examples of each are presented in Table 10.1 below.

Table 10.1 CPP and CQA Considerations that have Potential Risk Impact to a Cleaning Process

风险管理贯穿于生产系统整个设计和验证策略。风险管理是一个连续的过程。分析和评估关键的投料量和数据，采取风险缓解措施确保设计合理有效，证明目标系统符合预期用途。清洁和清洁验证要求由工艺系统、脏物和设备清洁相关（如化学和机械特性）的知识来确定。这些要求要通过设计审核，然后证实符合可接受标准，该可接受标准用于证明系统要求已经达

根据产品知识、工艺知识、法规和质量属性确定清洁要求，规定能够最好支持清洁生产系统和组分的方法。可能影响清洁的问题包括：脏物类型、清洁程序、设备设计、配置和现有的公共服务。工艺方面的知识用于确定CPPs和定义CQAs。例子见下表10.1.

Table 10.1 CPP and CQA Considerations that have Potential Risk Impact to a Cleaning Process

表**10.1** 对清洁程序有潜在风险影响的**CPP**和**CQA**

Critical process parameters **关键工艺参数**	**Criticai Quality Attributes** **关键质量属性**
工艺温度	目测或限度
工艺压力	清洁剂残留
工艺流程	产品残留
工艺时间	微生物残留限度
清洁剂浓度	滤水性/干燥
脏东西保持时间（赃物情况）	电导率/电阻率
清洁保持情况	

QRM involves elements of risk assessment, risk control and periodic review to ensure continuous and effective control. The quality risk management process is best supported by a team of Subject Matter Experts that have an appropriate level of experience from various areas such as operations, technical services, engineering, quality control, quality assurance and regulatory. The experience and diversity of the team provides the opportunityto identify and address all conditions that impact CPP and CQA for the cleaning or manufacturing process.

QRM涉及风险评估、风险控制和定期审核，从而保证连续和有效的控制。质量风险管理流程最好由来自各个领域的，如生产、技术、工程、质量控制、质量保证和药政，有一定经验的主题专家组来

构建。专家组成员的经验和多元化有助于鉴定和说明清洁或生产过程中影响CPP和CQA的所有情况。

10.2Techniques and Tools for Risk Management and Assessment

10.2 风险管理和评估的方法及工具

Techniques and tools for risk management include process mapping, brainstorming, Hazard Analysis and HACCP, FTA, Cause and Effect Analysis, HAZOP, and FMEA. Risk assessment is initiated early in the life cycle process starting in the planning, development and specification phases of the cleaning process. Risk evaluations are performed periodically. Feedback data is used to make decisions that impact the cleaning process.

风险管理的方法和工具包括过程分析、集体讨论、危害分析、HACCP（危害分析和关键环节控制点）、FTA（故障树分析）、因果分析、HAZOP（危险与可操作性分析）和FMEA（失效模式影响分析）。风险评估开始于清洁程序整个生命周期的初期阶段，从清洁程序的计划、发展和标准建立阶段开始。反馈数据用于对受影响的清洁程序做出决定。

Risk analysis is integral to the change management process. The impact of a proposed change is evaluated for quality and safety impacts, and the outcome of the assessment is used to drive the activities that are required to effectively implement the change. Low-risk change tasks (such as an increase in rinsing time) may require little to no additional testing. High-risk change tasks (such as a change in the nature of the cleaning solution) may require a significant level of testing. Risk analysis can also be used to determine the economic impact of a change. It may become evident that a proposed change offers no economic benefit; consequently the change is not implemented.

风险分析是变更控制不可或缺的一部分。变更要评估对质量和安全的影响，评估结果有助于变更的有效执行。低风险变更（如延长清洗时间）可能不需要额外检测。高风险变更（如清洗方法本质改变）可能需要相应程度的检测。风险分析也能用于确定变更对经济方面的影响。一个变更有可能很明显不会带来经济效益，因此不会执行该变更。

In summary, quality risk management is a systematic process that involves elements of assessments, development of controls and continuous review throughout the life cycle of the cleaning process. The risk assessment process is effective at identifying CPPs and CQAs. Risk management tools are used to generate data and drive decisions. This information is used to affect risk mitigation, and it reduces risk to an acceptable level. Risk assessments should be documented so that critical factors are identified, decision pathways are understood, and the information is effectively communicated to the stakeholders.

总而言之，质量风险管理是一个系统的流程，涉及清洁程序整个生命周期的评估、控制开发和连续审核。风险评估能有限鉴别CPPs和CQAs。风险管理工具用于生成数据和做出决策。这些信息会影响风险缓解，降低风险的可接受水平。应当记录风险评估，以便识别关键因素、了解决策思路和使信息有效的传达给利益相关者。

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11.1.2 equipment Grouping

Grouping of equipment is an efective method for encompassing equipment from a limited popula-tion of systems undergoing cleaning validation without redundant testing. The grouping strategy is based on designating equipment as “identical” or “similar,” based on design and cleanability. Once equipment has been placed within a designation, the designation defnes the cleaning validation requirements. If it involves identical equipment, a protocol with a minimum of three validation runs involving any combination of three equipment items in the group is performed. Provided an adequaterationale 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 equipment. For example, for storage tanks of the same size but of diferent complexity, such as the number of bafes, the more complex equipment is chosen as the worst case. For similar equipment of diferent 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).
Confirmatoryvalidation runs (perhaps only one run) are an option for other equipment (not a worst case) within the group.

11.1.2设备分组

要想让有个有限的群体系统包含设备而避免冗长的检测最终完成清洁验证，设备分组是一个高效的手段。分组策略是基于指定设备“相同”或”相似，“基于“设计”和“洁净力”。一旦设备定义为一个组系那么也就意味着清洁验证方面的要求也是一样。如果它涉及相同的设备，至少三个验证运行的方案应当含涉及的任何组合三个设备被执行。提供了一个确定设备项目是相同的充分的理由，则不需要执行验证条目中的每个运行。对于类似的设备，代表设备是最坏的情况下或也可能涉及设备托架。例如：

例如：对于储罐的大小相同，但是却有不同的复杂程度，比如过滤器的数量，更复杂的设备选为最坏的对象。对大小不同的类似设备，最大的和最小的（代表极端）可被选为正式验证运行（除非一个大小可以确定为最坏的情况下）。组内的验证运行(可能只有一个运行)对其他设备而言是一个选择(不是一个坏的情况下)。

11.1.3 Introduction ofa New Product or New equipment Into a Group

The introduction of a new product into an already validated group is then assessed using the same evaluation process to initially determine the worst-case product. It is recommended that when each new product is tested, a suitable control, such as the previous worst-case product, is included. Relative product cleanability is then used to determine validation requirements for that product on equipment used for other products in that group. The relative cleanability of the product in relation to the preceding worst-case product will dictate the validation requirements. Based on a risk assessment, introduction of an easier-to-clean product may just require laboratory and/or scale-up studies to confrm ease of cleaning or may require a confirmatory validation protocol. Introduction of a more difcult-to-clean product will require validation of that new worst-case product.

Based on risk considerations, introduction of new identical equipmentmay just involve determination that it is equivalent or may require an additional confrmatory validation protocol. Introduction of new similar equipment requires an evaluation if that new equipment represents a new worst case or a new extreme. If not anew worst case or new extreme, a confrmatory validation protocol using only a visually clean criterion can be used. If the new equipment is a new worst case or extreme, the validation requirements for the previous worst case or extreme should be repeatedfor the new worst case or extreme equipment.

11.1.3新产品或新设备引入一组

新产品的引入到一个已经验证的组内，然后使用相同的评估程序评估最初确定最坏的产品。建议每个新产品测试时，进行一个合适的控制，比如包括以前的最坏情形下的产品。相关产品的清洁性用于确定验证要求，产品组的设备用于其他产品。最坏情况下产品的相对清洁性决定产品的验证要求。风险评估的基础上，引入一种较易清洁产品可能只需要实验室和/或扩大研究去确认易于清洗或可能需要的验证方案。引入一个较难清洗的产品将会要求验证一个新的最坏情形下的产品。

基于风险的考虑，引入一个新的相同单元的设备可能涉及一个相同的假设或可能新增一个必要的验证程序。引入一个新的类似的设备如果新设备代表着一个最差条件或一个新的极端情况，则要求进

行评估；如果不是，则验证中只需用一个显而易见的清洁确认。如若新设备是一个新的最坏情形或极端情况，则这个新的最坏情形或极端情况将取代先前的来完成验证要求。

11.1.4 Conclusion

The use of product and equipment grouping may be usedto streamline cleaning validation programs while ensuring sufcient data to support the validation of procedures, processes and equipment associated with cleaning. The grouping program for a given facility or company should be in a well-defined validation program/validation master plan.

11.1.4 结论

产品和设备的分组化的运用将使有数据可以支持验证程序的清洁验证项目变得简单化，过程与设备通过清洁关联起来。对于一个现有厂房或企业应当很好的在验证项目或验证主计划中完成分组项目的定义。

11.2 Cleaning agent Issues

Equipment cleaning processes in the biopharmaceutical industry often involve a pre-rinse with water, an alkaline wash, an acid wash and a series of water rinses.

11.2清洁剂的问题

在生物制药企业设备的清洗程序通常是包括一个水的预冲洗，一个碱洗，一个酸洗及一系列的水漂洗。

11.2.1 sodium hydroxide Wash

A commodity alkali such as sodium hydroxide is often used for the alkaline wash step. Thehigh pH and alkalinity of sodium hydroxide solutions enhance solubility of most organic process residues, and in some cases facilitate hydrolysis. Sodium hydroxide is also widely available, relatively inexpensive and, being a single component, relatively easy to analyze and validate for cleaning agent removal. Commodity cleaners such as sodium hydroxide, however, may have limited efectiveness for tenaciously adhered or baked-on proteinaceous residues, cell debris and antifoams. They also have limited wetting characteristics and soil suspending ability. The higher pH of sodium hydroxide also facilitates the precipitation of salts or oxides of such ions as calcium, magnesium and iron, if those ions are present during the cleaning process.

11.2.1氢氧化钠洗涤

氢氧化钠作为一个常用的碱液经常用于碱洗的步骤中。它的较高PH值和强碱性加强了大多有机物的分解过程，在一些情况下，促进水解。同时氢氧化钠较易得到，极其便宜，组分单一，相当易于检测分析和证明清洁剂已被去除。日常腐蚀清洁剂如氢氧化钠，偶尔可能对较强的附着物、烤焦的蛋白残留物、细胞碎片和消泡剂只能起到一定限度的清洁效力。他们也有有限的润湿特性和土壤悬浮能力。如果在清洁程序中有钙、镁、铁的离子的氧化物，高PH值的氢氧化钠也能增加它们的沉淀。

11.2.2 acid Wash

Theaddition of an acid wash step after the caustic wash may overcome precipitation and buildup of inorganic compounds and help broaden the spectrum of soils cleaned although at the expense of adding another cycle. In addition, maintaining a clean surface and limiting the deposition and buildup of iron or other anodic contaminants may help minimize the potential for stainless steel corrosion and rouge formation.

11.2.2酸洗

在清洗步骤中增加酸洗可以避免沉淀物、累积的无机物、扩大污点被清洁的范围，但要增加另一个清洗循环的花费。另外还可能带来一个清洁表面的维护、有限的沉积物及长期形成铁或阳性离子一定程度的潜在不锈钢腐蚀和红锈现象。

11.2.3 Formulated detergents

Formulated detergents are multi-component cleaning agents that take advantage of several diferentcleaning mechanisms, thus providing broader spectrum efectiveness. In addition to the mechanisms of alkalinity and hydrolysis ofered by a commodity caustic, a formulated alkaline detergent

mightprovide improved wetting and soil penetration, emulsifcation, chelation of calcium, iron or other inorganic ions, and might facilitate dispersion of particulates in one wash step. Despite the use of chelating agents and the broad spectrum efectiveness of formulated detergents, rouge buildup may still be observed over a period of time, and a periodic derouging process may be necessary, particularly in applications that involve aggressive process conditions such as SIP.

11.2.3配方洗涤剂

配方洗涤剂是利用其清洁成分中多种不同的清洁机理的组合物，如此扩大了其清洁效力的范围。一个来自日常腐蚀清洁剂碱性和水解性的机理，一种配方中的碱性成分可能增强润湿性和离子的渗透力，乳化情况，钙、铁及其它无机离子的螯合作用，可能增加清洗过程中粒子的扩散力。先不说螯合剂的使用及对粒子扩散的效力，经过一定的时间还是会发现有红锈现象，定期的减少是必要的，特别是在涉及一些强烈的程序上如在线灭菌。

11.2.4 Issues in selection

A number of factors besides broad spectrum cleaning efectiveness need to be considered when selecting detergents. These include rinsability, quality, consistency, substrate compatibility, stability, safety, toxicity, assay suitability, environmental compliance and assured long-term availability.

11.2.4选择的问题

当选择洗涤剂时除了清洗效力及范围外有大量的因素需要考虑，包括但不限于：不稳定性、质量、一致性、与基质的相容性、稳定性、毒性、分析的适应性、环保及持久性。

11.3 special equipment Issues

11.3 特殊设备问题

11.3.1 Chromatography Columns

色谱分析柱

Chromatography columns are typically used in protein purifcation processes. In contrast to equipment like fermenter vessels or tanks used in purifcation that are cleaned empty, for batch-to-batch cleaning within a campaign of the same product, the columns are clean packed with resin after the batch is processed. The cleaning processes for the chromatography resin packed into the column are process specifc and depend on the type of resin used. Resin cleaning and reuse is out of scope of this document and is described in detail in PDA Technical Report No. 14, Validation of Column-Based Chromatography Processes for the Purifcation of Proteins. (19).

色谱分析柱典型应用是在肽的精制操作中。对比的设备如发酵罐或容器在精制操作中被清空，对于同样的品种一批接一批的清洁活动，色谱柱最终会被清洁的树脂所堵满。色谱柱的清洁程序是个特殊的程序将洁净的树脂重新填入柱中同时还取决于所用树脂的类型。树脂的清洁和活化就不在本书中作讲解，具体可见PDA第14号文件：应于用肽精制过程中色谱分析的确认。

Since chromatography columns are cleaned with resin packed into a column, the resin cleaning process also cleans the column housing. Therefore, after unpacking a column, product-and process-related impurities on the column surfaces are already removed to a certain extent. However, it is common practice to clean an empty column after a column is unpacked. Column frits or sieves are normally product dedicated due to their porosity and the difculties to validate removal of product-and process-related impurities. In moving from a campaign of one product to a new campaign of a diferent product, they are removed prior to column cleaning and stored for further use. Typically, a manual cleaning process using the same or similar cleaning agents as for tank cleaning is used for the cleaning of the column housing. After cleaning, the same cleaning validation principles (such as limits) applied to tanks can beutilized.

自从通过用树脂填充进行柱子方法来完成了色谱柱的清洁，树脂的清洁过程也完成了柱子本身的清

洁。因此，通过打开色谱柱，在柱表面的产品和过程相关的杂质也已经移动到一个可确认的范围内。但是这是一个惯例即当打开色谱柱后就清洁这个空的柱子。柱子的碎片和多孔通常与产品的多孔性和产品和过程相关的杂质去除的验证的困难性直接相关。在产品由一个更换为另一个产品的过程中，则是优先将柱子清洁完成后保藏好以便后期的使用。尤为特别的是对于色谱术腔体的清洁则是手工选择相同或相似的洗涤剂进行容器的清洁。清洁结束后，同样的在容器上的清洁验证原则（最低残留）也可利用。

11.3.2 Tangential Flow Filtration (TFF) Filter systems

11.3.2切向流过滤系统

Similar to chromatography columns, tangential flow filtration filter housings (also called filter holders) are cleaned together with the membranes after a batch has been processed. The cleaning processes for the filter membranes packed into the filter housing are process specific and depend on the type of membrane used. TFF membrane cleaning is out of scope of this document and is described in detail in PDA Technical Report No. 15, Validation of Tangential Flow Filtration in Biopharmaceutical Applications. (20)

与色谱柱一样，切向流过滤过滤器的外壳（也叫过滤介质保护）也是当一批结束后跟着微孔滤膜一起进行清洗。对于过滤器滤芯装入过滤器保护外壳的清洗程序是特殊的并取决于所用的滤芯型号。切向流过滤系统的清洁就不在本报告中进行讲述，具体可见PDA第15号技术报告：切向流过滤系统在生物制药中的应用。

11.3.3 Centrifuges

In many biotechnology processes, centrifuges are used at the end of fermentation to remove cells from cell cultures or to separate bacteria from the fermentation broth prior to further processing. Many centrifuges can be cleaned in place; others have to be manually cleaned.

Cleaning complex pieces of equipment like centrifuges can be challenging. For instance, not all surfaces which have been in contact with the fermentation broth can be easily reached. Special attention has to be given to hard-to-access areas of the equipment, both in the cleaning process and in the evaluation of that cleaning. After cleaning, the same cleaning validation principles (such as limits) applied to tanks can be utilized.

11.3.3离心机

在许多生物工艺流程中，离心机通常用于发酵工艺中的细胞分离或者在发酵前期与后面工序的细菌分离。大部分离心机可在在线清洗，一部分得进行手工清洗。

对于离心机组中的复杂组件的清洗应当是一个挑战。举个例来说：不是所有与发酵液接触的表面都能轻松地清洗到。在清洁程序和清洁评估中，应当特别地关注到设备的一些关键区域。清洁结束后，同样的在容器上的清洁验证原则（最低残留）也可利用。

11.4 multi-host Facilities

Cleaning validation is performed to demonstratethat residual material or cleaning agents remaining on shared equipment surfaces following the manufacture of one product are controlled to below acceptable levels so that the shared equipment may be utilized for the manufacture of a subsequent product without impacting the safety, identity, strength, quality or purity characteristics of the subsequent product. In order to maintain a successful cleaning validation program for a multi-host facility involving both cell culture and bacterial fermentation processes, thevalidation strategy must consider not only cleaning agent and process residues, but also specifc requirements for each process step necessary to maintain drug quality throughout the manufacturing process.

11.4多主机设备

清洁验证的证明是通过物料的残留或清洁剂在共有设备表面的残留。在一个产品的制造的可接受的

最低水平，在没有对接下来产品生产的安全、一致性、优点、质量或纯度特性冲击的提前下，共享设备将被在接下来的产品生产中利用。为了确保涉及细胞学和细菌发酵程序的多主机设备的清洁验证项目成功，验证的方案中不仅仅要考虑清洁剂和产物的残留，还有对整个生产制造中维持药品质量的必须的每一生产步骤中的特殊要求。

Robust cleaning validation programs for multi-host facilities should ensure that cleaning procedures are appropriate for all processes/systems used in the facilities. The successful cleaning validation program for a multi-host facility will ensure the cleaning/sanitization/changeover procedures control residual process residues to below acceptable levels for all products made in the facility.

对于多主机设备的强有力的清洁验证项目应当确保在设备上所有流程和系统都适用，并确保在线生产的所有产品的清洁、降解、品种更换的残留控制都在可接受的水平范围内。

11.5 Non-product Contact surfaces

Non-product contact surfaces may be defined in different ways by manufacturers. One way is to regard any equipment surface that does not directly contact the drug substance (the active) or drug product as non-product contact. Examples under this definition might be lyophilizers, equipment used solely to manufacture and transfer buffers and media, and equipment to process drug product after completion of primary packaging. Other companies may choose to define some of these surfaces as “indirect product contact,” since in the case of buffersand media, any residues left on equipment surfaces after cleaning will contact the next buffer/media and will eventually contact the drug substance manufactured with that next buffer/media. Because of the limited impact of these indirect or non-product contact surfaces, requirements for cleaning validation can be reduced or cleaning validation can be eliminated in certain situations.

11.5非直接接触产品的表面

制造商对非直接接触产品的表面有不同的定义。一种方式是把没有直接与药品物质（活性）或药品产物接触作为非直接接触。对于这种定义的最好例子为冻干器，设备在加工、转移缓冲和媒介的相对唯一，在药品的生产过程中已是完成初始包装。一些公司将会把这些表面定义为：“非直接接触表面”，经过缓冲和媒介，清洁后任何残留在设备表面的剩余物将会与下一个缓冲和媒介直接，而这将最终与药品物质接触。由于这些间接或非直接接触表面的有限影响，清洁验证的一些要求可减少或在某些确认的情况下可以取消。

11.5.1 equipment for Buffers

For buffers, which generally have components that are readily water soluble, cleaning is generally relatively easy and may be done with either water alone or a dilute caustic solution. Concerns about cross-contamination of buffers arenot necessarily based solely on the carryover of the buffer components, but on any efects residues might have on production efciency or production quality.

11.5.1设备缓冲区

对于缓冲区，一般都有极易水溶的成份，清洁一般相对容易，可单独用水完成或一些稀释的碱溶液。关于缓冲区的交叉污染的关注点不要基于缓冲区的各部件作为独立体，但是在一些有效的剩余物，可能要思考产品的有效性或质量。

Based on a risk analysis, cleaning validation of buffers may only involve acceptance criteria of visuallyclean and conductivity. Although some companies may also choose to include a measurement of TOC, conductivity is the better method because of the fact that the buffers are readily water soluble and highly conductive. Measurement of bioburden may also be utilized, depending on a risk analysis based on the growth promotion properties of the buffer. Measurement of specific residues may be appropriately done by rinse sampling because of the water solubility of the buffer components. Grouping of buffers and selecting the worst case for cleaning validation is also a valid (and common)

approach for cleaning validation of buffers.

在风险分析的基础上，缓冲区的清洁验证可能仅涉及表面的清洁和电导率的接受标准。但一些公司可能也会选择进行TOC（总有机碳量）的测量，电导率是一个较好的方法，因为缓冲区是水溶性和高电导性的。生物负载的测量也可能被利用，这就要基于对缓冲区生长特性的风险分析。对特殊残留物的测量可能通过利用缓冲区各部件的水溶性用冲淋取样的方法来实现。针对缓冲区的清洁验证对其分组及选择清洁验证中的最差条件是一个有效（常用）的途径。

11.5.2 equipment for media

The situation with media is similar to that of buffers, except that media are generally much more difficult to clean, such that cleaning solutions containing alkali are used. Concerns about media carryover are also not necessarily based on safety concerns related to carryover of the media components, but on any effects that media residues might have on production efficiency or production quality of drug substance made utilizing the next media batch. Cleaning validation may include the criteria of visually clean, with measurements of TOC, conductivity and/or bioburden after cleaning. TOC is used because of the organic nature of the media components. Conductivity confirms removal of the alkaline cleaning solution. Bioburden is measuredbecause the media typically enhances microbial growth. For concerns about endotoxin from gram-negative bacteria, endotoxin may also be evaluated. Because of the design of equipment for media manufacture, rinse sampling alone may be adequate. However, the solubility or degradation of media components should be considered as part of the risk analysis for performing rinse sampling only. Grouping of media and selecting the worst case for cleaning validation is also a valid (and common) approach for the cleaning validation of media.

11.5.2媒介设备

媒介设备的情况与缓冲区相似，除非此媒介物质非常难以清洁，这样就要考虑用碱洗的方法来处理了。媒介的遗留关注不是必需的，要基于相关媒介组分的残留安全性，不仅是媒介残留物在产品中的影响或是下一批次媒介物在药品中的质量影响。清洁验证应当包括清洗结束后的表面清洁的标准，总有机碳的测量、电导率或生物负载。总有机碳的测量是因为媒介给分中有有机物。电导性可保证碱的去除。生物负载的检测是因为媒介特别加强微生物的生长。对于革兰氏阴性菌的内毒素的关注也使得内毒素也需进行评估。由于媒介制造设备的设计，冲洗样品就可适用。但是媒介组分的溶解性和降解在仅执行冲淋取样的风险分析中应当考虑。针对媒介设备的清洁验证对其分组及选择清洁验证中的最差条件是一个有效（常用）的途径。

11.5.3 lyophilizers

Acceptable (meaning saleable and meeting all product specifcations) drug product never touches lyophilizer surfaces; contact of drug product with lyophilizer surfaces generally only occurs because of broken vials or vials that tip over and spill during loading. However, because of the close proximity of lyophilizer shelves to open product, and because of a perceived airborne transfer of residues on the shelves to open vials, cleaning validation is typically performed on lyophilizers used in formulation/full operations. Typically, only WFI is used for cleaning lyophilizers because of the concern of leaving cleaning solution residues inside the lyophilizer. Cleaning procedures for lyophilizers may alsoinclude a precleaning step to remove broken glass or spilled product before the validated cleaning procedure is performed. Carryover calculations for setting limits are typically not applicable to lyophilizers because the indirect contact with the next product precludes any scientifcally based calculation as conventionally performed for direct product contact surfaces. The most common acceptance criteria for cleaning validation of lyophilizers are a visually clean requirement and/or a measure of TOC. Since direct carryover calculations are not applicable, TOC limits are typically based on one of the following criteria: a 10 ppm TOC criterion in any desorbed swab sample, or a TOC limit the same as the TOC limit for any

direct product contact equipment immediately before or after the lyophilizer. The logic of the latter approach is that indirect contact equipment is less of a risk than direct product contact equipment; therefore, if the indirect is held to the same requirement as the direct, then the product should be acceptably protected. Bioburden may also be measured during cleaning validation of lyophilizers; however, lyophilizers generallyundergo an SIP process after cleaning.

11.5.3冷冻干燥机

可接受（意味着可满足供货及产品的工艺特性）的药品产物绝不会接触到冻干机的表面，药品组分与冻干机表面的接触一般仅发生在破瓶、倒瓶及装量时的药液溢出。但是由于打开产品与冻干机架子的较近距离、打开小瓶时能感知的架子上残留物的气体流动，在冻干机上的清洁验证就得明确及全部执行。典型的是仅用注射用水对冻干机进行清洗，只考虑了残留在冻干机中清洁溶液的剩余。冻干机的清洗程序应当包括在经验证的清洗程序执行前的预清洗程序将一些破瓶或溢出的产品处理掉。对于冻干机来说产品安全残留（下一品种）没有必要进行计算，因为这个标准一般是通过前后两个产品间与设备表面的直接接触的面积来进行计算的。最常用的冻干机清洁验证标准是表观上的清洁标准、总有机碳的测量。自产品安全残留（下一品种）不再适用后，总有机碳的限度已以下面标准为代表：所有标签擦拭样品的10个ppm或产品直接接触冻干机表面之前或之后的总有机碳限度。逻辑上来说间接接触设备表面的风险比直接接触设备表面的风险要低，所以，如果间接接触设备的产品与直接接触共用设备，则产品肯定是有保护的。在冻干机的清洁验证中生物负载也应当进行测量，但是它一般又是在清洗后就进行在线灭菌程序。

11.5.4 Packaging equipment

Once the drug substance is in its primary packaging, the risk of cross-contamination is relatively 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 broken vials, which release product. Cleaning processes for such situations should be considered; however, because contamination of the next product may only involve contamination of the outside of the primary packaging, cleaning validation becomes a major concern only if that spilled product has some unusual toxicity concerns. In those cases, a dedicated line or a cleaning step known to deactivate or degrade that drug active should be considered. Such a degradation process may appropriately be confrmed in a laboratory study demonstrating degradation or deactivation of the active.

11．5.4包装设备

一旦药品进入到其主要包装工序，交叉污染的风险也就相对低了。在包装线上当主要的包装操作完成后应当有清洁程序但无需验证。交叉污染主要的关注内容是那些药品跑出来的破损的物。清洗程序应当考虑这些情况，但是因为下一品种的关键包装可能会被这些污染物污染，对于一些有异常毒性的产品清洁验证应当重点考虑。在这些情况下，一条专属的包装线或一个已知的可降解药物或使其无活性的清洁方法应当考虑。这样一个降解程序在实验室研究中应当适当的确认以表明可降解或能钝化其活性。

11.6 Viruses, mycoplasma and Prions

The biological nature of materials and processes used in biotechnology production presents uniquechallenges for equipment cleaning and cleaning verifcation. Besides product and product-related residues and those residues that may remain from the cleaning process itself, viruses, mycoplasma and prions are another concern for product contamination. However, viruses are not routinely addressed in cleaning validation protocols or programs, but in viral clearance studies and/or as part of process validation.

11.6病毒、支原体及朊病毒

生物原材料和生物工艺学的过程在设备清洁和清洁验证中显现了其特有挑战。此外产品、产品相关

的残留物、清洁程序自身的残留物，病毒、支原体和朊病毒又是产品污染的另一个关注点。但是在清洁验证方案和程序中，病毒不是一般的清洗处理。应当是病毒的去除研究或作为验证程序的一部分。

11.6.1 Control steps

While the primary control measures are viral clearance process steps, testing for viruses and mycoplasma in the unprocessed bulk, and exclusion of raw materials that might contain viruses, mycoplasma and prions, specially designed cleaning processes might also be needed in some cases. Control of raw materials is essential, especially for plasma and plasma-derived products and those derived from animal materials –through vendor certifcation, incoming QA inspection and QC testing. Recombinant and "non-animal origin" materials should be used wherever practicable throughout all processing steps; however, viruses have been found to contaminate non-animal raw materials due to exposure during raw material storage, either at the raw material vendor or at the manufacturing site due to adventitious viral contamination. Also, mycoplasma that can replicate in mammalian cell culture often have a plant source and may be a contaminant in plant peptones. Since mycoplasma contamination can also be due to humans, proper gowning and personal hygiene are critical to control contamination. Additionally, sterilization ofequipment used in cell culture, fermentation and finished product manufacturing may provide additional assurance of product that is free of viruses and mycoplasma.

11.6.1控制方法

最初的控制措施是通过除菌过滤的方法进行，在没有加工的物体中检测病毒及支原体，排除一些未加工物料可能含有病毒、支原体和朊病毒，特别是在一些清洁程序的设计中一定要进行。对未加工物料的控制是必须的，特别是血浆、血浆制品和那些直接从一些小商贩确认而来自的动物体物质，需经过QA的检查和QC的检测。经过所有的检测程序后那些重组体和非动物源物料才可随处使用。但是，病毒可以在非动物源未加工物料的贮藏期间暴露下使其污染，亦或在供应商处、在制造生产处受到病毒的污染。同时，支原体在具有充足水源的条件下会在哺乳动物细胞中复制生长，也可能成为蛋白冻培养基中的污染物。既然支原体污染物可归结于人自身，适合的净化服和人员卫生确认是控制污染的手段。此外，细胞培养、发酵和产品的生产制造中设备的灭菌，其无病毒和支原体的结果可能会为产品提供一个额外的保证。

11.6.2 Control by Cleaning

Equipment cleaning using caustics and/or acids at appropriate ranges for the cleaning parameters of time, temperature, concentration and action is also essential to successful biocontamination control. The use of cleaning solutions containing sodium or potassium hydroxide is widely practiced in the industry. NaOH has been shown to be efective for inactivating most viruses. A U.S. FDA/CBER guidance provides a regulatory perspective on prion inactivation methods:

"TSE agents are quite resistant to most disinfecting regimens. There is no current consensus on specific details of decontamination requirements for blood products. However, methods of destruction of TSE-implicated material include steam autoclaving at 132°C for 1-4 hours, incineration, or treatment

11.6.2清洁控制

设备清洁要达到成功的控制生物污染，需对清洁时机、温度、浓度和动作的参数控制适当的范围内，使用必要腐蚀剂或酸。在工业上较广泛使用到氢氧化钠或氢氧化钾作为清洗溶液。氢氧化钠被证明对于大多数的病毒的钝化是有效的。美国食品药品监督管理局和生物学研究评价中心的指南中提供了一个关于朊病毒钝化方法的控制观点：

"试验辅助设备的组分对于大多数的消毒程序具有充足的耐受性。对于血液制品的净化要求目前没有共识的具体细节。但是消除试验辅助设备相关材质的方法包括：高压蒸汽灭菌在132°C，灭菌1~4小时；焚烧；或……

11.5.4 Packaging Equipment

Once the drug substance is in its primary packaging, the risk of cross-contamination is relatively 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 broken vials, which release product. Cleaning processes for such situations should be considered; however, because contamination ofthe next product may only involve contamination of the outside of the primary packaging, cleaning validation becomes a major concern only if that spilled product has some unusual toxicity concerns. In those cases, a dedicated line or a cleaning step knownto deactivate or degrade that drug active should be considered. Such a degradation process may appropriately be confirmed in a laboratory study demonstrating degradation or deactivation of the active.

11.5.4 包装设备

当原料药内包装完成后，此时交叉污染的风险相对较低。包装线的清洁应在内包装完成后进行且不需要清洁验证。交叉污染的主要风险来自于破损的小瓶，产品可由此泄露。此种情况下的清洁程序需要特别考虑；然而，由于对下批产品的污染可能仅涉及内包装材料的外表面，清洁验证仅在溢出的产品有特殊毒性时才需要重点关注。在此类情况下，需要考虑使用专用生产线或可以去除或降低产品活性的清洁方法。可以通过实验室研究证明方法对产品失活或降低活性的有效性。

11.6 Viruses, Mycoplasma and Prions

The biological nature of materials and processes used in biotechnology production presents unique challenges for equipment cleaning and cleaning verification. Besides product and product-related residues and those residues that may remain from the cleaning process itself, viruses, mycoplasma and prions are another concern for product contamination. However, viruses are not routinely addressed in cleaning validation protocols or programs, but in viral clearance studies and/or as part of process validation.

11.6 病毒，支原体和朊粒

生物技术生产中使用的物料和工艺的生物特性对设备清洁和清洁确认带来了特有的挑战。除了产品和与产品相关的残留，以及清洁工艺本身可能带来的残留之外，还需要考虑病毒，支原体和朊粒对产品的污染。然而，病毒通常在病毒清除研究中考察和/或作为工艺验证的一部分，而不包含在清洁验证草案及程序中。

11.6.1 Control Steps

While the primary control measures are viral clearance process steps, testing for viruses and mycoplasma in the unprocessed bulk, and exclusion of raw materials that might contain viruses, mycoplasma and prions, specially designed cleaning processes might also be needed in some cases. Control of raw materials is essential, especially for plasma and plasma-derived products and those derived from animal materials –through vendor certification, incoming QA inspection and QC testing. Recombinant and “non-animal origin” materials should be used wherever practicable throughout all processing steps; however, viruses have been found to contaminate non-animal raw materials due to exposure during raw material storage, either at the raw material vendor or at the manufacturing site due to adventitious viral contamination. Also, mycoplasma that can replicate in mammalian cell culture often havea plant source and may be a contaminant in plant peptones. Since mycoplasma contamination can also be due to humans, proper gowning and personal hygiene are critical to control contamination. Additionally, sterilization of equipment used in cell culture, fermentation and finished product manufacturing may provide additional assurance of product that is free of viruses and mycoplasma.

11.6.1 控制步骤

虽然病毒清除工艺步骤，检测未加工半成品中的病毒及支原体，不使用可能含有病毒、支原体和朊

粒的原料是主要的控制手段，但在某些情况下可能仍需要特殊设计的清洁程序。其中原料控制是关键，通过供应商的证明，进厂QA检查及QC的检验进行控制，特别是对血浆，源于血浆的产品及动物源原料。在可能的情况下，工艺的任何阶段都应使用重组及非动物源的原料；但是曾经发现非动物源的原料在储存期间由于暴露而被病毒污染，不论是在供应商处还是生产厂家都有可能污染外来病毒的可能性。同时，可在哺乳动物的细胞培养物中增殖的支原体通常来自于植物，可能是植物蛋白的一种污染物。支原体污染也可能来自于人，因此适当的更衣及个人卫生对控制污染非常关键。另外，对用于细胞培养，发酵及成品生产的设备进行灭菌也可进一步保证产品无病毒及支原体。

11.6.2 Control by Cleaning

Equipment cleaning using caustics and/or acids at appropriate ranges for the cleaning parameters of time, temperature, concentration and action is also essential to successful biocontamination control. The use of cleaning solutions containing sodiumor potassium hydroxide is widely practiced in the industry. NaOH has been shown to be effective for inactivating most viruses. A U.S. FDA/CBER guidance provides a regulatory perspective on prion inactivation methods:

“TSE agents are quite resistant to most disinfecting regimens. There is no current consensus on specific details of decontamination requirements for blood products. However, methods of destruction of TSE-implicated material include steam autoclaving at 132°C for 1-4 hours, incineration, or treatment with 1 N NaOH or concentrated sodium hypochlorite for at least 1 hour. These treatments are known to diminish (but may not completely eliminate) infectivity.” ***(21)***

11.6.2 清洁控制

使用腐蚀性和/或酸性溶剂对设配进行清洗时，适当范围内的清洁参数包括时间、温度、浓度和功能也是控制生物污染的关键。含有氢氧化钠或氢氧化钾的清洁剂已被广泛应用。氢氧化钠对大部分的病毒都具有灭活的效果。美国FDA/CBER的一篇指南提供了对朊粒灭活方法的官方视点：

“TSE对大多数的消毒方法都具有很强的耐受性。目前对于血液制品的净化要求没有统一的意见。然而，通过132°C下蒸汽灭菌1-4个小时、焚烧或使用1N的氢氧化钠溶液或浓次氯酸钠溶液处理1小时以上的方式可以破坏TSE相关物。这些方法都可以降低传染性（虽然可能不能完全消除）”。

11.6.3 Conclusion

Although cleaning processes are generally not designed to remove viral, mycoplasma or prion contaminants, a well-designed, robust cleaning procedure can be an effective process partner in a facility’s overall biocontamination control strategy.

11.6.3 结论

虽然清洁程序的设计通常并不用于去除病毒，支原体及朊粒，但一个设计完善，健全的清洁程序可以成为工厂生物全面污染控制策略的有效部分。

11.7 Single-Use Equipment

Single-use equipment or components may be considered in place of reusable equipment that requires cleaning. Single-use technology has significantly evolved over the lastdecade and is being rapidly implemented in biopharmaceutical manufacturing since the introduction of the single-use bioreactor. Single-use equipment may include anything from carboys, storage bags, bioprocess containers, filter systems, tubing and connection devices to bioreactors. Many of these components are available presterilized (e.g., by gamma irradiation). Such single-use items offer possibilities to simplify the handling of critical process steps and significantly reduce contamination risks, especially for multiproduct facilities and for contract manufacturers. The economic and operational advantages of single-use equipment stem largely from eliminating cleaning and sterilization, reducing the utilities that support these operations, and enabling rapid equipment setup and turnaround.

11.7 一次性设备

一次性设备或部件可以用来代替需要清洁的重复性使用设备。一次性技术在过去的十年中有了显著的发展，自从引入一次性生物反应器以来，一次性技术被快速的运用于生物制药的生产。
一次性设备包括各种玻璃瓶、储藏袋，生物工艺容器，过滤系统，管路，连接装置及生物反应器。其中许多部件都可以事先灭菌（如通过伽马射线）。这些一次性工具为简化关键工艺步骤的操作及显著降低污染风险提供了可能，特别是对于多品种生产设施及合同生产商。一次性设备在经济及操作方面的优势很大程度上要归功于它可以省略清洁及灭菌步骤，从而减少此类设施的使用，并可加快设备的组装及周转。

Along with the benefits of single-use equipments, there are risks and limitations to consider. Most single-use items are polymeric materials. All polymeric product-contact materials and components used in cGMP manufacturing must be assessed to determine if the polymer is safe, and if it is compatible with the solution it is in contact with. Thorough evaluation of potential extractables and leachables is necessary to ensure the safety and quality of the drug product and to maintain compliance with appropriate regulatory requirements for extractables/leachables. Most companies address this as part of process validation and/or qualification of the single-use item.

伴随着一次性设备的优势，一次性设备也存在需要考虑的风险及局限性。大多数的一次性设备都是聚合物材质。所有用于cGMP生产的直接接触产品的聚合物材料和部件都需要评估其安全性以及和与其所接触的溶液的相容性。需要彻底评估潜在的浸出物和可提取物以确保产品的安全性及质量并保持和浸出物和可提取物的相关法规的一致性。大多数公司都将此评估作为工艺验证和/或一次性设备确认的一部分。

11.8 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 quality and performance attributes of raw and in-process materials and processes, with the goal of ensuring final product quality.” ***(22)***

The U.S. FDA further notes that “the term ‘analytical’ in PAT is viewed broadly to include chemical, physical, microbiological, mathematical, and risk analysis conducted in an integrated manner.” Much has been published about PAT in general and about PAT in many processes; the reader should consult those references for general background on PAT. However, there are limited publications about PAT in cleaning processes and cleaning validation ***(23-26)*** as compared to PAT for other manufacturing operations. The emphasis for PAT here is for the use of a feedback loop from the analytical measurement to control a cleaning process or cleaning process step. It should be noted that consistent with PAT principles, the timely measurement could be in-line, on-line or at-line.

“Timely measurements” have long been used in cleaning processes to assist in the design of *rinse cycle times* in automated CIP systems, including those in the biotechnology industry. For example,a common practice in the design of the rinsing process has been to measure conductivity of thefinal rinse as a function of rinse time. Conductivity is a useful parameter for this determination,since cleaning in biotechnology manufacturing usually involves highly alkaline and/or acidic cleaningagents, which possess significant conductivity (in addition to the conductivity of the manufacturedproduct and/or its degradants). If evaluated over several cleaning process runs in the design phase, aminimum time to consistently complete the rinsing process can be effectively determined. A safetyfactor (additional time) may be included as part of this determination. While such a study in thedesign phase would be appropriate for a PAT application, unless it combines the timely measurementwith a feedback mechanism to control the cleaning process during commercial cleaning processes, itwould not be considered PAT. As described *in this paragraph*, the purpose of the timely measurementis not to control the rinsing process, but to assist in selecting a *fixed* rinse time.

11.8 过程分析技术

美国FDA将过程分析技术定义为一个系统，即作为生产过程的分析及控制，依据生产过程中的即时检测(也就是过程中检测)，关键质量参数的控制，原材料和中间产品质量的控制及生产过程，确保最终产品质量达到认可质量标准的程序。

美国FDA进一步指出过程分析技术中“技术”一词广义上被视为集合了化学、物理、微生物、数学及风险分析的综合分析方法。对于PAT有很多基础性资料及不同工艺下PAT的应用，读者可以通过阅读相关资料了解PAT的整体背景。然而，相对于生产过程，关于清洁程序和清洁验证的PAT资料却很少。本文强调的是，PAT是通过分析技术的回馈机制控制清洁程序或某一步骤的方法。需要说明的是与PAT技术的原则相一致，即时测量可以是在线，原位或就地测量。

“即时测量”在清洁程序中的应用已经很久，用于协助设计自动在线清洁系统的淋洗周期，包括在生物技术领域的应用。例如，一个常见的应用为设计淋洗程序时通过测量最终淋洗水的电导率考察淋洗时间。电导率在此处是一个有用的参数，因为生物技术生产后的清洗通常会使用强酸强碱性清洗剂，清洗中会产生高电导率（包括产品本身和/或其降解产物产生的电导率）。如果在设计阶段考察若干组清洁程序的运行，可以有效的确定清洁程序需要的最少时间。并且测定时可以考虑引入安全系数（额外的时间）。然而只有在正式清洁程序中加入即时测量的反馈机制以控制清洁程序，此时在设计阶段的研究才是过程分析技术的应用，否则不能被视为过程分析技术。本段的例子中，即时测量的目的不是为了控制清洁程序，而是用于确定固定的淋洗时间。

11.8.1 PAT for Cleaning Process Control

The more relevant use of PAT for cleaning processes is the use of a timely measurement to define the completion of a cleaning process step. In this case, the achievement of a certain analytical measurement is a controlling mechanism for completion of that step. In the situation referred to previously about measuring conductivity online, if it is possible to determine that the achievement of a certain conductivity correlates 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 that predetermined conductivity value. In addition, consistent with PAT principles, it would be expected that the achievement of that conductivity value would be within a defined time window. The U.S. FDA PAT guidance states “Within the PAT framework, a process end point is not a fixed time; rather it is the achievement of the desired material attributes. This, however, does not mean that process time is not considered. A range of acceptable process times (process window) is likely to be achieved during the manufacturing phase and should be evaluated, and considerations for addressing significant deviations from acceptable process times should be developed.”***(22)*** For example, achievement of a desired conductivity in a very short time could be due to insufficient cleaning solution in the cleaning process. Achievement of the desired conductivity in a very long time may be the result of a clogged spray device. In both cases, a final conductivity is recorded and a final rinse time is recorded. However, in the traditional approach time is the step-controlling parameter, and conductivity is the monitoring parameter. In a PAT approach, conductivity could be the step-controlling parameter, and time would be the monitoring parameter.

清洁程序中和PAT最相关的应用是利用即时测量以确定清洁程序的完成。此应用下，确定的某种分析方法是步骤完成的控制机制。之前提到的在线测定电导率，如果可以将电导率与淋洗程序的结束建立关联，电导率就可能应用于PAT方法。此时，淋洗时间不是固定的，而是会随到达预设的电导率时使用的时间而不断变化。另外，与PAT原则保持一致，到达预设电导率的时间应该有一个确定的范围。美国FDA的PAT指南指出“PAT框架下，工艺结束点没有固定的时间；而是通过获得预期的参数值确定。但这并不意味着可以不考虑工艺时间。生产中应有可接受的工艺时间范围（工艺窗口）并加以评估，并应制定对于严重偏离可接受的工艺时间时的相关规程。

例如，很短时间内就到达预定电导率可能是由于清洁程序缺乏足够的清洁剂引起的。很长时间内才到达预定电导率可能是由于喷雾装置堵塞造成的。以上两种情况下，最终电导率和最终淋洗时间都应被。在传统方法中，时间是作为步骤控制参数而电导率只是监控参数，但在PAT方法中，电导率也可作为步骤控制参数，而时间则作为监控参数。

Sometimes there is an inappropriate objection to the use of PAT in this way, because it seems to violate the cleaning validation principle of not cleaning until clean (or testing until it's clean). However, one of the features of PAT is that traditional rules of what is done for validation may not apply. As noted in the U.S. FDA's PAT guidance, "Systems that promote greater product and process understanding can provide a high assurance of quality on every batch and provide alternative, effective mechanisms to demonstrate validation (per 21 CFR 211.100(a), i.e., production and process controls are designed to ensure quality). In a PAT framework, validation can be demonstrated through continuous quality control whereby the process is continually monitored, evaluated, and adjusted using validated inprocess measurements, tests, controls, and process end points." ***(22)***

对于此种PAT的使用方式有时会有不恰当的反对意见，认为这样做似乎违反了清洁验证的原则，也就是清洁直到干净为止（另一种说法是测试直到干净为止）。然而，PAT的一个特性就是清洁验证的传统理念可能并不适用于PAT。美国FDA的PAT指南指出，"通过系统提升产品及对工艺的理解可以对每批产品提供高度的质量保证并提供了另一种有效的方式达到验证的目的（根据21 CFR 211.100(a)，也就是生产及工艺控制被设计用于保障质量）。在PAT框架下，验证可通过连续的质量控制，即使用验证过的手段、检测、控制及工艺结束点以对工艺进行持续的监控、评估及调整"。

While this example of conductivity as a timely measurement to control the rinse process has been used, there are at least theoretically other opportunities for timely measurement to assist in the cleaning process design. For example, timely TOC measurements during the washing step may be indicative of the minimum time needed to complete the washing step (before rinsing is initiated). By this, it is meant that as proteinaceous soils are removed from the equipment surfaces in the washing step, it would be expected that the TOC in the wash solution would increase and then level off at a time when no more soil is removed (that is, the wash step is complete).

本例说明了电导率可作为即时测量参数控制淋洗程序，理论上其他参数也可应用于清洁程序的设计中。比如，冲洗阶段即时TOC的测量可能对于确定完成冲洗步骤的最短时间有指导意义（开始淋洗前）。它可以显示蛋白质类污垢在冲洗阶段被从设备表面去除，因为冲洗水中TOC的值会先升高，当没有更多的污垢冲洗出来时TOC值则会降低（表明冲洗完成）。

11.8.2 PAT Measurement Tools for Biotechnology Cleaning Processes生物技术清洁程序的**PAT**测试工具

Currently, the most common tools with potential PAT application in biotechnology cleaning processes are conductivity and TOC, because these can be measured online in the cleaning or rinse solution. Surfaces techniques, such as NIR for surfaces, may not be practical for *timely* control, because such techniques involve measuring for residues *after* the cleaning process is completed, not during the cleaning process.

目前，生物技术领域的清洁程序最常见的PAT应用是电导率及TOC，因为对清洗或淋洗溶液可以在线测量。表面分析技术，如近红外可能并不适用于即时控制，因为这类技术需要在清洗结束后检测残留而不是在清洗过程中检测。

Conductivity sensors are readily available for in-line measurements and have been widely used for in-line monitoring (but not necessarily for control). Online TOC does not involve an in-line sensor, but rather a "sipper tube" which diverts a stream from the process piping to the online instrument (U.S. FDA calls this "on-line in a diverted stream"). One concern about the use of TOC in this way is the delay between taking the sample and the output of the actual measurement. Another concern is that if the instrument is

continually taking and measuring samples during a cleaning process, earlier samples with high TOC values may carry over to the following sample and cause a false high reading. Of course, if the process is performed until the desired TOC value is achieved, there is an assurance that the process is adequate, because that possible carryover situation reflects a worst case.

在线电导传感器很容易获得而且已经广泛用于在线检测（并不一定用于控制）。在线TOC并不具备在线传感器，而是通过管路将液体从工艺管路转移至在线仪器（美国FDA称之为“转移流在线”）。这种方式需要考虑取样和实际测试之间的延迟。另外还需考虑在清洗过程中如果仪器连续取样测试，早期高含量TOC的样品可能对之后的样品产生残留效应而造成检测结果偏高。当然，如果清洗一直持续进行，直至达到预期的TOC值，就可保证整个程序是适当的，因为可能的残留代表了最差条件。

11.8.3 Additional Considerations for PAT

PAT的其他考虑

It should be noted that in the conductivity example described in **Section 11.8.1**, all aspects of traditional cleaning validation are not avoided. If conductivity were the measure of a residual cleaning agent, and if only sampling rinse water were acceptable for determining residues of a cleaning agent, a PAT approach of measuring conductivity asa rinse step control parameter would also provide assurance that the cleaning agent was adequately removed for each and every cleaning process. However, it would not address issues of residues of the active and/or bioburden. Those residues would have to be measured in the traditional manner, unless a timely measurement of those residues could be utilized.

必须指出的是，在11.8.1节提到的电导率的例子，传统清洁验证的各个方面都不能避免。如果电导率用量测试清洁剂的残留，而且仅有淋洗水用于测定清洁剂的残留，通过PAT技术测试电导率作为淋洗步骤的控制参数也可提供每一清洁程序中清洁剂是否清洗完全的保证。然而，这不适用于活性物质和/或生物负载的去除。这些残留需使用传统方式测量，除非出现新可针对此类残留的即时测量方式。

It should be clarified that rapid and/or online methods by themselves do not necessarily constitute PAT. As discussed previously, online conductivity can be a routine monitoring tool in a cleaning process step without controlling a process step. Online TOC (other than during the design phase) is not the use of PAT, unless the achievement of a certain analytical measurement of TOC determines and/or controls the completion of a cleaning process step. The same is the case with rapid microbiological methods. Rapid methods may enable one to obtain lab data faster, but unless those measurements determine and/or control the end of a process step, they are just rapid monitoring tools, not PAT tools (although they have the potential to bePAT tools).

需要澄清的是，快速和/或在线检测技术本身并不是PAT。如前所述，在线电导率可以作为清洁程序的常规监测工具而并不控制程序步骤。在线TOC（除了在设计阶段）并不是PAT，除非TOC的测定可以控制清洁程序的完成。这同样适用于快速微生物检测法。快速的方法可以加速获得实验室数据，但只要测定不能控制工艺步骤，它们就仅仅是快速检测工具，而不能称之为PAT工具（虽然它们有成为PAT工具的可能）。

The examples given illustrate the use of PAT for process design and for process step completion. In an ideal world, PAT would be used for real-time release of cleaned equipment and would be used instead of cleaning validation. However, at this time the tools to utilize PAT to confirm that equipment surfaces are appropriately clean (measuring removal of active, cleaning agent, bioburden and endotoxin in the case of biotechnology manufacturing) have not been adequately developed to enable real-time release for cleaning biotechnology equipment.

以上的例子描述了在工艺设计及工艺步骤完成时应用PAT。理想情况下，PAT可用于清洁设备实时放

行从而取代清洁验证。但现实状况是目前使用PAT以确认设备表面的清洁（在生物技术生产中测量活性物质，清洁剂，生物负载及内毒素）还不足以支持生物技术设备清洁的实时放行。

11.9 Product Changeover产品转换

Much biotechnology manufacturing involves campaigning. In a campaign, the same product is made again and again. However, typically between each batch in a campaign, validated cleaning is performed. At the end of a campaign, some additional steps may be taken to prepare the equipment for the subsequent campaign of a *different* product. This extra precaution typically involves performing an additional cycle of the same validated cleaning process used for cleaning between batches in a campaign. Because of concern about possible migration of residues (particularly product active) into gasket materials, or more accurately, into the interstices between gaskets and stainless steel surfaces, changeover of soft parts such as gaskets may also be done after the initial cleaning. During changing of soft parts, a more comprehensive visual examination of the equipment surfaces is made. Following reassembly of the equipment, the validated cleaning process is repeated. Routine monitoring of both the initial cleaning and the final cleaning is performed as is normally done. Some companies also might perform a specific analytical test (such as an ELISA procedure) as an extra check for the previous active protein in the final rinse water of the second cleaning. It should be recognized, however, that the likelihood of any native protein surviving one cleaning process, much less two cleaning processes, is very remote.

很多生物技术生产涉及连续生产。连续生产时，相同的产品不断被生产。然而，通常在连续生产时批次间会进行已验证过的清洁。连续生产结束后，可能会有额外的措施来为接下来不同产品的生产做准备。额外的措施通常包括将批次间已验证过的清洁方法重复运行一次。由于残留（特别是活性产物）可能会迁移至垫片处，确切的说是垫片和不锈钢表面之间的缝隙中，首次清洗后可能需要更换软性部件，如垫片。更换软性部件时，应对设备表面进行更全面的目视检查。设备重新组装后，应重复已验证的清洁规程。对首次及末次清洗的常规监测应像往常一样进行。一些公司可能还会进行特殊的测试（如ELISA）作为对二次清洗时最终淋洗水中活性蛋白的额外检查。需要认识到的是，在一次清洗后残留下来的天然蛋白在二次清洗后仍然残留的可能性是微乎其微的。

An alternative is not to change out those soft parts based on data showing no migration of residues into interstices between gaskets and stainless steel surfaces or analysis based on potential carryover. Such data can be based on studies on commercial equipment, on scale-up equipment, and/or in a laboratory simulation. In such cases, one validated cleaning cycle is used both between batches of one campaign and for a campaign changeover.

另一种办法是不更换软性部件，但需要数据支持残留不会进入垫片和不锈钢表面之间的缝隙或基于对潜在残留的分析评估。数据可以基于对生产设备的研究，等比例大规模设备和/或通过实验室模拟的方式。此种情况下，连续生产中批次之间的清洗和不同品种生产间的清洗采用同一种清洗方法。

Certain equipment is generally dedicated to a given product. This includes chromatography resins and ultrafilters. Cleaning may be done on these items within a campaign; however, at the end of the campaign the resins and ultrafilters are cleaned, but typically are not used for campaigns involving different products.

某些设备通常专门用于某种产品，如色谱树脂和超滤。清洗可能在连续生产后进行；然而，连续生产结束后树脂和超滤被清洗后，通常不会用于不同产品的连续生产。

11.10 Clean Hold Considerations

Following cleaning, equipment that is to be reused should be stored in a manner to protect it from contamination during storage. Criteria used to determine acceptability of storage conditions may include lack of bioburden proliferation, endotoxin level and visual examination. A major regulatory concern is the

control of bioburden proliferation during the storage of equipment. Even if equipment is sterilized prior to use, it is prudent to measure bioburden after the clean hold time to ensure that the subsequent sterilization is not excessively challenged. This is also important from the standpoint of the control of pyrogens from gram-negative bacteria, which may not be removed or inactivated by sterilization processes. ***(8)*** Storage instructions should be specified in a control document, such as the cleaning procedure or approved storage procedure.

清洁后，设备再次使用前应该以合适的方式放置以保证不被污染。衡量放置条件的标准可包括没有生物负载的增仓、内毒素水平及目视检查。一个官方的主要考虑点是设备放置期间生物负载的增长。即使设备在使用前会灭菌，在清洁保持时间后测量生物负载仍是稳妥的方法，以此确认之后的灭菌不会过于有挑战性。这对于热原的控制也非常重要，因为热原有可能在灭菌时没有去除或失活。必须有相关的文件规定设备放置的说明，比如写入清洁规程或批准的放置规程中。

The best procedures are to store cleaned equipment in a dry state or in a solution that inhibits the proliferation of bioburden. If equipment is to be stored in a dry state, manufacturing controls should be in place to ensure that equipment is sufficiently drained and dried upon completion of the cleaning process, 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 manner to prevent external recontamination. If stored in a dry state (that can be unequivocally established as dry), and if protected from external contamination, formal studies to demonstrate lack of bioburden proliferation may not be necessary. Based on sound scientific principles, bioburden will not proliferate on clean, dry surfaces. If stored in an inhibiting solution, the solution should be known to inhibit bioburden growth (such as dilute caustic) or data should be developed to demonstrate inhibition.

清洁后的设备放置时最好保持干燥状态，或者储存在可以防止微生物繁殖的溶液中。如果设备将保持在干燥状态，须有相应的生产控制保证设备充分排干并在清洗完成后干燥完全，同时尽量减少清洁完成后设备在冷却过程中冷凝水的聚集。另外，设备放置时最好能够防止外界的二次污染。如果设备干燥放置（需明确证实干燥状态），同时能避免外界污染，就可能不需要针对生物负载增殖的正式的研究。因为基于合理的科学原则，生物负载在干净并干燥的表面不会增长。如果存储在抑制剂中，需使用已知可以防止微生物生长的溶液（如稀碱溶液）或有数据支持其抑制作用。

If the equipment is stored with a possibility of water in all or parts of the equipment, there are two common strategies to control microbial proliferation during the storage of equipment. One strategy is to establish an acceptable time between the end of cleaning and the beginning of the next use (which may be sterilization, sanitization, or a manufacturing process step) by performing a clean hold validation. After a predetermined storage time, sampling by a suitable method is performed and the post-hold data is compared to the data at the beginning of storage. If rinse sampling is used, it should be ambient temperature water so that whatis measured is the bioburden remaining on surfaces (the use of a hot water rinse may reduce the bioburden in the rinse solution). Bioburden (and possibly endotoxin) levels in the equipment are measured to ensure that levels would not challenge the sterilization or sanitization procedures or exceed in-process manufacturing specifications.

如果仪器放置时内部部分或全部可能存有水，有两种常用的策略来控制微生物的繁殖。一是设置清洁结束后到下次使用（可能是灭菌、消毒或生产）前的时间，这需要通过验证确定。在一个预定的放置时间后，通过合适的方法取样，检测结果与放置前的结果相比较。如果使用淋洗水，必须在室温下，以保证测定的是残留在表面的生物负载（使用热水可能会降低生物负载水平）。测量设备的生物负载（可能还需要内毒素）水平，以此保证在此水平下不会对灭菌或消毒产生影响或超出生产中控标准。

If clean hold validation is not performed, or if the validated clean hold time is exceeded, a validated

water (usually hot water) flush may be used before sterilization, sanitization, or use of the equipment to reduce any microbial proliferation that might have occurred during storage to an acceptable level before further manufacturing or processing on the equipment. After the water flush, sampling (by rinse, swab or plating) is performed. Bioburden (and optionally endotoxin) levels in the equipment are measured to ensure that levels would not challenge the sterilization or sanitization procedures or exceed in-process manufacturing
specifications.
如果没有做过清洁保持验证，或者超出了清洁保持时间，可使用已验证的水（通常是热水）在灭菌、消毒或使用设备前进行冲洗，以此降低放置时可能产生的微生物繁殖，从而在下一步生产或处理时使微生物达到可接受的水平。水冲洗后需要取样（淋洗样、擦拭样或平板）。设备的生物负载（可能还需要内毒素）水平经测试确保不会对灭菌或消毒产生影响或超出生产中控标准。
For clean hold time studies using rinse water being fed from process lines, a few common approaches to establishing the acceptable amount of rinse water to use are based on the minimum working volume of the system or the minimum CIP rinse based on the design. Bioburden values in any rinse sample should be compared to the measured bioburden values based on the equivalent rinse sampling at the beginning of storage. It is preferable to collect the entire volume of rinse solution and agitate it for a specified period of time to ensure homogeneity before collecting the sub-sample for testing.
使用工艺管道的淋洗水做清洁保持时间研究时，通常的几种建立可接受的淋洗水的使用量的方式是基于系统的最小工作容量或设计的最小CIP淋洗量。任何淋洗水样品的生物负载值都需要和放置开始时样品结果对比。建议收集所有的淋洗溶液，搅拌一定时间完全均匀后再二次取样测试。
For buffer and media vessels, when operational controls are in place to minimize bioburden, and when a risk assessment demonstrates that there is minimal risk to product quality as a result of the control procedures, a clean hold validation may not be necessary.
对于缓冲液及培养基容器，当有操作控制可以最大程度降低生物负载并且风险评估表明控制程序可将对产品质量的风险降至最低时，清洁保持验证不是必须的。
Validation of clean hold studies on a given piece of equipment should be able to be applicable to all products using that equipment and to all cleaning processes for that equipment, provided the final state of the cleaned equipment and the storage conditions are consistent. If a validated clean hold time is exceeded, an assessment should be made as to the need for corrective action. Appropriate corrective actions before use or further processing may include cleaning the equipment again using a validated cleaning process or 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, the impact of these changes on the clean hold studies should be evaluated.
对特定设备的清洁保持时间的验证需要覆盖涉及该设备所有的产品品种及设备所有的清洁方式，以证明设备最终清洁后与放置期间状态的一致。如果超出了验证的清洁保持时间，需要评估是否需要纠正措施。再次使用前的适当的纠正措施可能包括使用验证的清洁规程再次清洗设备或使用验证过的热水冲洗以使生物负载达到可接受的水平。当设备，生产工艺和/或清洁规程产生变更时，需要评估变更对清洁保持研究的影响。

12.0 Regulatory Issues

法规问题

Most regulatory documents dealing with cleaning validation do not make any explicit comments about biotechnology manufacturing or about how cleaning validation might be different for biotechnology as compared to other pharmaceutical manufacturing. The general principles laid out in regulatory documents, i.e., limits should be “practical, achievable, and verifiable,”(8) apply equally to biotechnology

manufacturing and small molecule pharmaceutical manufacturing.
大多数法规文件在处理生物制造清洁验证中没有给出明确的结论或没有生物类清洁验证与其他药品的不同点。同时适用于生物技术和小分子药物生产的法规文件的一般原则，即限制应该是“实际、可行和可验证”的（8）。
Below are specific regulatory comments relevant to biotechnology cleaning validation:
下面是生物技术清洁验证相关的具体法规意见：
1.The WHO Working document QS/03.055/Rev.1 includes a statement about the use of ELISA as an analytical technique for biopharmaceuticals. (27) However, that statement is not of much help, since most biopharmaeutcials degrade in the cleaning process.
WHO工作文件QS/03.055/ Rev.1中包含使用ELISA（酶联免疫吸附测定）作为一种生物分析技术的说明。（27）然而由于生物药品在清洁过程中的降解，该说明并没有太大的帮助。
2. The U.S. FDA’s “Q&A on CGMP”(updated 2005) provides a rationale for allowing the use of TOC for cleaning validation purposes. (28) While it does not specifically mention use for biotechnology,the biotechnology industry is among the biggest users of TOC for cleaning validation.
FDA“CGMP问与答”（2005年更新）为允许TOC用于清洁验证提供了理论基础。(28)尽管它没有专门提及用于生物技术，生物技术行业是应用TOC进行清洁验证的最大用户。
3. The U.S. FDA inspection guide for biotechnology has the following statements about “cleaning procedures:”
FDA生物制品检查指南中关于“清洁程序”描述如下：
“Validation of the cleaning procedures for the processing of equipment, including columns, should be carried out. This is especially critical for a multi-product facility. The manufacturer should have determined the degree of effectiveness of the cleaning procedure for each BDP [Biotech-derived product] or intermediate used in that particular piece of equipment.
工艺设备包括柱子，应进行清洁程序的验证。这对于多产品设施尤其重要。制造商应确定每个BDP[生物技术衍生产物]或设备特定区域中间体清洁程序的有效性。
“Validation data should verify that the cleaning process will reduce the specific residues to an acceptable level. However, it may not be possible to remove absolutely every trace of material, even with a reasonable number of cleaning cycles. The permissible residue level, generally expressed in parts per million (ppm), should be justified by the manufacturer. Cleaning should remove endotoxins, bacteria, toxic elements, and contaminating proteins, while not adversely affecting the performance of the column.”(29)
“验证数据应确认清洁程序能将特定残留物降低至可接受水平。但是，即使进行足够次数的清洁，完全去除物料的残留是不可能的。允许的残留物水平，通常用百万分数表示（ppm），应当由生产商合理制定。清洁应能去除内毒素，细菌，有毒元素和杂蛋白，而不对柱的性能产生不利影响。” (29)
Following these two paragraphs are additional commentson cleaning procedure, limit and analytical/sampling issues. However, other than the explicit comment about including residues of bacteria and endotoxin, there is little that is specific to biotechnology manufacturing.
下面这两段是清洁程序中关于限度和分析/采样问题的补充意见。然而不同于对包括细菌和内毒素在内的明确意见，对于特定生物技术制造的意见很少。
4. The U.S. FDA guidance for lyophilization of parenterals states the following:
FDA无菌冻干制剂指南规定如下：
“One could conclude that if contamination is found on a chamber surface after lyophilization, then dosage units in the chamber could also be contaminated. It is a good practice as part of the validation of cleaning of the lyophilization chamber to sample the surfaces both before and after

cleaning."(30)
"人们可以得出这样的结论，如果在冻干后的腔室表面发现污染，那么腔室内的药品也可能被污染。清洁验证中在清洁前后分别取表面样品是一个很好的做法。"(30)
This probably means that if contamination of shelves from external sources (such as hydraulic fluid) is found after lyophilization (and before cleaning), it is likely that the same contaminant is in vials. However, if that is of concern, that is a maintenance issue and probably belongs as part of preventive maintenance rather than cleaning validation. Note that this statement has an implicit assumption that cleaning validation is performed for vial lyophilization.
这可能意味着，如果冻干后（清洁之前）在板框上发现有外源性污染（例如液压流体），它很可能同样污染了药品瓶。但如果这是令人关注的，这是一个维护问题，可能属于预防性维护的一部分而不是清洁验证。注意这种说法有一个隐含的假设即清洁验证是针对冻干药品瓶进行的。
5. The Health Canada, Health Products and Food Branch Inspectorate Guidance, Cleaning Validation Guidelines (11) states the following about biotechnology manufacturing:

加拿大卫生部，健康产品和食品监督局指南，清洁验证指南(11)对于生物技术制造说明如下：
"Relevant process equipment cleaning validation methods are required for biological drugs because of their inherent characteristics (proteins are sticky by nature), parenteral product purity requirements,the complexity of equipment and the broad spectrum of materials which need to be cleaned."
"生物药品相关工艺设备的清洁验证方法是必需的，因为它们的固有特性（蛋白性质粘稠）、非经胃肠道给药的纯度要求、设备的复杂性以及被清洁物料的广谱生物活性"。
It furthermore states the following about bracketing (grouping) for biotechnology manufacturing:
对包括（分类）生物技术制造的进一步声明：
"For biological drugs, including vaccines, bracketing may be considered acceptable for similar products and/or equipment provided appropriate justification, based on sound, scientific rationale is given.Some examples are cleaningof fermentors of the same design but with different vessel capacity used for the same type of recombinant proteins expressed in the same rodent cell line and cultivated in closely related growth media; a multi-antigen vaccine used to represent the individual antigen or other combinations of them when validating the same or similar equipment that is used at stages of formulation (adsorption) and/or holding. Validation of cleaning of fermentors should be done upon individual pathogen basis."
"对于生物药品，包括疫苗，当能给定基于完善、科学合理的依据时，可以考虑接受相似的产品和/或设备。一些案例是清洗基于相同设计但容量不同的、用于在密切相关的培养介质中培养的相同类型啮齿动物细胞系重组蛋白的发酵罐；多抗原疫苗用于代表个体抗原或在提取（吸附）和/或保持工序验证相同或相似设备的抗原组合。发酵罐的清洁验证应在个体病原体的基础上进行。"
6. ICH Q7 Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients (10) contains in Section 18.0, "Specific guidance for APIs manufactured by cell culture/fermentation."It provides GMP guidance on the cell culture/fermentation manufacturing process for biotechnological product and some small molecules.
ICH Q7 原料药GMP指南(10)包含在章节18.0，"通过细胞培养/发酵生产制造原料药的特殊指南。"它提供了采用细胞培养/发酵工艺生产的生物产品和一些小分子药物的GMP指南。
At the beginning of the section, it states that,"in general, the degree of control for biotechnological processes used to produce proteins and polypeptides is greater than that for classical fermentation processes."It further explains that,"APIs produced by classical fermentation are normally low molecular

weight products such as antibiotics, amino acids, vitamins, and carbohydrates."
该章节开始部分指出，"总的来说，对用于蛋白质和多肽生产的生物技术工艺的控制，比经典的发酵工艺更严格。"。它进一步解释，"采用经典发酵工艺生产的原料药通常是低分子量产品，如抗生素，氨基酸，维生素，和糖类。"
Q7 states the following regarding equipment cleaning for cell culture/fermentation:
ICH Q7关于细胞培养/发酵设备清洁的声明如下：
"Cell culture equipment should be cleaned and sterilized after use. As appropriate, fermentation equipment should be cleaned, sanitized, or sterilized."
"Shared (multi-product) equipment may warrant additional testing after cleaning between product campaigns, as appropriate, to minimize the risk of cross-contamination."
"细胞培养设备使用后应清洗并灭菌。必要时发酵设备应清洗、消毒或灭菌。"
"共用（多产品）设备换品种清洁后，适当的情况下可进行额外测试以减少交叉污染风险。"
Q7 states the following regarding equipment cleaning for harvesting, isolation and purification:
ICH Q7中关于收集、分离和精制设备清洁的声明如下：
"All equipment should be properly cleaned and, as appropriate, sanitized after use. Multiple successive batching without cleaning can be used if intermediate or API quality is not compromised."
"所有设备使用后都应该适当清洁，必要时应消毒。如果不影响中间体或原料药质量，可以连续投料多批后清洁。"
Q7 states the following regarding equipment cleaning for viral removal/inactivation steps:
ICH Q7关于病毒清除/灭活步骤设备清洁的声明如下：
"The same equipment is not normally used for different purification steps. However, if the same equipment is to be used, the equipment should be appropriately cleaned and sanitized before reuse. Appropriate precautions should be taken to prevent potential virus carryover (e.g., through equipment or environment) from previous steps."
"同一台设备通常不用于不同的纯化步骤。然而如果使用同一台设备，该设备再次使用前应进行适当清洁和消毒。应采取适当的预防措施防止前工序病毒残留（例如，通过设备或环境）。"
7. ICH Q5A, Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin states the following regarding validation of column cleaning and regenerating from viral inactivation perspective:
ICH Q5A，来源于人或动物细胞系的生物技术产品的病毒安全性评价中关于从病毒灭活角度验证分离柱的清洁和再生的声明如下：
"Assurance should be provided that any virus potentially retained by the production system would be adequately destroyed or removed prior to reuse of the system. For example, such evidence may be provided by demonstrating that the cleaning and regeneration procedures do inactivateor remove virus."(31)
系统被再次使用前必须保证生产系统中任何可能残留的病毒能被充分灭活或清除。例如，可通过提供证据证实分离柱经过清洗和再生过程确实将病毒灭活或清除了。
While these are specific comments from guidance documents, it should be recognized that regulatory inspectors may (and should) have additional expectations for cleaning validation in biotechnology based on current industry practices and on their past experience with similar companies.
虽然这些都是指南文件中的具体意见，但应该认识到基于现行的行业实践及过去在类似公司的经验，检查员可能（而且应该）对生物技术行业的清洁验证有额外期望。
13.0 References 参考文献
不翻译

14.0 Suggested Reading 推荐阅读

不翻译

15.0 Appendix-Carryover Calculations 附录-残留计算

Note: In the calculation examples that follow, the recovery based on sampling (percent recovery) is not included. For companies that utilize the sampling recovery to"correct"the limit, that factor should be included in their calculations.

注：在后面的计算实例中，不包括基于取样的回收（回收率）。对于利用取样回收率修正限度的公司，该因素应包括在他们的计算中。

Example 1:This example is based on the dose of the active for formulation/fill manufacturing. It is based on a 1/1000 minimum therapeutic daily dose of the cleaned active.

例1：本例是基于制剂/填充生产中活性成分的剂量。它基于被清洁活性成分最小日治疗剂量的1/1000。

MinTD: Minimum Therapeutic Daily Dose of the active of cleaned product

MinTD:清洁产品活性成分最小日治疗剂量

MBS: Minimum Batch Size of next drug product made in the same equipment

MBS: 同一设备生产的下一个药品的最小批量

MaxDD: Maximum Daily Dosage of next drug product made in the same equipment

MaxDD:同一设备生产的下一个药品的最大日治疗剂量

SF: Safety Factor

SF: 安全因子

Example for products A and B: if

以产品A和B为例：假设

•MinTD = 25 mg (or 25,000 µg)

•MBS= Minimum Batch Size of the following drug product B = 1000 L

•MaxDD= Maximum Daily Dosage units of drug product B = 10 mL

•SF = 1000

•MinTD = 25 mg (或25,000µg)

•MBS= 下一产品B的最小批量= 1000 L

•MaxDD= 产品B的最大日治疗剂量= 10 mL

SF = 1000

The limit in the next product is calculated by dividing the MinTD by the SF and the MaxDD:

下一产品中残留限度通过MinTD除以SF和MaxDD计算：

$$\text{Limit in next product 下一产品的残留限度} = \frac{25.000\text{ug（MinTD）}}{1000\text{（SF）}\times 10\text{ml（MaxDD）}} = 2.5\mu g/mL$$

Since this calculated value is more stringent than 10 ppm (10µg/g, or approximately 10µg/mL), this value will be used for subsequent calculations.

由于该计算结果比10ppm更严格（10µg/g，或约10µg/mL），后续计算将使用此结果。

The Maximum Allowable Carryover (MAC) is calculated by multiplying the limit in the next product by the MBS:

最大允许残留量（MAC）是由残留限度乘以下一产品的最小批量计算得出：

MAC = 2.5µg/mL×1,000,000 mL =2,500,000µg

The limit per surface area can then be calculated by dividing the MAC by the shared surface area between the two products. Continuing with the same example, if the shared surface area is 120,000 cm2,

then the limit per surface area is:
单位表面积限值可以通过MAC除以两种产品的共线面积来计算。用相同的示例继续，假设共线面积120,000 cm2，则单位表面积限值为：
Limit per surface area单位表面积限值= 2,500,000µg/120,000cm2= 20.8µg/cm2
The limit (mass) per swab can be calculated by multiplying the limit per area by the area swabbed. If the area swabbed is 100 cm2, then the limit per swab is:
每棉签限度可以通过单位面积的限值乘以擦拭面积来计算。假设擦拭面积为100cm2，则每棉签的限值为：
Limit per swab每棉签限度= 20.8µg/cm2×100cm2= 2080µg
The limit in the desorbed swab sample can be calculated by dividing the limit per swab by the amount of solvent (water) used to desorb the swab. If the amount of water used for desorption is 20 mL, the limit in the desorbed swab sample is:
棉签洗脱样品的限度可通过将每棉签限度除以洗脱用溶剂（水）量计算。假设洗脱所用的水量为20mL，洗脱棉签样品的限度为：
Limit in desorbed swab sample棉签洗脱样品限度= 2080µg/20 mL = 104µg/mL (or 104 ppm)
If the active were a protein containing 50% carbon, the TOC limit (net of the blank) would be 52 ppm TOC.
如果活性成分为含碳50％的蛋白质，则TOC法限度（扣除空白）将是52ppm。
Example 2: This example is based on the dose of the active for bulk drug manufacturing, assuming the entire equipment train is shared surface area. It is based on 1/1000 minimum therapeutic daily dose of the cleaned active. [Note: The purpose of this calculation is to illustrate the low TOC levels likely if the carryover calculation utilized the entire bulk active equipment train (excluding dedicated items).]
本例基于原料药制造中活性成分剂量，假设整个培养设备的表面是共用的。它基于被清洁成分1/1000最小日治疗剂量。[注：本计算的目的是为了说明如果残留计算使用整个活性成分培养设备（不含专用项目）时可能的低TOC水平。]
MinTD: Minimum Therapeutic Daily Dose of the active of cleaned product
MinTD:清洁产品活性成分最小日治疗剂量
MBS: Minimum Batch Size of next drug product made in the same equipment
MBS: 同一设备生产的下一个药品的最小批量
MaxDD: Maximum Daily Dosage of next drug product made in the same equipment
MaxDD:同一设备生产的下一个药品的最大日治疗剂量
SF: Safety Factor
SF: 安全因子
Example for products A and B: if
以产品A和B为例：假设
•MinTD = 25 mg (or 25,000µg)
•MBS of the following drug active B = 200 g
•MaxDD= Maximum mass of daily dosage unit of active B = 100 mg (or 0.100 g)
•SF = 1000
•MinTD = 25 mg (或25,000µg)
•MBS= 下一产品B的最小批量= 200g
•MaxDD= 产品B的最大日治疗剂量= 100 mg (or 0.100g)
•SF = 1000
The limit in the next drug active is calculated by dividing the MinTD by the SF and the MaxDD:

在下一产品中活性成分限值通过MinTD除以SF和MaxDD计算：

$$\text{Limit in next product下一产品中限度} = \frac{25.000ug（MinTD）}{1000（SF）x0.100g（MaxDD）} = 250\mu g/g$$

If the default limit for bulk active manufacturing is 50 ppm, and sincethis calculated value is above 50ppm (50µg/g), the value of 50 ppm will be used for subsequent calculations.

如果原料药生产的默认限度为50ppm，并且这个计算出的值高于50ppm（50µg/ g），则结果50ppm将被用于后续计算。

The MAC is calculated by multiplying the limit in the next product by the MBS:

最大允许残留量（MAC）由残留限度乘以下一产品最小批量得出：

MAC 最大允许残留量= 50µg/g×200 g = 10,000µg

The limit per surface area can then be calculated by dividing the MAC by the shared surface area between the two products. Continuing with the same example, the shared surface area is 1,000,000 cm2. Then, the limit per surface area is:

单位表面积限值可以通过MAC除以两种产品的共线面积来计算。用相同的示例继续，假设共线面积1,000,000 cm2，则单位表面积限值为：

Limit per area单位面积限值= 10,000µg/1,000,000cm2= 0.010µg/cm2

The limit (mass) per swab can be calculated by multiplying the limit per area by thearea swabbed. If the area swabbed is 100cm2, then the limit per swab is:

每棉签限度可以通过单位面积的限值乘以擦拭面积来计算。假设擦拭面积为100cm2，则每棉签的限值为：

Limit per swab每棉签限度= 0.010µg/cm2×100cm2= 1.0µg

The limit in the desorbed swab sample can be calculated by dividing the limit per swab by the amount of solvent (water) used to desorb the swab. If the amount of water used for desorption is 20 mL, the limit in the desorbed swab sample is:

棉签洗脱样品的限度可通过将每棉签限度除以洗脱用溶剂（水）量计算。假设洗脱所用的水量为20mL，洗脱棉签样品的限度为：

Limit in desorbed swab sample = 1.0µg/20mL = 0.050µg/mL (or0.050 ppm)

If the active were a protein containing 50% carbon, the TOC limit (net of the blank) would be 0.025 ppm TOC (or 25 ppb). This concentration is not measureable by TOC in cleaningvalidation samples.

如果活性成分为含碳50％的蛋白质，则TOC法限度（扣除空白）将是0.025ppm（或25ppb）。此浓度的清洁验证样品使用TOC方法是不可测量的。

Example 3:This example is based on the toxicity of a cleaning agent for formulation/fill manufacturing.It is based on allowing no more than 1/100,000 of the LD_{50}(mg/kg of body weight in an animal model) of the cleaning agent by an intravenous route in the maximum therapeutic daily dose of the next drug product.

例3：本例基于配制/填充生产用清洁剂的毒性。基于下一产品静脉给药最大日治疗剂量时不超过清洁剂半数致死量的1/100,000（动物试验中mg/kg体重）。

LD_{50}: Lethal Dose for Cleaning Agent

LD_{50}:清洁剂致死剂量（此处待定）

BW: Body Weight of patient taking product B

BW:服用药物B患者的体重

MBS: Minimum Batch Size of next drug product made in the same equipment

MBS: 共线设备生产下一产品的最小批量

MaxDD: Maximum Daily Dosage of next drug product made in the same equipment
MaxDD: 共线设备生产下一产品的最大日剂量
CF: Conversion Factor
CF: 转换因子
Example for cleaning agent A and next product B, if:
以清洁剂A和下一产品B为例，假设：
•LD_{50}= 100 mg/kg
•BW = 60 kg
•MBS = Minimum batch size of the following drug product B = 1000 L
•MaxDD = Maximum daily dosage units of drug product B = 10 mL
•CF = 100,000
Note that the product of the $LD_{50}$and the BW, which is then divided by the CF, is sometimes called the ADI (Acceptable Daily Intake). Some companies may calculate the ADI by first converting the $LD_{50}$to a NOEL (No Observable Effective Level), and then converting the NOEL to an ADI. Either formulation is acceptable and should result in the same ADI value.
注意以产品的LD_{50}和BW除以CF的结果有时也被称为可接受的每日摄入量（ADI）。有些公司可能首先将LD50换为NOEL（无效剂量），然后通过NOEL来计算ADI。任一方式都是可以接受的并应使用同一ADI值计算。
The limit in the next product is calculated by multiplying the LD50 by the BW and dividing the resultant product by the MaxDD and by the CF:
下一产品的限度通过LD_{50}乘以BW除以最终产品的MaxDD和CF计算：

$$\text{Limit in next product} = \frac{\text{100mg/kg（LD50）x60KG（BW）}}{\text{100000（SF）x10ml（MaxDD）}} = 0.006 \text{ mg/mL (or 6µg/mL)}$$

Since thisvalue is more stringent than 10 ppm (10µg/g or approximately 10µg/mL) cleaning agent solids, this calculated value will be used for subsequent calculations.
如果清洁剂的残留固体计算结果严于10ppm（为10µg/ g或约10µg/mL），使用此结果进行后续计算。
The MAC is calculated by multiplying the limit in the next product by the MBS:
最大允许残留量通过下一产品中残留限度乘以最小批量计算：
MAC = 6µg/mL×1,000,000 mL = 6,000,000µg
The limit per surface area can then be calculated by dividing the MAC by the shared surface area. Continuing with the same example, if the shared surfacearea is 120,000cm_2, then the limit per surface area is:
单位表面积限值可以通过MAC除以共线面积来计算。用相同的示例继续，假设共线面积120,000 cm_2，则单位表面积限值为：
Limit per area单位表面积限值= 6,000,000µg/120,000 cm_2= 50µg/cm_2
The limit (mass) per swab can be calculated by multiplying the limit per area by the area swabbed. If the area swabbed is 100cm_2, then the limit per swab is:
每棉签限度可以通过单位面积的限值乘以擦拭面积来计算。假设擦拭面积为100cm_2，则每棉签的限值为：
Limit per swab每棉签限度= 50µg/cm2×100 cm2= 5,000µg
The limit in the desorbed swab sample can be calculated by dividing the limitper swab by the amount of solvent (water) used to desorb the swab. If the amount of water used for desorption is 20 mL, the limit in the desorbed swab sample is:

棉签洗脱样品的限度可通过将每棉签限度除以洗脱用溶剂（水）量计算。假设洗脱所用的水量为20mL，洗脱棉签样品的限度为：
Limit in desorbed swab sample = 5,000µg/20 mL = 250µg/mL (or 250 ppm)
洗脱棉签样品的限度= 5,000µg/20 mL = 250µg/mL (或250 ppm)
It is likely in this situation that the manufacturer would utilize a more conservative value for measuring the cleaning agent. For example, utilizing a conductivity value of 5µS/cm would result in a concentration significantly below 250 ppm for most cleaning agents.
很可能在此情况下制造商将采用一个更保守的值用于测量所述清洗剂。例如，采用电导率结果为5µS/ cm时，大多数清洁剂的浓度将显著低于250ppm。
16.0 List of Acronyms 缩略语表
ADI: Acceptable Daily Intake
ADI:可接受的每日摄入量
BCA: Bicinchoninic Acid
BCA:喹啉酸
CAPA: Corrective and Preventive Actions
CAPA: 纠正与预防措施
CBER: Center For Biological Evaluation and Research
CBER:生物评价与研究中心
CGMPs: Current Good Manufacturing Practices
CGMPs:现行药品生产质量管理规范（美国GMP）
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
CTP: Critical Process Parameters
CPP:关键工艺参数
DOE: Design of Experiments
DOE:实验设计
ELISA: Enzyme-Linked ImmunoSorbent 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
FEP: Fluorinated Etyhlene Propylene
FEP:氟化乙丙烯
FMEA: Failure Mode and Effects Analysis
FMEA:失效模式与效果分析
FTA: Fault Tree Analysis
FTA: 故障树分析

HACCP: Hazard Analysis and Critical Control Points
HACCP:危害分析和关键控制点
HAZOP: Hazard Operability Analysis
HAZOP: 危险与可操作性分析
HPLC: High Performance Liquid Chromatography
HPLC: 高效液相色谱法
ICH: International Conference on Harmonisation
ICH:人用药物注册技术要求国际协调会议
LCD: Liquid Crystal Display
LCD: 液晶显示器
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
NIR: Near Infrared
NIR:近红外
PAT: Process Analytical Technology
PAT:过程分析技术
PCR: Polymerase Chain Reaction
PCR:聚合酶链反应
PETG: PolyEthylene Terephthalate Glycolmodified
PETG:聚对苯二甲酸乙二醇酯
PQ: Performance Qualification (or Process Qualification)
PQ: 性能确认（或工艺验证）
PTFE: PolyTetraFluoroEthylene
PTFE:聚四氟乙烯
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
QRM: Quality Risk Management
QRM: Quality Risk Management
QRM:质量风险管理
RSD: Relative Standard Deviation
RSD: 相对标准偏差
SDS PAGE: Sodium Dodecyl Sulfate PolyAcrylamide Gel Electrophoresis
SDS PAGE: 十二烷基硫酸钠聚丙烯酰胺凝胶电泳
SIP: Steam-In-Place
SIP:在线蒸汽灭菌
SME: Subject Matter Expert

SME: 主题专家
SOP: Standard Operating Procedure
SOP:标准操作程序
TACT: Time, Action, Concentration and Temperature
TACT:时间、作用、浓度和温度
TFF: Tangential Flow Filtration
TFF:切向流过滤
TNTC: Too Numerous To Count
TNTC:无法计数
TOC: Total Organic Carbon
TOC:总有机碳
TSE: Transmissible Spongiform Encephalopathy
TSE: 传染性海绵状脑病
WFI: Water for Injection
WFI:注射用水