Annex 4

附件 4

Supplementary guidelines on good manufacturing practices: validation

药品生产质量管理规范补充指南：验证

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1. Introduction

简介

Validation is an essential part of good manufacturing practices (GMP). It is, therefore, an element of the quality assurance programme associated with a particular product or process. The basic principles of quality assurance have as their goal the production of products that are fit for their intended use. These principles are as follows:
验证是药品生产管理规范（GMP）的一个重要组成部分；也正因如此，所以它同时也是产品或工艺的质量保证计划的一个不可或缺的要素。质量保证的基本原则以生产出符合设计用途的产品为目的，它的主要内容为：

Quality, safety and efficacy must be designed and built into the product.
要事先设计质量、安全和效力，并使之在产品中实现。
Quality cannot be inspected or tested into the product.
不能仅仅只考察和检验成品的质量。

Each critical step of the manufacturing process must be validated. Other steps in the process must be under control to maximize the probability that the finished product consistently and predictably meets all quality and design specifications.
生产工艺的每一关键步骤都必须经过验证，非关键步骤也必须得到控制，从而实现在最大程度上生产出符合全部质量和既定标准的产品的目的。
Validation of processes and systems is fundamental to achieving these goals. It is by design and validation that a manufacturer can establish confidence that the manufactured products will consistently meet their product specifi cations.
工艺和系统的验证是实现上述目标的基础之一。通过对生产的设计和验证，可使生产出的产品持续符合标准，并建立一定的置信区间。

Documentation associated with validation includes:
与验证有关的文件如下：

— standard operating procedures (SOPs)
标准操作规程（SOP）
— specifi cations
合格标准
— validation master plan (VMP)
验证主计划（VMP）
— qualification protocols and reports
确认方案和确认报告
— validation protocols and reports. The implementation of validation work requires considerable resources such as:
验证方案和验证报告。执行验证工作时，需要的资源有：
Time: generally validation work is subject to rigorous time schedules.
*时间：*通常，验证工作必须严格按照时间表的安排开展。
Financial: validation often requires the time of specialized personnel and expensive technology.
*资金：*验证工作的执行常常需要专业人员和昂贵的技术支持。
Human: validation requires the collaboration of experts from various dis-ciplines (e.g. a multidisciplinary team, comprising quality assurance, en-gineering, manufacturing and other disciplines, depending on the product and process to be validated).
*人员：*验证工作的开展要求有不同领域的专家的合作（如一支由来自多个领域的专家组成的验证团队，根据待验证的产品和工艺的要求，包括质量保证、工程、生产和其它领域）。

These guidelines aim to give guidance to inspectors of pharmaceutical manu-facturing facilities and manufacturers of pharmaceutical products on the requirements for validation. The main part covers the general principles of validation and qualification. In addition to the main part, appendices on vali-dation and qualification (e.g. cleaning, computer and computerized systems, equipment, utilities and systems, and analytical methods) are included.
这些指导方针能给药品生产设施的检查员及药品生产商提供关于验证要求的指导。正文部分的内容主要是关于验证和确认，附录中另有其它方面的内容（如清洁、计算机和计算机化系统、设备、公用工程和公用系统、分析方法等）。

2. Scope

范围

2.1 These guidelines focus mainly on the overall concept of validation and are intended as a basic guide for use by GMP inspectors and manufacturers. It is not the intention to be prescriptive in specific validation require-ments. This document serves as general guidance only, and the principles may be considered useful in its application in the manufacture and control of active pharmaceutical ingredients (APIs) and fi nished pharmaceutical products. Validation of specific processes and products, for example in ster-ile product manufacture, requires much more consideration and a detailed approach that is beyond the scope of this document.
这里给出的指导方针主要涵盖了关于验证的所有方面，可供GMP检查员和生产商作为基本指南使用，但不可将本文视作验证要求的专门说明文章；而应当仅将本文视为一般的指南。在递交关于活性药物成分（API）和药物成品的生产和控制资料时，本文列出的基本原则也可作为参考。特定工艺和产品的验证，如灭菌生产，通常需要考虑更多的方面以及详细的方法，本文的内容不足以满足它们的需要。

2.2 There are many factors affecting the different types of validation and it is, therefore, not intended to define and address all aspects related to one particular type of validation here.
验证的类型虽然繁多，但却有许多共同的因素能对之形成影响；因此，本文不会列举和阐述某种特定类型的验证的所有方面。

2.3 Manufacturers should plan validation in a manner that will ensure regulatory compliance and ensuring that product quality, safety and consis-tency are not compromised.
设计验证时，生产商应当要保证验证程序符合法规的要求，并能保证该程序能验证产品的质量、安全和工艺的持续性。

2.4 The general text in the main part of these guidelines may be appli-cable to validation and qualification of premises, equipment, utilities and systems, and processes and procedures. More specific principles of quali-fication and validation are addressed in the appendices. Semi-automatic or fully automatic clean-in-place (CIP) systems and other special cases should be treated separately.
这里列出的指导方适用于平面布局、设备、公用工程和工用系统、工艺和规程的验证和确认，更多的关于验证和确认的专属方法可参见附录；半自动或全自动在线清洁（CIP）系统和其它特殊系统应当单独对待。

3. Glossary

术语

The definitions given below apply to the terms used in these guidelines. They may have different meanings in other contexts.

以下是指导方针中使用的术语的定义；需注意，它们在其他文献中出现时，可能有不同的含义。

calibration

校准

The set of operations that establish, under specified conditions, the relation-ship between values indicated by an instrument or system for measuring (for example, weight, temperature and pH), recording, and controlling, or the values represented by a material measure, and the corresponding known values of a reference standard. Limits for acceptance of the results of measuring should be established.

在规定的条件下，用来建立测量用（例如测量重量、温度和pH值）、记录用、控制用仪器或系统、及物料测量仪器测得的值与已知参照标准的相应值之间的关系的粗操作；在该项操作中，还应建立测量结果的合格限。

computer validation

计算机验证

Documented evidence which provides a high degree of assurance that a computerized system analyses, controls and records data correctly and that data processing complies with predetermined specifi cations.

用以保证计算机化系统可提供正确的分析、控制和记录数据及保证数据处理符合既定标准的文件证明。

Commissioning

试运行

The setting up, adjustment and testing of equipment or a system to ensure that it meets all the requirements, as specified in the user requirement speci-fication, and capacities as specified by the designer or developer. Commis-sioning is carried out before qualification and validation.

根据用户需求说明书所述及设计人员或研发人员的能力，用来保证设备或仪器的装配、调整和测试符合要求，及保证设备或仪器满足其设计和研发人员的要求的活动。试运行应先于确认和验证执行。

concurrent validation

同步验证

Validation carried out during routine production of products intended for sale.

针对销售产品的常规生产过程进行的验证。

cleaning validation

清洁验证

Documented evidence to establish that cleaning procedures are remov-ing residues to predetermined levels of acceptability, taking into con-sideration factors such as batch size, dosing, toxicology and equipment size.

在考虑了批量、剂量、毒理学和设备大小因素的前提下，用以表明清洁方法去除残余物的能力可满足既定合格标准的文件证明。

design qualification (DQ)

设计确认（DQ）

Documented evidence that the premises, supporting systems, utilities, equipment and processes have been designed in accordance with the re-quirements of GMP.
用以表明厂房建筑、支持系统、公用工程、设备和工艺的设计符合GMP要求的证明文件。

good engineering practices (GEP)
工程设计规范（GEP）
Established engineering methods and standards that are applied throughout the project life-cycle to deliver appropriate, cost-effective solutions.
对于项目的整个运作周期，建立了工程方法和技术标准来设计适当且又低本高效的解决方法。

installation qualification (IQ)
安装确认（IQ）
The performance of tests to ensure that the installations (such as machines, measuring devices, utilities and manufacturing areas) used in a manufactur-ing process are appropriately selected and correctly installed and operate in accordance with established specifi cations.
为证明某一生产工艺中使用到的设备（如设备、测量仪器、公用工程和生产区域）的安装地点的选择、设备的安装和运行达到设定的要求而进行的各种运行试验。

operational qualification (OQ)
运行确认（OQ）
Documented verification that the system or subsystem performs as intended over all anticipated operating ranges.
为证明系统或系统的组成设备达到设定的运行要求而进行的文件化确认工作。

performance qualification (PQ)
性能确认（PQ）
Documented verification that the equipment or system operates consistently and gives reproducibility within defi ned specifications and parameters for prolonged periods. (In the context of systems, the term “process validation” may also be used.)
为证明设备或系统可长期实现设计性能的文件化确认工作，如正确运转并表现出良好的再现性。（就系统而言，性能确认即“工艺验证”。）

process validation
工艺验证
Documented evidence which provides a high degree of assurance that a specific process will consistently result in a product that meets its predeter-mined specifications and quality characteristics.
为证明某工艺可持续生产出符合既定标准且拥有规定的质量特性的产品的文件化工作。

prospective validation
前验证
Validation carried out during the development stage on the basis of a risk analysis of the

production process, which is broken down into individual steps; these are then evaluated on the basis of past experience to determine whether they may lead to critical situations.
在生产工艺投入使用前的研发阶段开展的验证工作；它通常以风险分析为基础，并被分解为单个步骤来验证。根据过去的经验对前验证进行评估，判断该工艺是否会导致关键情况的出现。

qualification

确认

Action of proving and documenting that any premises, systems and equip-ment are properly installed, and/or work correctly and lead to the expected results. Qualification is often a part (the initial stage) of validation, but the individual qualification steps alone do not constitute process validation.
为证明所有厂房建筑、系统和设备均正确安装且/或正确运行，并能实现预期结果的文件化证明活动。确认常常是验证的（起始阶段的）一个部分，但单独的确认步骤不是验证。

retrospective validation

回顾性验证

Involves the evaluation of past experience of production on the condition that composition, procedures, and equipment remain unchanged.
在产品组成、操作规程和设备不发生改变的情况下，评估分析生产的历史数据。

revalidation

再验证

Repeated validation of an approved process (or a part thereof) to ensure continued compliance with established requirements.
重复对获准工艺（或工艺的某个部分）的验证，以证实已验证状态没有发生漂移、工艺依然符合既定要求。

standard operating procedure (SOP)

标准操作规程（SOP）

An authorized written procedure giving instructions for performing opera-tions not necessarily specific to a given product or material but of a more general nature (e.g. equipment operation, maintenance and cleaning; vali-dation; cleaning of premises and environmental control; sampling and in-spection). Certain SOPs may be used to supplement product-specifi c master batch production documentation.
具有约束力的书面规程，它描述了如何进行操作。标准操作规程所针对的内容广泛，其中包括但不限于给定的产品或物料（还可用来说明如设备的操作、维护和清洁；验证；厂房建筑的清洁和环境控制；取样和检查等）。某些特定的SOP可视为某些产品专属的批生产主文件的补充部分。

validation

验证

Action of proving and documenting that any process, procedure or method actually and consistently leads to the expected results.
为证明工艺、程序或方法在实际使用中能持续实现预期结果的文件化证明活动。

validation protocol (or plan) (VP)

验证方案（或计划）（VP）

A document describing the activities to be performed in a validation, in-cluding the acceptance criteria for the approval of a manufacturing process — or a part thereof — for routine use.

一个阐述如何进行对常规生产工艺——或生产工艺的一部分——进行验证并确定其验证合格标准的文件。

validation report (VR)

验证报告（VR）

A document in which the records, results and evaluation of a completed validation programme are assembled and summarized. It may also contain proposals for the improvement of processes and/or equipment.

已完成的验证方案的记录、结果和评估文件。它常常包括工艺和/或设备的改进措施的内容。

validation master plan (VMP)

验证主计划（VMP）

The VMP is a high-level document that establishes an umbrella validation plan for the entire project and summarizes the manufacturer's overall phi-losophy and approach, to be used for establishing performance adequacy. It provides information on the manufacturer's validation work programme and defines details of and timescales for the validation work to be performed, including a statement of the responsibilities of those implementing the plan.

VMP是整个项目工程的验证计划的概述文件，它总结了生产商采用的所有方法，可用来证明性能的完备能力。验证主计划里有关于生产商的验证计划的资料，待执行的验证工作的时间表，还包括执行验证计划的人员的职责。

verification

核查

The application of methods, procedures, tests and other evaluations, in ad-dition to monitoring, to determine compliance with the GMP principles.

为检查GMP条例的落实力度，而使用的除监控之外的方法、程序、试验和其它评估分析措施。

worst case

最差状况

A condition or set of conditions encompassing the upper and lower processing limits for operating parameters and circumstances, within SOPs, which pose the greatest chance of product or process failure when compared to ideal con-ditions. Such conditions do not necessarily include product or process failure.

系指导致产品或工艺失败的概率高于正常运行工艺的某个条件或一组条件（包括SOP中规定的运行参数和状态的上限和下限），这些状况不一定包括产品或工艺的失败。

4. Relationship between validation and qualifi cation

验证和确认之间的联系

Validation and qualification are essentially components of the same concept. The term qualification is normally used for equipment, utilities and systems, and validation for processes. In this sense, qualification is part of validation.
验证和确认系同一概念的基本组成部分，即是说它们是同义词。“确认”这个词往往用在设备、公用工程和系统以及工艺验证中；在这层意义上，确认是验证的一部分。

5. Validation

验证

5.1 Approaches to validation
验证方法

5.1.1 There are two basic approaches to validation — one based on evi-dence obtained through testing (prospective and concurrent validation), and one based on the analysis of accumulated (historical) data (retrospective validation). Whenever possible, prospective validation is preferred. Retro-spective validation is no longer encouraged and is, in any case, not appli-cable to the manufacturing of sterile products.
验证有两种基本方法——其一是以试验（前验证和同步验证）获取的证据为基础，另一种则以积累的（历史）数据（回顾性验证）为基础。验证时，应当尽可能的使用前验证，而不鼓励执行回顾性验证；要特别指出的是，无论何时，回顾性验证都不适用于无菌产品的生产。

5.1.2 Both prospective and concurrent validation, may include:
前验证和同步验证可能包括的内容如下：

- extensive product testing, which may involve extensive sample testing (with the estimation of confidence limits for individual results) and the demonstration of intra- and inter-batch homogeneity;
大量产品测试，包括大量的样品测试（以及单个结果的置信限的评估）和批间及批内均一性的证明；
- simulation process trials;
模拟生产试验；
- challenge/worst case tests, which determine the robustness of the process; and
挑战性/最差状况试验，以证明工艺的耐用性；以及
- control of process parameters being monitored during normal production runs to obtain additional information on the reliability of the process.
监控正常运行的生产过程的工艺参数的控制措施，以获取可证明该工艺的可靠性的资料。

5.2 Scope of validation
验证范围

5.2.1 There should be an appropriate and sufficient system including organizational

structure and documentation infrastructure, sufficient personnel and financial resources to perform validation tasks in a timely manner. Management and persons responsible for quality assurance should be involved.
为了及时执行验证工作，应当建立一个适当且能满足需要的系统，包括组织机构和文件管理的下层组织结构、充足的人力和财政资源，同时还应指定质量保证的管理和责任人。

5.2.2 Personnel with appropriate qualifications and experience should be responsible for performing validation. They should represent different departments depending on the validation work to be performed.
执行验证工作的人员应当具备相应的资格和经验，并对验证负责。根据待执行的验证工作的需要，决定由哪些部门的人员参与验证工作的执行。

5.2.3 There should be proper preparation and planning before validation is performed. There should be a specific programme for validation activities.
执行验证之前，应有充分的准备和计划。应针对具体的验证活动，制订专门的计划。

5.2.4 Validation should be performed in a structured way according to the documented procedures and protocols.
应根据成文的程序和方案，以设计好的方式执行验证工作。

5.2.5 Validation should be performed:
验证应：

— for new premises, equipment, utilities and systems, and processes and procedures;
在新的厂房建筑、设备、公用工程和系统、工艺和方法上执行；
— at periodic intervals; and
定期执行；
— when major changes have been made.
在发生了重大变更后执行。

(Periodic revalidation or periodic requalification may be substituted, where appropriate, with periodic evaluation of data and information to establish whether requalification or revalidation is required.)
（在适当的情况下，可用数据和资料的定期评估代替定期再验证或定期再确认，以确定是否需要进行再验证或再确认。）

5.2.6 Validation should be performed in accordance with written protocols. A written report on the outcome of the validation should be produced.
应根据书面方案执行验证。验证的结果应当以书面报告的形式给出。

5.2.7 Validation should be done over a period of time, e.g. at least three consecutive batches (full production scale) should be validated, to demon-strate consistency. Worst case situations should be considered.
验证项目的执行时间的设定应能证明验证对象的持续性。如验证应当至少在三个连续批上开展（生产规模）。验证时，要考虑最差状况。

5.2.8 There should be a clear distinction between in-process controls and validation. In-process tests are performed during the manufacture of each batch according to specifications and methods devised during the develop-ment phase. Their objective is to

monitor the process continuously.
过程控制和验证之间应有明显的区别。为监测工艺的连续性，应根据针对研发阶段设计的技术标准和方法，开展每批产品生产的过程测试。

5.2.9 When a new manufacturing formula or method is adopted, steps should be taken to demonstrate its suitability for routine processing. The defined process, using the materials and equipment specifi ed, should be shown to result in the consistent yield of a product of the required quality.
采用新的生产配方或方法时，应证明它们对常规工艺的适应性。验证时，应使用规定的物料和设备，运行既定的工艺，持续得到的产品质量应符合要求。

5.2.10 Manufacturers should identify what validation work is needed to prove that critical aspects of their operations are appropriately controlled. Significant changes to the facilities or the equipment, and processes that may affect the quality of the product should be validated. A risk assessment approach should be used to determine the scope and extent of validation required.
生产商需明白为了证明他们的操作的关键问题得到了合理的控制，应采取哪些验证工作。比如，对产品质量可能产生影响的厂房设施、设备和工艺的重大变更是需要验证的。为确定需要开展的验证的范围和验证的程度，可使用风险评估的方法。

6. Qualification

确认

6.1 Qualification should be completed before process validation is per-formed. The process of qualification should be a logical, systematic process and should start from the design phase of the premises, equipment, utilities and equipment.
确认应当先于工艺验证完成。确认工作应当是一个有条理的、系统的过程，并应从厂房建筑、设备、公用工程和公用设备的设计阶段着手开始。
6.2 Depending on the function and operation of the equipment, utility or system, only installation qualification (IQ) and operational qualification (OQ) may be required, as the correct operation of the equipment, utility or system could be considered to be a sufficient indicator of its performance (refer to Section 11 for IQ, OQ and performance qualifi cation (PQ)). (The equipment, utility and system should then be maintained, monitored and calibrated according to a regular schedule.)
考虑到设备、公用设施或系统的具体功能和运作情况，可能只需要进行安装确认（IQ）和运行确认（OQ），因为这些设备、公用设备或系统的正确运转已经可以证明它们的性能（更多信息请查阅第11部分-IQ、OQ和性能确认（PQ））。（这些设备、公用设施和系统的维护、监控和校准应当根据计划定期执行。）
6.3 Major equipment and critical utilities and systems, however, require IQ, OQ and PQ.
对主要的设备、关键的公用设施和系统，还需要开展IQ、OQ和PQ。

7. Calibration and verification

校准和核查

7.1 Calibration and verification of equipment, instruments and other devices, as

applicable, used in production and quality control, should be performed at regular intervals.
用于生产和质量控制的设备、仪器和其它器械应定期进行校准和核查。
7.2 Personnel who carry out calibration and preventive maintenance should have appropriate qualifications and training.
执行校准和预防维护的人员应当具备相应的资格且得到过适当的培训。
7.3 A calibration programme should be available and should provide infor-mation such as calibration standards and limits, responsible persons, calibra-tion intervals, records and actions to be taken when problems are identifi ed.
应制订好校准计划，准备好资料，如校准标准和限度、负责人、校准间隔、记录和发生问题后所采取的措施。
7.4 There should be traceability to standards (e.g. national, regional or international standards) used in the calibration.
应当有可追溯的校准标准（如国家标准、地区标准或国际标准等）。
7.5 Calibrated equipment, instruments and other devices should be la-belled, coded or otherwise identified to indicate the status of calibration and the date on which recalibration is due.
对于校准过的设备、仪器和其他器械，应贴好标签，编好代码或使用其它可指示校准状态和下次校准日期的方式来对之进行标识。
7.6 When the equipment, instruments and other devices have not been used for a certain period of time, their function and calibration status should be verified and shown to be satisfactory before use.
如设备、仪器或其它器械已长时间未使用，在使用它们之前，应核实它们的功能和校准状态，确实它们可供使用。

2 Validation master plan

验证主计划

The validation master plan (VMP) should reflect the key elements of the validation programme. It should be concise and clear and contain at least the following:
验证主计划（VMP）应能反映验证项目的关键元素，它的内容应当简洁明了，且涵盖下列内容：

— a validation policy
验证方法
— organizational structure of validation activities
验证活动的组织机构
— summary of facilities, systems, equipment and processes validated and to be validated
已验证和待验证的设施、系统、设备和工艺的总览
— documentation format (e.g. protocol and report format)
文件格式（如方案和报告的格式）
— planning and scheduling
计划和进度设计
— change control
变更控制

— references to existing documents.
现有文件的参考资料。

9. Qualification and validation protocols

确认和验证方案

9.1 There should be qualification and validation protocols describing the qualification and validation study to be performed.
应有说明待执行的确认和验证的确认和验证方案。

9.2 As a minimum the protocols should include the following signifi cant background information:
方案中，应含有的重要背景资料至少应涵盖下列内容：

— the objectives of the study
研究对象
— the site of the study
研究地点
— the responsible personnel
负责人
— description of SOPs to be followed
需要遵从的SOP的说明
— equipment to be used; standards and criteria for the relevant products and processes
将用到的设备；相关产品和工艺的技术标准和合格指标
— the type of validation
验证的类型
— the processes and/or parameters
工艺和/或参数
— sampling, testing and monitoring requirements
取样、测试和监控的要求
— predetermined acceptance criteria for drawing conclusions.
用以推导结论的既定合格标准。

9.3 There should be a description of the way in which the results will be analysed.
应说明用以分析结果的方法。

9.4 The protocol should be approved prior to use. Any changes to a pro-tocol should be approved prior to implementation of the change.
在投入使用之前，这些方案应得到批准。如变更了方案，那么，在将这些变更投入使用之前，这些方案的变更也需要获得批准。

10. Qualification and validation reports

确认和验证报告

10.1 There should be written reports on the qualification and validation performed.
应有已执行的确认和验证活动的书面报告。

10.2 Reports should reflect the protocols followed and include at least the title and objective of the study; reference to the protocol; details of material, equipment, programmes and cycles used; procedures and test methods.
报告的内容应表明方案已执行，且至少要说明研究的标题和对象、方案的参考资料、使用到的物料、设备、计划和时间的明细、程序及实验方法。

10.3 The results should be evaluated, analysed and compared against the pre-determined acceptance criteria. The results should meet the acceptance criteria; deviations and out-of-limit results should be investigated. If these deviations are accepted, this should be justified. Where necessary further studies should be performed.
要对结果进行评估和分析，并用既定的合格标准与之比较。结果应当符合合格标准，如发现有偏差和超出接受限度的结果，应对之展开调查。如果这些偏差尚在接受范围内，需给出相应证明。需要时，要展开进一步的研究。

10.4 The departments responsible for the qualification and validation work should approve the completed report.
完成的报告应得到确认和验证工作的负责部门的批准。

10.5 The conclusion of the report should state whether or not the outcome of the qualification and/or validation was considered successful.
报告中给出的结论应阐述了该确认和/或验证工作的结果是否成功。

10.6 The quality assurance department should approve the report after the final review. The criteria for approval should be in accordance with the company's quality assurance system.
终审之后，报告应得到质量保证部门的批准。审批标准应严格遵循企业的质量保证系统的要求。

10.7 Any deviations found during the validation process should be acted upon and documented as such. Corrective actions may be required.
应按照规定，记录验证过程中发现的所有偏差。需要时，采取相应的纠偏措施。

2 Qualification stages

确认程序

11.1 There are four stages of qualification:
有四种确认：

— design qualifi cation (DQ);
设计确认（DQ）
— installation qualifi cation (IQ);
安装确认（IQ）
— operational qualification (OQ); and
运行确认（OQ）；以及
— performance qualifi cation (PQ).
性能确认（PQ）。

11.2 All SOPs for operation, maintenance and calibration should be prepared during

qualification.
确认工作阶段，应准备操作、维护和校准的SOP。

11.3. Training should be provided to operators and training records should be maintained.
应对操作人员进行培训，并保存培训记录。

Design qualifi cation
设计确认

11.4 Design qualification should provide documented evidence that the design specifications were met.
设计确认的活动应能给出工作对象达到设计标准的文件化证明。

Installation qualifi cation
安装确认

11.5 Installation qualification should provide documented evidence that the installation was complete and satisfactory.
安装确认的活动应能给出工作对象已正确安装的文件化证明。

11.6 The purchase specifications, drawings, manuals, spare parts lists and vendor details should be verified during installation qualifi cation.
采购标准、图纸、使用手册、零部件清单和供应商的详细资料都应在安装确认阶段得到确认和核实。

11.7 Control and measuring devices should be calibrated.
应校准控制和测量仪器。

Operational qualifi cation
运行确认

11.8 Operational qualification should provide documented evidence that utilities, systems or equipment and all its components operate in accor-dance with operational specifi cations.
运行确认的活动应可提供公用工程、系统或设备及其所有部件的运行均符合运行技术标准的文件化证明。

11.9 Tests should be designed to demonstrate satisfactory operation over the normal operating range as well as at the limits of its operating condi-tions (including worst case conditions).
设计此阶段进行的试验时，应确保在正常运行范围及运行条件的上下限值（包括最差状况）的情况下运行时，确认对象都能实现满意的运行结果。

11.10 Operation controls, alarms, switches, displays and other operational components should be tested.
应检测操作控制装置、报警装置、开关、显示屏和其他操作部件。

11.11 Measurements made in accordance with a statistical approach should be fully described.
应充分说明测量活动与统计方法一致。

Performance qualification
性能确认

11.12 Performance qualification should provide documented evidence that utilities, systems or equipment and all its components can consistently per-form in accordance with the specifications under routine use.
性能确认活动应能给出文件证明，说明在常规使用时，公用工程、系统或设备及其所有部件的性能均符合标准，且具备持续性。

11.13 Test results should be collected over a suitable period of time to prove consistency.
为证明结果的持续性，应以适当的时间间隔采集试验结果。

Requalification
再确认

11.14 Requalification should be done in accordance with a defi ned schedule. The frequency of requalification may be determined on the basis of factors such as the analysis of results relating to calibration, verification and maintenance.
应按照事先制订的时间表执行再确认工作。可根据校准相关结果的分析、核实确认和维护等因素确定执行再确认的频率。

11.15 There should be periodic requalification, as well as requalifi cation after changes (such as changes to utilities, systems, equipment; maintenance work; and movement). (See also point 5.2.5 above and section 12 below.)
应定期开展再确认工作；发生变更后，也应再次进行确认（如公用工程、系统、设备、维护工作和设备/设施的位置变动等变更）。（见下文第12部分及上文的5.2.5）

11.16 Requalification should be considered as part of the change control procedure.
应将再确认视为变更控制程序的组成部分。

Revalidation
再验证

11.17 Processes and procedures should be revalidated to ensure that they remain capable of achieving the intended results.
为确保工艺和方法能实现预期效果，应执行再验证。

11.18 There should be periodic revalidation, as well as revalidation after changes. (See also points 5.2.5 above, point 11.21 below and section 12 below.)
应定期执行再验证；变更后，也应再次进行验证。（见上文的5.2.5，下文的11.21和第12部分）

11.19 Revalidation should be done in accordance with a defi ned schedule.
应根据既定的时间表执行再验证。

11.20 The frequency and extent of revalidation should be determined using a risk-based approach together with a review of historical data.
可在风险评估和审查历史数据的基础上，确定再验证的执行频率和执行等级。

Periodic revalidation
定期再验证

11.21 Periodic revalidation should be performed to assess process changes that may occur gradually over a period of time, or because of wear of equipment.
为了评估可能的工艺变更，或设备磨损造成的该变，更应开展定期再验证，

11.22 The following should be considered when periodic revalidation is performed:
执行定期再验证时，应考虑下列问题：

— master formulae and specifi cations;
主配方及技术标准
— SOPs;
SOP
— records (e.g. of calibration, maintenance and cleaning); and
记录（如校准、维护和清洁记录）；以及
— analytical methods.
分析方法

Revalidation after change
变更后的再验证

11.23 Revalidation should be performed following a change that could have an effect on the process, procedure, quality of the product and/or the product characteristics. Revalidation should be considered as part of the change control procedure.
发生了可能对工艺、方法、产品质量和/或产品特性有所影响的变更后，应当执行再验证。可将再验证视为变更控制程序的组成部分。

11.24 The extent of revalidation will depend on the nature and signifi cance of the change(s).
再验证的执行程度视变更的性质和重要性而定。

11.25 Changes should not adversely affect product quality or process characteristics.
变更不得对产品质量或工艺特性产生不利影响。

11.26 Changes requiring revalidation should be defined in the validation plan and may include:
应在验证计划中阐明何种变更要求再验证的执行，这些变更可能包括：

- changes in starting materials (including physical properties, such as density, viscosity or particle size distribution that may affect the process or product);
起始物料的变更（包括物料的物理性质如密度、黏度或粒径分布等可能对工艺或产品造成影响的变更）；
- change of starting material manufacturer;
起始物料供应商的变更；
- transfer of processes to a different site (including change of facilities and installations which influence the process);
生产工艺转移到其它地点（包括厂房设施和安装等对工艺有影响的变更）；
- changes of primary packaging material (e.g. substituting plastic for glass);
内包材的变更（如用玻璃取代塑料）；
- changes in the manufacturing process (e.g. mixing times or drying temperatures);
生产工艺的变更（如混合时间或干燥温度）；

- changes in the equipment (e.g. addition of automatic detection systems, installation of new equipment, major revisions to machinery or apparatus and breakdowns);
  设备变更（如自动检测系统的新增、新设备的安装、设备或仪器的重要修改和故障）；
- production area and support system changes (e.g. rearrangement of areas, or a new water treatment method);
  生产区域和支持系统的变更（如区域的重新安排或新的水处理系统的使用）；
- appearance of negative quality trends;
  质量负趋势的出现；
- appearance of new findings based on current knowledge, e.g. new tech-nology;
  在现有知识的基础上，有了新的发现，如新技术；
- support system changes.
  支持系统的变更。

Changes of equipment which involve the replacement of equipment on a “like-for-like” basis would not normally require a revalidation. For exam-ple, installation of a new centrifugal pump to replace an older model would not necessarily require revalidation.
在“相等”的基础上进行的设备变更，即相同的设备之间发生的替换，通常不需要再验证。例如，用新的离心泵取代同样的旧设备是无需再验证的。

12. Change control

变更控制

12.1 Changes should be controlled in accordance with a SOP as changes may have an impact on a qualified utility, system or piece of equipment, and a validated process and/or procedure.
因为变更可能会对确认过的公用工程、系统或设备、已验证的工艺和/或程序产生影响，所以要按照SOP对变更进行控制。

12.2 The procedure should describe the actions to be taken, including the need for and extent of qualification or validation to be done.
在变更的控制程序中，应说明需要采取的措施，包括阐明是否需要确认或验证，以及需要执行的确认或验证的等级。

12.3 Changes should be formally requested, documented and approved before implementation. Records should be maintained.
应正式提出变更请求，而后对变更进行记录和审批，最后得到批准的变更方可执行。变更记录要保存。

2 Personnel

人员

13.1 Personnel should demonstrate that they are appropriately qualifi ed, where relevant.
应证明人员拥有相应的资格。

13.2 Personnel requiring qualification include, for example:

以下是需要进行资格确认的人员的例子：

— laboratory analysts;
试验室的检验员；
— personnel following critical procedures;
实施关键步骤的人员；
— personnel doing data entry in computerized systems; and
负责将数据录入计算机系统的人员；以及
— risk assessors.
风险评估员。

Appendix 1

附录 1

Validation of heating, ventilation and air-conditioning systems

采暖、通风和空气净化系统的验证

1. General

概要

1.1 The heating, ventilation and air-conditioning (HVAC) system plays an important role in the protection of the product, the personnel and the environment.
采暖、通风和空气净化（HVAC）系统在保护产品、人员和环境上扮演着重要的角色。

1.2 For all HVAC installation components, subsystems or parameters, critical parameters and non-critical parameters should be determined.
应确定HVAC的所有安装部件、下游系统或参数、关键参数和非关键参数。

1.3 Some of the parameters of a typical HVAC system that should be qualifi ed include:
需要确认的典型的HVAC系统的某些参数有：

— room temperature and humidity;
室内温度和湿度；
— supply air and return air quantities;
供风和回风量；
— room pressure, air change rate, flow patterns, particle count and cleanup rates; and
室内压力、空气交换率、气流类型、粒子计数和清除率；以及
— unidirectional flow velocities and HEPA filter penetration tests.
单向气流的流速和HEPA过滤器的渗透试验。

2. Commissioning

试运行

2.1 Commissioning should involve the setting up, balancing, adjustment and testing of the entire HVAC system, to ensure that the system meets all the requirements, as specified in the user requirement specifi cation, and capacities as specified by the designer or developer.
试运行应包括整个HVAC系统的安装、平衡、调整和测试，以确保该系统符合用户需要说明书中规定的所有要求，并证明该系统可实现设计者或研发者所定义的性能。

2.2 The installation records of the system should provide documented evidence of all measured capacities of the system.
系统的安装记录应包括已测试的该系统的所有性能的资料。

2.3 The data should include items such as the design and measured figures for airflows, water flows, system pressures and electrical amperages. These should be contained in the operating and maintenance manuals (O & M manuals).
需要记录的数据应当包括气流、水流、系统压力和电流的设计值和测量值。这些数据在操作和维护手册（O&M手册）中都有说明。

2.4 Acceptable tolerances for all system parameters should be specifi ed prior to commencing the physical installation.
安装系统之前，应阐明所有系统参数的可接受公差。

2.5 Training should be provided to personnel after installation of the system, and should include how to perform operation and maintenance.
安装系统之后，应对人员进行包括如何进行系统操作和维护的知识在内的培训。

2.6 O & M manuals, schematic drawings, protocols and reports should be maintained as reference documents for any future changes and upgrades to the system.
应将O&M手册、系统图纸、方案和报告作为参考资料保存，以备将来的变更和系统更新使用。

2.7 Commissioning should be a precursor to system qualification and validation.
试运行应当先于系统确认和验证执行。

Qualification

资格

3.1 Manufacturers should qualify HVAC systems using a risk-based ap-proach. The basic concepts of qualification of HVAC systems are set out in Fig. 1 below.
制造商应当在风险评估的基础上对HVAC系统进行确认。HVAC系统确认的基本概念见图1。

3.2 The qualification of the HVAC system should be described in a validation master plan (VMP).
应使用验证主文件（VMP）说明HVAC系统的确认工作。

3.3 The validation master plan should define the nature and extent of testing and the test procedures and protocols to be followed.
在验证主文件中，应当阐明试验的性质和试验执行的程度，且要说明需要遵循的试验程序和方案。

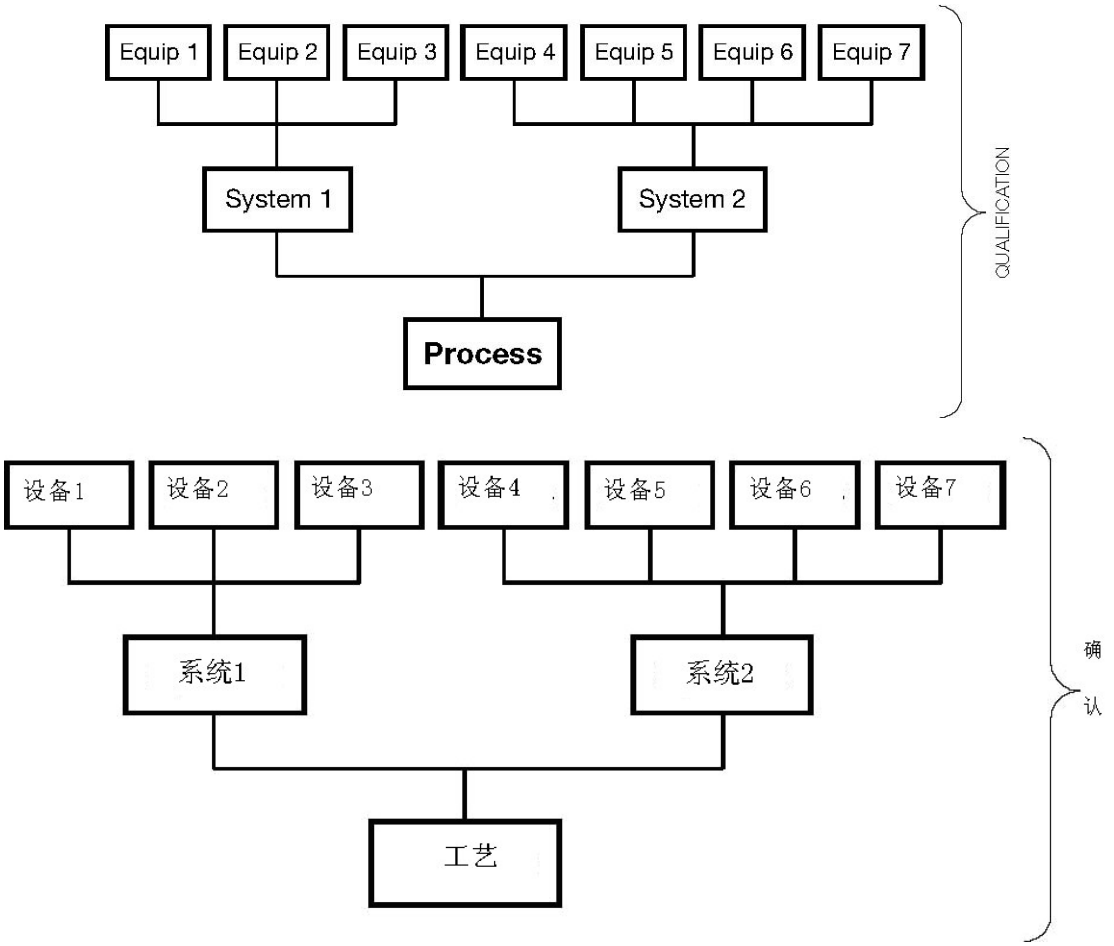
3.4 Stages of the qualification of the HVAC system should include de-sign qualification (DQ), installation qualification (IQ), operational qualifi -cation (OQ), and performance qualifi cation (PQ).
HVAC系统的确认程序应包括设计确认（DQ）、安装确认（IQ）、运行确认（OQ）和性能确认（PQ）。

3.5 Critical and non-critical parameters for all HVAC installation com-ponents, subsystems and controls should be determined by means of a risk analysis.
应以风险分析的方法，确定HVAC系统的所有安装部件、下游系统和控制装置的关键和非关键参数。

3.6 Any parameter that may affect the quality of the pharmaceutical product should be considered a critical parameter.
任何可能对药品质量构成影响的参数都应视作关键参数。

3.7 All critical parameters should be included in the qualifi cation process.
应确认所有关键参数。

Figure 1
图 1
Qualification is a part of validation
确认是验证的组成部分



Note: A realistic approach to differentiating between critical and non-critical parameters is required, to avoid making the validation process unnecessarily complex.
Example:
*注：*为了给验证过程减少不必要的赘余步骤，应建立可区分关键和非关键参数的现实方法。
例：

- *The humidity of the room where the product is exposed should be considered a critical parameter when a humidity-sensitive product is being manufactured. The humidity sensors and the humidity monitoring system should, therefore, be qualified. The heat transfer system, chemi-cal drier or steam humidifier, which is producing the humidity-controlled air, is further removed from the product and may not require operational qualifi cation.*
  如产品对湿度敏感，那么，与产品有接触的区域内的室内湿度也应视为关键参数。在这种情况下，湿度探测器和湿度监控系统都需要确认；而空气湿度控制装置，如热交换系统、化学干燥器或蒸汽增湿器，因为远离产品，因而也可以不必进行运行确认。
- *A room cleanliness classifi cation is a critical parameter and, therefore, the room air-change rates and high-efficiency particulate air (HEPA) filters should be critical parameters and require qualification. Items such as the fan generating the airflow and the primary and second-ary filters are non-critical parameters, and may not require operational qualifi cation.*
  考虑到室内洁净级别是一个关键参数，因此，室内的空气交换次数和高效空气过滤器（HEPA）都是需要确认的关键参数；而产生气流的风扇、一级和二级过滤器都不是关键参数，也不要求运行确认。

3.8 Non-critical systems and components should be subject to good engineering practice (GEP) and may not necessarily require full qualifi cation.
对于不一定需要全面确认的非关键系统和部件，应遵守工程设计规范的要求。

3.9 A change control procedure should be followed when changes are planned to the HVAC system, its components, and controls, that may affect critical parameters.
计划对HVAC系统和该系统的部件、控制装置实施可能对关键参数构成影响的变更时，应遵循变更控制程序。

3.10 Acceptance criteria and limits should be defined during the design stage.
在设计阶段，应制定合格标准和限度。

3.11 The manufacturer should define design conditions, normal operat-ing ranges, operating ranges, and alert and action limits.
制造商应说明设计条件、正常运行范围、运行范围、警戒和行动限度。

3.12 Design condition and normal operating ranges should be identified and set to realistically achievable parameters.
应说明设计条件和正常运行范围，并将之设置成现实可行的参数。

3.13 All parameters should fall within the design condition range during system operational qualification. Conditions may go out of the design condition range during normal operating procedures but they should remain within the operating range.

在系统运行确认期间，所有参数都应在设计条件范围内。正常运行时，条件参数可能会超出条件的设计范围，但不超出运行范围。

3.14 Out-of-limit results (e.g. action limit deviations) should be recorded and form part of the batch manufacturing records.
要记录超出限度的结果（如行动限偏差），并将这些结果视为批生产记录的一部分。

3.15 The relationships between design conditions, operating range and qualified acceptance criteria are given in Figure 2.
设计条件、运行范围和已确认的合格标准之间的关系见图2。

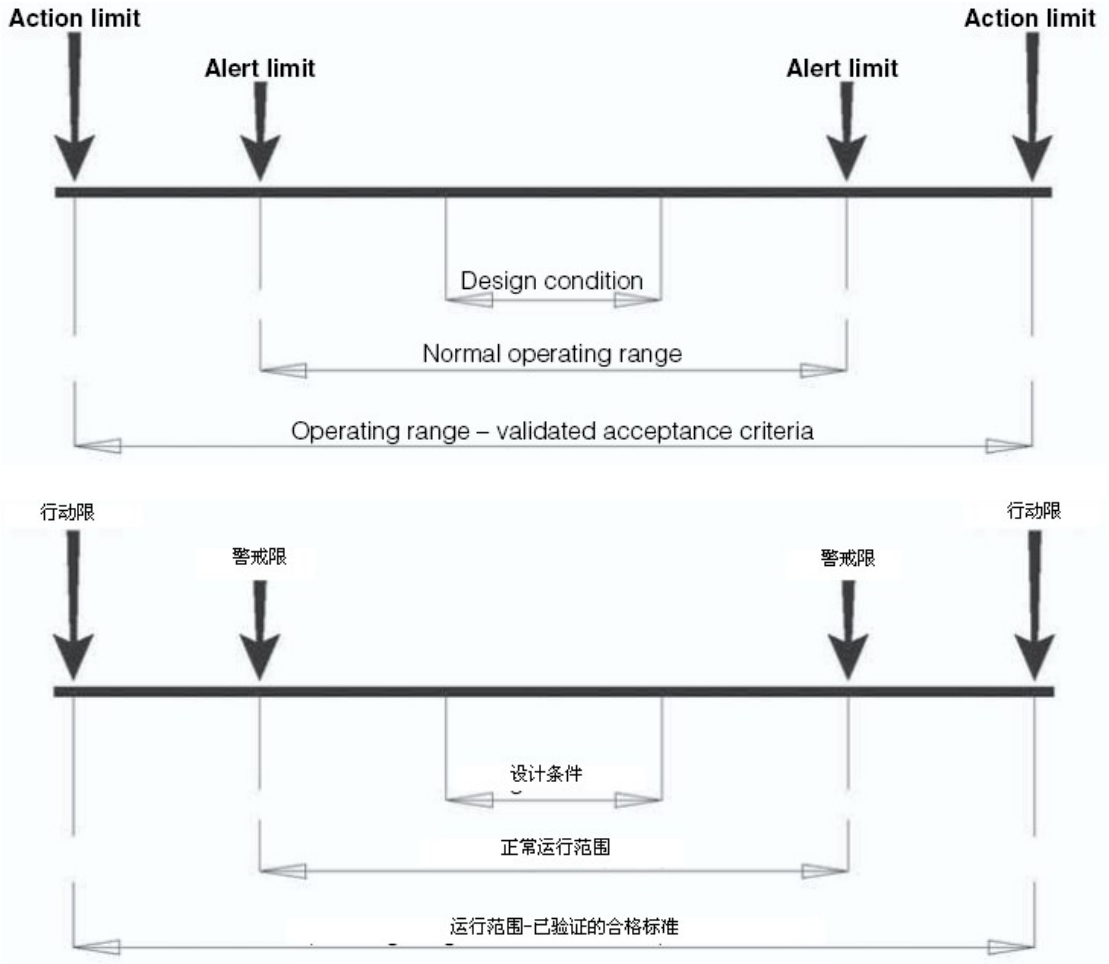
3.16 A narrow range of relative humidities coupled with a wide range of temperatures is unacceptable as changes in temperature will automatically give rise to variations in the relative humidity.
相对湿度的范围过小、同时温度的范围过大，这种情况是不可取的；这是因为温度的变化会导致相对湿度的变化。

Figure 2

图 2

System operating ranges

系统运行范围，



3.17 Some of the typical HVAC system parameters that should be quali-fied for a pharmaceutical facility may include:

就药品生产设施而言，应确认的典型的HVAC系统参数如下：

— temperature
温度
— relative humidity
相对湿度
— supply air quantities for all diffusers
所有送风口的供气量
— return air or exhaust air quantities
回风量或排气量
— room air-change rates
室内空气交换次数
— room pressures (pressure differentials)
室内压强（压差）
— room airflow patterns
室内气流类型
— unidirectional flow velocities
单向流的流速
— containment system velocities
隔离系统中的流速
— HEPA filter penetration tests
HEPA过滤器的渗透试验
— room particle counts
室内粒子计数
— room clean-up rates
室内清场频率
— microbiological air and surface counts where appropriate
适当的情况下，空气和表面微生物计数
— operation of de-dusting
除尘操作
— warning/alarm systems where applicable.
如情况允许，还有警报/报警系统

3.18 The maximum time interval between tests should be defined by the manufacturer. The type of facility under test and the product level of protec-tion should be considered.
Note: Table 1 gives intervals for reference purposes only. The actual test periods may be more or less frequent, depending on the product and process.
在考虑了待测设施的类型和产品的保护等级的情况下，制造商应说明两次测试之间的最大时间间隔。
*注：*表1中给出的时间间隔仅可作为参考。根据产品和工艺的具体情况，实际采用试验频率可能更高或较低。

3.19 Periodic requalification of parameters should be done at regular intervals, e.g. annually.
参数的定期再确认应严格按照时间设定执行，如每年一次等。

3.20 Requalifi cation should also be done when any change, which could affect system performance, takes place.
如发生了可能对系统性能产生影响的变更，也应再次对系统确认。

3.21 Clean-up times normally relate to the time it takes to “clean up” the room from one condition to another, e.g. the relationship between “at-rest” and “operational” conditions in the clean area may be used as the criteria for clean-up tests. Therefore, the clean-up time can be expressed as the time taken to change from an “operational” condition to an “at-rest” condition.
清场次数通常与某区域的状态转换所耗费的时间有关，如洁净区的“静态”与“动态”之间的关系可作为清场试验的标准。正因如此，可用从“动态”向“静态”转换所花费的时间来表示清场次数。

Table 1.
表 1
Strategic tests (for reference purposes only)
关键试验（仅供参考）

Schedule of tests to demonstrate continuing compliance 用以证明依从性的持续性的试验的进度表			
Test parameter 试验参数	Clean area 洁净区	Max. time interval 最大时间间隔	Test procedure 测试程序
Particle count test (verification of cleanliness) 尘埃粒子计数试验（洁净度的确认）	All classes 所有洁净等级	6 months 6个月	Dust particle counts to be carried out and printouts of results produced. No. of readings and positions of tests to be in accordance with ISO 14644-1 Annex B 开展尘埃粒子计数，并打印测试结果。各测试点的读数和测试点的分布须符合附件B ISO14644-1的要求。
Air pressure difference(To verify absence of cross-contamination) 大气压差（为确认无交叉污染）	All classes 所有洁净等级	12 months 12个月	Log of pressure differential readings to be produced or critical plants should be logged daily, preferably continuously. A 15 Pa pressure dif-ferential between

			different zones is recommended. In accordance with ISO 14644-3 Annex B5 应每天测量压差或关键车间，并取结果的对数值，该项测量最好不要间断；根据附件B5 ISO 14644-3，建议不同区域之间的压差为15Pa。
Airfl ow volume(To verify air change rates) 气流量（确认空气交换次数）	All classes 所有洁净等级	12 months 12个月	Airflow readings for supply air and return air grilles to be measured and air change rates to be calculated. In accordance with ISO 14644-3 Annex B13 测量送风口和回风口的气流速度，并计算空气交换次数。 依据：附件B13 ISO 14644-3
Airfl ow velocity (To verify unidirectional flow or containment conditions) 气流速度（为确认单向流或隔离条件）	All classes 所有洁净等级	12 months 12个月	Air velocities for containment systems and unidirectional flow protection systems to be measured. In accordance with ISO 14644-3 Annex B4 测量隔离系统和单向流保护系统中的气流速度。 依据：附件B4 ISO14644-3

Source: ISO 14644 Standard, given for reference purposes only.
*来源：*ISO 14644标准；仅供参考用。

4. Reference

参考文献

1. Supplementary guidelines on good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fortieth report*. Geneva, World Health Organization, 2006 (WHO Technical Report Series, No. 937), Annex 2.

Appendix 2

附录 2

Validation of water systems for pharmaceutical use

制药用水系统的验证

1. General

概要

1.1 All water-treatment systems should be subject to planned mainte-nance, validation and monitoring.
应针对所有水处理系统，计划其维护、验证和监控。
1.2 Validation of water systems should consist of at least three phases: Phase 1: investigational phase; Phase 2: short-term control; and Phase 3: long-term control.
水系统的验证至少分三个阶段：1.调查阶段；2.短期控制；3.长期控制。
1.3 During the period following phase 3 (typically running for one year) the objective should be to demonstrate that the system is under control over a long period of time. Sampling may be reduced from, e.g. daily to weekly.
第三阶段（通常为一年）完成之后，接下来的任务是证明该系统能在相当长的时期内处于受控状态，这时，取样频率可减少为一日一次至每周一次。
1.4 The validation performed and revalidation requirements should be included in the “Water quality manual”.
应在“水质量手册”中说明已执行的验证和再验证的要求。

2. Start-up and commissioning of water systems

水系统的启用和试运行

2.1 Planned, well-defined, successful and well-documented commission-ing is an essential precursor to successful validation of water systems. The commissioning work should include setting to work, system set-up, controls, loop tuning and recording of all system performance parameters. If it is in-tended to use or refer to commissioning data

within the validation work then the quality of the commissioning work and associated data and documenta-tion must be commensurate with the validation plan requirements.
计划良好、定义完整、成功并拥有优秀的文件的试运行是成功的水系统验证的先决条件，它的工作内容包括运行设置、系统安装、控制、回路调整和记录所有的系统性能参数。如某项试运行或试运行的数据为验证活动所囊括，那么该试运行工作的质量和相关数据及文件必须符合验证计划的要求。

3 Qualification

确认

3.1 Water for pharmaceutical use (WPU), purified water (PW), highly purified water (HPW) and water for injections (WFI) systems are all con-sidered to be direct impact, quality critical systems that should be qualifi ed. The qualification should follow the validation convention of design review or design qualification (DQ), installation qualification (IQ), operational qualification (OQ) and performance qualifi cation (PQ).
制药用水（WPU）、纯化水（PW）、高度纯化水（HPW）和注射用水（WFI）系统都是能对产品质量产生直接影响的关键质量系统，因此需要对它们全部开展确认活动。确认活动的开展应遵循的验证规定有设计审核或设计确认（DQ）、安装确认（IQ）、运行确认（OQ）和性能确认（PQ）。

3.2 This guidance does not define the standard requirements for the con-ventional validation stages DQ, IQ and OQ, but concentrates on the par-ticular PQ approach that should be used for WPU systems to demonstrate their consistent and reliable performance. A three-phase approach should be used to satisfy the objective of proving the reliability and robustness of the system in service over an extended period.
本指南并未详细说明DQ、IQ和OQ的常规验证阶段，而将重点放在说明用以证明WPU系统性能的连续性和可靠性的PQ方法上；为证明该系统在相当长的时期内的可靠性和耐用性，可将该过程分为三个阶段。

Phase 1. A test period of 2–4 weeks should be spent monitoring the sys-tem intensively. During this period the system should operate continuously without failure or performance deviation. The following procedures should be included in the testing approach.
第一阶段 应在2-4周的测试期内对该系统进行密集监控。在这段时间里，运行未间断的水系统应不出现故障，也不会有性能偏差。下面列出的是测试方法应囊括的步骤：

- Undertake chemical and microbiological testing in accordance with a defi ned plan.
  根据既定计划，采用化学和微生物试验。
- Sample the incoming feed-water to verify its quality.
  为确认水质，对进水采样。
- Sample after each step in the purification process daily.
  每天都对纯化工艺的每一步骤的水进行采样。
- Sample at each point of use and at other defined sampling points daily.
  每天对每个使用点及指定的取样点采样。
- Develop appropriate operating ranges.

研究制订适当的运行范围。

- Develop and finalize operating, cleaning, sanitizing and maintenance procedures.
  研究并完成操作、清洁、卫生和维护规程。
- Demonstrate production and delivery of product water of the required quality and quantity.
  证明产水的生产和输送符合质量和数量的要求。
- Use and refine the standard operating procedures (SOPs) for operation, maintenance, sanitization and troubleshooting.
  在执行系统操作、维护、卫生和解决故障时，使用且不断完善标准操作规程（SOP）。
- Verify provisional alert and action levels.
  确认临时的警戒线的行动限
- Develop and refine the test-failure procedure.
  研究并不断完善失败试验的处理规程。

Phase 2. A further test period of 2–4 weeks should be spent carrying out further intensive monitoring while deploying all the refined SOPs after the satisfactory completion of phase 1. The sampling scheme should be gener-ally the same as in phase 1. Water can be used for manufacturing purposes during this phase. The approach should also:

第二阶段 圆满完成第一阶段后，接下来的2-4星期，应在使用所有完善后的SOP的同时，实施进一步的密集监控，取样计划也应当与第一阶段大致相同。这个阶段生产得到的水可用于生产。就目的而言，该阶段应：

— demonstrate consistent operation within established ranges; and
证明系统的持续运行不超出既定范围；

— demonstrate consistent production and delivery of water of the required quan-tity and quality when the system is operated in accordance with the SOPs.
在按照SOP操作的同时，证明水的持续生产和运输符合质量和数量的要求。

Phase 3. Phase 3 typically runs for one year after the satisfactory comple-tion of phase 2. Water can be used for manufacturing purposes during this phase which has the following objectives and features:

第三阶段 完成第二阶段后，通常需要再花一年来实施第三阶段。第三阶段生产得到的水可供生产使用。这个阶段的活动应当：

- Demonstrate extended reliable performance.
  证明在延长的时期内，系统性能仍然可靠。
- Ensure that seasonal variations are evaluated.
  确保已经评估了季节性差异。
- The sample locations, sampling frequencies and tests should be reduced to the normal routine pattern based on established procedures proven during phases 1 and 2.
  在第一和第二阶段里证实的既定规程的基础上，取样点、取样频率和试验都应减少至正常的日常模式。

Reference

参考文献

1. *WHO good manufacturing practices: water for pharmaceutical use.* Geneva, World Health Organization 2005 (WHO Technical Report Series, No. 929), Annex 3.

Appendix 3

附录 3

Cleaning validation

清洁验证

模拟批生产法

10 Analytical methods
分析方法

11 Establishing acceptable limits
建立合格限度

1. Principle

基本原则

1.1 The objectives of good manufacturing practices (GMP) include the prevention of possible contamination and cross-contamination of pharma-ceutical starting materials and products.
药品生产管理规范针对的对象还包括预防制药生产的起始物料和产品潜在的污染和交叉污染。

1.2 Pharmaceutical products can be contaminated by a variety of substances such as contaminants associated with microbes, previous products (both active pharmaceutical ingredients (API) and excipient residues), residues of cleaning agents, airborne materials, such as dust and particulate matter, lubricants and ancillary material, such as disinfectants, and decomposition residues from:
药品可能会受到微生物、前批产品（活性药物成分（API）和辅料残留）、清洁剂的残留、空气中的物质如尘埃和颗粒物质等、润滑剂和辅助物料如消毒剂残留和分解后的残余物质，这些污染可能源自：

— product residue breakdown occasioned by, e.g. the use of strong acids and alkalis during the cleaning process; and
偶然的残留产品的分解，如因为清洁过程使用的强酸和强碱而造成的物质的分解；

— breakdown products of the detergents, acids and alkalis that may be used as part of the cleaning process.
清洁过程中可能使用的清洁剂、酸和碱的分解。

1.3 Adequate cleaning procedures play an important role in preventing contamination and cross-contamination. Validation of cleaning methods provides documented evidence that an approved cleaning procedure will provide clean equipment, suitable for its intended use.
良好的清洁方法能有效预防污染和交叉污染。清洁方法的验证的文件资料可证明获准的清洁方法能够在清洁设备上获得令人满意的效果。

1.4 The objective of cleaning validation is to prove that the equipment is consistently cleaned of product, detergent and microbial residues to an ac-ceptable level, to prevent possible contamination and cross-contamination.
清洁验证的目的在于证明所使用的清洁方法能持续有效地去除产品、清洁剂和微生物残留，产生令人满意的清洁效果，从而实现对潜在的污染和交换污染的预防。

1.5 Cleaning validation is not necessarily required for non-critical clean-ing such as that which takes place between batches of the same product (or different lots of the same intermediate in a bulk process), or of fl oors, walls, the outside of vessels, and following

some intermediate steps.
非关键对象的清洁，如同一产品不同批次（或同一工艺中的同一种简体的不同小批）的生产之间的清洁、地面、墙、容器外表面和针对中间产品的某些后续步骤是不一定要求验证的。
1.6 Cleaning validation should be considered important in multiproduct facilities and should be performed among others, for equipment, sanitiza-tion procedures and garment laundering.
对于有多种产品的工厂，清洁验证尤为重要。除了厂房设施的清洁以外，设备、卫生规程和洗衣程序也需要验证。

2. Scope

范围

2.1 These guidelines describe the general aspects of cleaning validation, excluding specialized cleaning or inactivation that may be required, e.g. for removal of viral or mycoplasmal contaminants in the biological manufac-turing industry.
这里给出的指南对清洁验证进行了大致说明，但某些可能需要实施的特别的清洁或钝化程序（如生物制品生产车间内，对滤过性病毒或支原体污染的去除）的验证则不在此列。
2.2 Normally cleaning validation would be applicable for critical clean-ing such as cleaning between manufacturing of one product and another, of surfaces that come into contact with products, drug products and API.
往往只有关键对象的清洁需要验证，如在更换生产的产品之间对生产区域的清洁，或与产品、制剂和API直接接触的表面的清洁。

3. General

概要

3.1 There should be written SOPs detailing the cleaning process for equipment and apparatus. The cleaning procedures should be validated.
应当有详细说明设备和仪器的清洁方法的书面SOP，并验证这些清洁程序。
3.2 The manufacturer should have a cleaning policy and an appropriate procedure for cleaning validation, covering:
生产商应当制定有清洁方针，并为清洁验证制定合适的程序，其内容应包括：

- surfaces that come into contact with the product;
  与产品直接接触的表面；
- cleaning after product changeover (when one pharmaceutical formula-tion is being changed for another, completely different formulation);
  更换生产的产品之间的清洁（用一种药品配方替代另一种完全不同的配方）；
- between batches in campaigns (when the same formula is being manufac-tured over a period of time, and on different days);
  开始不同批次的产品生产之前的清洁（当某种配方的产品已持续生产了一段时间时，每天重新开始生产之前，都要求对现场进行清洁）；
- bracketing products for cleaning validation. (This often arises where products

contain substances with similar properties (such as solubili-ty) or the same substance in different strengths. An acceptable strategy is to first manufacture the more dilute form (not necessarily the lowest dose) and then the most concentrated form. There are sometimes “fam-ilies” of products which differ slightly as to actives or excipients.); and
生产相似的产品所需的清洁验证（当产品的成分性质相似（如溶解度）或含有不同含量的同种物质时，往往需要。出现这种情况时，可先生产稀释倍数较大（不一定是最低剂量）的产品形式，再生产浓度较大的产品。有时，可能会出现同一“家族”的产品，它们的差别不大，仅在活性成分或辅料上有微小的区别）；

- periodic evaluation and revalidation of the number of batches manufac-tured between cleaning validations.
对两次清洁验证之间生产的产品批次进行定期评估和开展再验证。

3.3. At least three consecutive applications of the cleaning procedure should be performed and shown to be successful to prove that the method is validated.
至少应对三个连续生产的批次实施清洁程序，当且仅当这三次清洁程序的实施都取得了满意的效果时，方可证明该清洁方法的效力。

2 Cleaning validation protocols and reports

清洁验证的方案和报告

4.1 Cleaning validation protocols
清洁验证的方案

4.1.1 Cleaning validation should be described in cleaning validation protocols, which should be formally approved, e.g. by the quality control or quality assurance unit.
在清洁验证方案中，必须描述清洁验证。这份清洁验证方案应得到如质量控制或质量保证部门的批准。

4.1.2 In preparing the cleaning validation protocol, the following should be considered:
准备清洁验证方案时，需要考虑的问题如下：

— disassembly of system;
系统的拆卸；
— precleaning;
预清洗；
— cleaning agent, concentration, solution volume, water quality;
清洁剂、清洁溶液的浓度、数量、水质等；
— time and temperature;
时间和温度；
— flow rate, pressure and rinsing;
流速、压强和淋洗；
— complexity and design of the equipment;
设备的复杂程度和设计；
— training of operators; and
操作者的培训；

— size of the system.
系统的大小。

4.1.3 The cleaning validation protocol should include:
清洁验证方案的内容有：

- the objectives of the validation process;
  验证的目的；
- the people responsible for performing and approving the validation study;
  负责实施和批准验证研究的责任人；
- the description of the equipment to be used, including a list of the equip-ment, make, model, serial number or other unique code;
  将用到的设备的说明，包括设备清单、制造商、型号、序列号或其它独有的代码；
- the interval between the end of production and the commencement of the cleaning procedure (interval may be part of the validation challenge study itself)
  生产结束至开始清洁之间的时间间隔（该时间间隔本身可能就是挑战性验证研究的组成部分）
  — the maximum period that equipment may be left dirty before being cleaned as well as the establishment of the time that should elapse after cleaning and before use;
  生产结束至开始清洁之间的最长时间，以及清洁过后至开始生产之前的时间间隔的确定；
- the levels of microorganisms (bioburden);
  微生物数量（生物负载）；
- the cleaning procedures (documented in an existing SOP, including defi -nition of any automated process) to be used for each product, each manu-facturing system or each piece of equipment;
  每种产品、生产系统和设备的清洁程序（可在现有的SOP中查阅到这些清洁程序，其中所有自动化程序也要清楚说明）；
- all the equipment used for routine monitoring, e.g. conductivity meters, pH meters and total organic carbon analysers;
  用于日常监控的所有设备，如电导率仪、pH计和总有机碳测定仪等；
- the number of cleaning cycles to be performed consecutively;
  需要连续运转的清洁周期的数量；
- the sampling procedures to be used (direct sampling, rinse sampling, in-process monitoring and sampling locations) and the rationale for their use;
  将用到的取样规程（说明取样方法、淋洗取样法、过程监控和取样点）和取样方法的原理；
- the data on recovery studies (efficiency of the recovery of the sampling technique should be established);
  回收试验的数据（应确定取样技术的回收率的效力）
- the analytical methods (specifi city and sensitivity) including the limit of detection and the limit of quantifi cation;
  说明分析方法（专属性和灵敏度），包括检测限和定量限；

- the acceptance criteria (with rationale for setting the specific limits) in-cluding a margin for error and for sampling effi ciency;
  合格标准（说明专属限度的设置原理），包括误差和取样效率的安全因子；
- the choice of the cleaning agent should be documented and approved by the quality unit and should be scientifi cally justified on the basis of, e.g.
  应记录清洁剂的选择并由质量部门审批。针对该选择过程，应能在以下几个方面给出科学合理的证据：
  — the solubility of the materials to be removed;
    待去除的物质的溶解度；
  — the design and construction of the equipment and surface materials to be cleaned;
    设备的设计和构造，以及待清洁的表面物质；
  — the safety of the cleaning agent;
    清洁剂的安全性；
  — the ease of removal and detection;
    其本身被清除和检测的难易程度；
  — the product attributes;
    产品的性质；
  — the minimum temperature and volume of cleaning agent and rinse solution; and
    清洁剂和淋洗溶液的温度和体积的最小值；
  — the manufacturer's recommendations;
    生产商的建议；
- revalidation requirements.
  关于再验证的要求。

4.1.4 Cleaning procedures for products and processes which are very simi-lar do not need to be individually validated. A validation study of the “worst case” may be considered acceptable. There should be a justified validation programme for this approach referred to as “bracketing”, addressing critical issues relating to the selected product, equipment or process.
如产品和工艺的清洁程序很相似，那么无需分别对它们验证。验证时，需注意“最差状况”也可能属于可接受的范畴。对这些相似的产品（同一“家族”）和工艺的清洁方法，应有合理的验证项目阐明被选为验证对象的产品、设备或工艺的关键问题。

4.1.5 Where “bracketing” of products is done, consideration should be given to type of products and equipment.
但确定了哪些产品属于同一“家族”之后，接下来就应考虑产品和设备的类型。

4.1.6 Bracketing by product should be done only when the products con-cerned are similar in nature or property and will be processed using the same equipment. Identical cleaning procedures should then be used for these products.
仅对性质或属性相似、且生产时用到的设备也相同的产品才可被视为属于同一“家族”。同一“家族”的产品，可使用同样的清洁方法。

4.1.7 When a representative product is chosen, this should be the one that is most difficult to clean.

挑选典型产品时，应选择最难清洁的产品。

4.1.8 Bracketing by equipment should be done only when it is similar equipment, or the same equipment in different sizes (e.g. 300-l, 500-l and 1000-l tanks). An alternative approach may be to validate the smallest and the largest sizes separately.
仅相似的设备、或仅在大小上有差别的同种设备（如300-1、500-1和1000-1水槽）方可视为属于同一“家族”。验证最小和最大的设备时，可分别选用不同的方法。

4.2 Cleaning validation reports
清洁验证报告

4.2.1 The relevant cleaning records (signed by the operator, checked by production and reviewed by quality assurance) and source data (original results) should be kept. The results of the cleaning validation should be pre-sented in cleaning validation reports stating the outcome and conclusion.
应保存相关的清洁记录（上有操作员的签名，由生产部门复查，并由质量保证部门的复核）和数据（原始数据）。清洁验证的报告中，应说明验证的结果，并阐明验证的成果和结论。

5. Personnel

人员

5.1 Personnel or operators who perform cleaning routinely should be trained and should be effectively supervised.
应培训执行日常清洁的人员或操作员，并监督其清洁过程。

6. Equipment

设备

6.1 Normally only procedures for the cleaning of surfaces of the equip-ment that come into contact with the product need to be validated. Consid-eration should be given to “non-contact” parts of the equipment into which product or any process material may migrate. Critical areas should be identi-fied (independently from method of cleaning), particularly in large systems employing semi-automatic or fully automatic clean-in-place systems.
就设备清洁而言，通常只需要验证直接接触产品的设备表面的清洁方法，但也不能就此忽略不与产品直接接触的设备表面，这是因为在生产过程中，这些表面也有沾染到产品和中间物料的可能。应确定哪些区域属于关键区域（该过程不隶属清洁方法），一般来说，使用了半自动或全自动在线清洁设备的大型系统属于关键区域。
6.2 Dedicated equipment should be used for products which are diffi cult to clean, equipment which is difficult to clean, or for products with a high safety risk where it is not possible to achieve the required cleaning accep-tance limits using a validated cleaning procedure.
应有专门的设备和验证过的清洁程序供清洁难以清洁的产品和设备，以及清洁效果难以达到合格标准的、具有高度安全风险的产品。
6.3 Ideally, there should be one process for cleaning a piece of equipment or system. This

will depend on the products being produced, whether the cleaning occurs between batches of the same product (as in a large campaign) or whether the cleaning occurs between batches of different products.
最好为每件设备和每个系统分别制订清洁程序；具体生产的产品决定程序的制订，不论是同种产品不同批次的生产（一次大的生产），还是不同产品的生产，都应分别制订清洁规程。
6.4 The design of equipment may influence the effectiveness of the cleaning process. Consideration should therefore be given to the design of the equipment when preparing the cleaning validation protocol, e.g. V-blenders, transfer pumps or fi lling lines.
设备的设计可能会影响清洁工艺的效果。因此起草清洁验证方案时，要考虑设备的设计因素，如V-搅拌机、传送泵和灌装生产线等。

7. Detergents

清洁剂

7.1 Detergents should facilitate the cleaning process and be easily re-movable. Detergents that have persistent residues such as cationic deter-gents which adhere very strongly to glass and are difficult to remove, should be avoided where possible.
清洁剂应适合清洁工艺的要求，并且本身易被清除。阳离子清洁剂对玻璃有很强的吸附作用，且难以去除，因此，应尽可能避免使用这类能导致难以去除的残留出现的清洁剂。
7.2 The composition of the detergent should be known to the manufac-turer and its removal during rinsing, demonstrated.
药品生产商应清楚清洁剂的组成，且淋洗工艺对于清洁剂的清除效果也应得到证实。
7.3 Acceptable limits for detergent residues after cleaning should be de-fined. The possibility of detergent breakdown should also be considered when validating cleaning procedures.
应规定清洁后，清洁剂的残留限度。验证清洁程序时，应考虑到可能发生的清洁剂的降解。
7.4 Detergents should be released by quality control and, where pos-sible, should meet local food standards or regulations.
选用的清洁剂应当得到质量控制部门的认可，有时还可能需要符合当地的食品标准或管理条例的要求。

8. Microbiology

微生物

8.1 The need to include measures to prevent microbial growth and re-move contamination where it has occurred should be considered.
应考虑对预防微生物生长以及污染发生后如何去除污染的方法的需求。
8.2 There should be documented evidence to indicate that routine clean-ing and storage of equipment does not allow microbial proliferation.
应有说明日常清洁和设备的贮存不利于微生物生长的文件证明。
8.3 The period and conditions for storage of unclean equipment before cleaning, and the

time between cleaning and equipment reuse, should form part of the validation of cleaning procedures.
验证清洁程序时，还应验证未清洁设备的贮存时间和贮存条件，清洁后至再次使用设备之间的时间间隔。

8.4 Equipment should be stored in a dry condition after cleaning. Stagnant water should not be allowed to remain in equipment after cleaning.
清洁后，设备上不得有积水，且应贮存在干燥环境中。

8.5 Control of the bioburden through adequate cleaning and appropriate storage of equipment is important to ensure that subsequent sterilization or sanitization procedures achieve the necessary assurance of sterility, and the control of pyrogens in sterile processing. Equipment sterilization processes may not be adequate to achieve significant inactivation or removal of pyrogens.
为确保后续的灭菌或卫生规程可实现无菌工艺要求的无菌保证水平和热原控制，应重视良好的清洁和适当的贮存对设备上的生物负载所起的控制作用；单凭设备灭菌工艺，可能不足以满足灭活和去除热原的要求。

9 Sampling

取样

9.1 General

概要

9.1.1 Equipment should normally be cleaned as soon as possible after use. This may be especially important for operations with topical products, sus-pensions and bulk drug or where the drying of residues will directly affect the efficiency of a cleaning procedure.
通常，使用设备后，应尽快清洁；尤其是用来生产那些残留物干燥后能直接影响清洁程序的产品、混悬液和散装药品的设备。

9.1.2 Two methods of sampling are considered to be acceptable. These are direct surface sampling and rinse samples. A combination of the two methods is generally the most desirable.
可使用的取样方法有两种：表面直接取样和淋洗水取样。一般来说，最好同时使用这两种方法。

9.1.3 The practice of resampling should not be used before or during cleaning and operations and is acceptable only in rare cases. Constant retesting and resampling can show that the cleaning process is not validated because these retests actually document the presence of unacceptable residue and contaminants resulting from an ineffective cleaning process.
在清洁和使用设备之前，或在清洁和使用过程中，都不应重新取样；在这些时期，只有极少数的情况，方可重新取样。不断的重新检验和取样得到的结果可能显示该清洁工艺无效，这是因为，只有导致残留限度超标和污染物出现的无效的清洁工艺才需要重新检验。

9.2 Direct surface sampling (direct method)

表面直接取样（直接法）

Note: This method of sampling is the most commonly used and involves taking an inert material (e.g. cotton wool) on the end of a probe (referred to as a "swab") and rubbing it methodically across a surface. The type of sampling material used and its potential impact on the test data is important as the sampling material may interfere with the test. (For example, the adhesive used in swabs has been found to interfere with the analysis of samples.)
*注：*这种方法是最常用的。通常使用一端缠绕有不掉纤维的材料（如棉花）的棒（通常称为药签）擦拭取样表面，从而达到取样的目的。要注意的是，药签头的材料对检测可能会产生干扰，因而对实验结果可能有显著影响。（例如，已证实药签上使用的粘合剂会感染样品分析。）

9.2.1 Factors that should be considered include the supplier of the swab, area swabbed, number of swabs used, whether they are wet or dry swabs, swab handling and swabbing technique.
需要考虑的与药签有关的因素有：药签的供应商、擦拭面积、药签的使用量、药签的状态是润湿还是干燥、药签的贮存和擦拭方法等。

9.2.2 The location from which the sample is taken should take into consideration the composition of the equipment (e.g. glass or steel) and the location (e.g. blades, tank walls or fittings). Worst case locations should be considered. The protocol should identify the sampling locations.
选择取样点时，应考虑到设备的构造（如玻璃材料或钢铁材料）、安装位置（如锟刀、贮槽壁和其它装置等）。应当考虑最差状况的安装位置，并在方案中阐明取样点的选择。

9.2.3 Critical areas, i.e. those hardest to clean, should be identifi ed, par-ticularly in large systems that employ semi-automatic or fully automatic clean-in-place systems.
应确定哪些区域属于关键区域（如最难清洁的区域），尤其是那些使用了半自动或全自动在线清洁设备的大型系统的区域。

9.2.4 The sampling medium and solvent used should be appropriate to the task.
采用的取样方法和溶剂应当能满足检验的需要。

9.3 Rinse samples (indirect method)
淋洗水取样（间接取样）

Note: This method allows sampling of a large surface, of areas that are in-accessible or that cannot be routinely disassembled and provides an overall picture. Rinse samples may give sufficient evidence of adequate cleaning where accessibility of equipment parts can preclude direct surface sam-pling, and may be useful for checking for residues of cleaning agents, e.g. detergents.
*注：*该方法为大面积取样方法，对不易接触到的表面和不便经常拆卸的设备也能取样。淋洗水取样不仅可证明不易直接取样的设备表面的清洁效果，而且在检查清洁剂残留时也十分有用。

9.3.1 Rinse samples should be used in combination with other sampling methods such as surface sampling.
淋洗水取样可与表面直接取样等取样方法一同使用。

9.3.2. There should be evidence that samples are accurately recovered. For example, a recovery of > 80% is considered good, > 50% reasonable and < 50% questionable.
应证明样品的回收率。例如，大于80%的回收率可视为良好；大于50%也属于合理，可以接受；若小于50%，则该样品的质量很可疑。

9.4 Batch placebo method
模拟批生产法

Note: This method relies on the manufacture of a placebo batch which is then checked for carry-over of the previous product. It is an expensive and laborious process. It is difficult to provide assurance that the contaminants will be dislodged from the equipment surface uniformly. Additionally, if the particles of the contaminant or residue are large enough, they may not be uniformly dispersed in the placebo batch.
*注：*该法要求模拟一个批次的生产，然后检查前批生产的残留污染，也因为这样，这种方法耗资且耗时。要想给出已经清除全部设备表面的污染的证明，是很不轻松的工作。此外，若污染物或残留物的颗粒太大，它们也可能不会全部转移到模拟生产的批次中去。

9.4.1 The batch placebo method should be used in conjunction with rinse and/or surface sampling method(s).
模拟批生产法应与淋洗取样和/或表面直接取样法联合使用。

9.4.2 Samples should be taken throughout the process of manufacture. Traces of the preceding products should be sought in these samples. (Note that the sensitivity of the assay may be greatly reduced by dilution of the contaminant.)
生产过程也应取样。应通过这些样品，追踪生产的前批产品的痕迹。（注意：因为污染物的稀释，分析实验的灵敏度也会大大降低。）

10. Analytical methods

分析方法

10.1 The analytical methods should be validated before the cleaning vali-dation is performed.
执行清洁验证前，应验证分析方法。
10.2 The methods chosen should detect residuals or contaminants specific for the substance(s) being assayed at an appropriate level of cleanliness (sensitivity).
选用的方法应能检测待分析物中特定的残留物或污染物的含量（灵敏度）。
10.3 Validation of the analytical method should include as appropriate:
分析方法验证应包括以下内容：
— precision, linearity and selectivity (the latter if specific analytes are targeted);
精确度、线性和选择性（选择性仅针对特定的分析物而言）；
— limit of detection (LOD);
检测限（LOD）；
— limit of quantitation (LOQ);
定量限（LOQ）；

— recovery, by spiking with the analyte; and
添加了标准样的分析物的回收率；
— reproducibility.
再现性。

10.4 The detection limit for each analytical method should be suffi ciently sensitive to detect the established acceptable level of the residue or contaminants.
每种分析方法的检测限的灵敏程度应足以检测残留物或污染物的合格限度的量。

10.5 Suitable methods that are sensitive and specific should be used where possible and may include chromatographic methods (e.g. high pres-sure liquid chromotography (HPLC), gas chromotography (GC), and high pressure thin-layer chromatography (HPTLC)). Other methods may include (alone or in combination) measurement of total organic carbon (TOC), pH, or conductivity; ultraviolet (UV) spectroscopy; and enzyme-linked immu-nosorbent assay (ELISA).
分析方法应当具备专属性和一定的灵敏度，如色谱（如高效液相色谱（HPLC）、气相色谱（GC）、高效波层色谱（HPTLC））。其它可能用到的方法还有（单独使用或联合使用）总有机碳（TOC）、pH和电导率测定法、紫外（UV）吸收光谱和酶联免疫吸附分析法（ELISA）。

2 Establishing acceptable limits

建立合格限度

Note: uniform distribution of contaminants is not guaranteed.
*注：*不能保证污染物的分布是均匀的。

11.1 The acceptance criteria established for contaminant levels in the sample should be practical, achievable and verifiable. The rationale for the residue limits established should be logical, and based on the knowledge of the materials involved.
要根据物料的性质和残留限度的确定原理，建立污染物残留的合格标准；建立的限度应是现实的、可行的和可以证明的。

11.2 Each situation should be assessed individually. The manner in which limits are established should be carefully considered. In establishing re-sidual limits it may not be adequate to focus only on the principal reactant, because other chemical variations may be more difficult to remove.
应当分别评估每种情况，仔细选择建立限度的方式。确定限度时，仅仅考虑主要反应物是不够的，因为其它的化学反应的产物可能更难以去除。

11.3 Where necessary, screening using thin-layer chromatography should be performed in addition to chemical analyses.
需要时，可用薄层色谱法作为化学分析方法的补充。

11.4 There should be no residue from the previous product, from reaction by-products and degradants, or from the cleaning process itself (e.g. deter-gents or solvents).
不应检测出前批产品、副产物、降解物和清洁工艺本身造成的物质（如清洁剂和溶剂）的残留。

11.5 The limit-setting approach can:

限度设置方法可以是：

- be product-specifi c;
  产品专一的；
- group products into families and choose a worst case product;
  先将产品归入家族，然后再选择最差状况的产品；
- group products into groups according to risk, e.g. very soluble products, products with similar potency, highly toxic, or difficult to detect products;
  根据风险将产品归类，如极易溶产品、效能相似的产品、剧毒产品和难检测产品等；
- use different safety factors for different dosage forms based on physi-ological response (this method is essential for potent materials).
  根据不同的生理反应，针对不同的剂型使用不同安全因子（尤其是针对活性成分）。

11.6 Limits may be expressed as a concentration in a subsequent product (ppm), limit per surface area (mcg/cm^2), or in rinse water as ppm.
产品中，前次生产的残留限度以浓度（ppm）和每单位表面积的限度（mcg/cm）表示；对淋洗水样品，可用ppm表示。

11.7 The sensitivity of the analytical methods should be defined to enable reasonable limits to be set.
为便于设置合理的残留限度，应说明分析方法的灵敏度。

11.8 The rationale for selecting limits for carry-over of product residues should meet defi ned criteria.
产品残留限度的选择原理应符合既定标准的要求。

11.9 The three most commonly used criteria are:
常用的三种标准有：

- visually clean. (No residue should be visible on equipment after clean-ing.) Spiking studies should determine the concentration at which most active ingredients are visible. This criterion may not be suitable for high-potency, low-dosage drugs;
  不得有肉眼可见的残留物。（清洁后，设备上不得有肉眼可见的残留物）
- no more than 10 ppm of one product will appear in another product (basis for heavy metals in starting materials); and
  先加工产品在后续加工产品中的残留限度不得超过10ppm（根据起始物料的重金属限度）；
- no more than 0.1% of the normal therapeutic dose of one product will appear in the maximum daily dose of a subsequent product.
  服用最大日剂量的后续加工产品而带入体内的先加工产品的量不得超过后者正常治疗剂量的0.1% 。

11.10 The most stringent of three options should be used.
应选择这三种标准中最严格的标准。

11.11 Certain allergenic ingredients (e.g. penicillins and cephalosporins) and highly potent material (e.g. anovulent steroids, potent steroids and cytotoxics) should be undetectable by the best available analytical methods. (In practice this may mean that

dedicated manufacturing facilities should be used for the manufacturing and processing of such products.)
选用的最佳分析方法应能检测出特定的致敏物质（如青霉素和头孢菌素）和高效物质（如可抑制排卵的甾体类物质、效价很强的类固醇和细菌毒素等）。（在生产实践中，指应有生产和加工这类产品的专用生产设施。）

Appendix 4

附录 4

Analytical method validation

分析方法验证

1. Principle

基本原理

1.1 This appendix presents some information on the characteristics that should be considered during validation of analytical methods. Approaches other than those specified in this appendix may be followed and may be acceptable. Manufacturers should choose the validation protocol and procedures most suitable for testing of their product.
这则附录给出了在分析方法验证过程中需要注意的关于方法特性的一些资料，但并不保证这些资料并能完全代表需要注意的所有内容，该附录未提及的其它方法也可能是验证过程中需要遵循且可行的。生产商应当根据他们的产品的需要，选择最适合自己要求的验证方案和验证程序。
1.2 The manufacturer should demonstrate (through validation) that the analytical procedure is suitable for its intended purpose.

供应商应当证明（以验证的方式）所选用的分析方法能满足预期期望。
1.3 Analytical methods, whether or not they indicate stability, should be validated.
所有的分析方法，不论是否属于稳定性指示方法，都应经过验证。
1.4 The analytical method should be validated by research and development before being transferred to the quality control unit when appropriate.
将分析方法技术转移到质量控制部门之前，应适当以研发的方式对分析方法进行验证。

2. General

概述

2.1 There should be specifications for both, materials and products. The tests to be performed should be described in the documentation on standard test methods.
针对物料和产品，都应当制订有相应的合格标准；针对需要执行的试验，应以文件形式说明标准的试验方法。
2.2 Specifications and standard test methods in pharmacopoeias ("pharmacopoeial methods"), or suitably developed specifications or test methods ("non-pharmacopoeial methods") as approved by the national drug regulatory authority may be used.
可使用的合格标准和检验方法有：1.药典中列出的各项标准和标准检验方法（即"药典方法"）；2.自主研发的标准和检验方法，且已经通过国家药政机构证实可行的。
2.3 Well-characterized reference materials, with documented purity, should be used in the validation study.
验证研究中使用的参照标准物料应当是特性已清晰明了的，且纯度已经得到证明的。
2.4 The most common analytical procedures include identification tests, assay of drug substances and pharmaceutical products, quantitative tests for content of impurities and limit tests for impurities. Other analytical procedures include dissolution testing and determination of particle size.
常见的分析方法有：鉴别试验，药物成分和诊疗用品的含量分析方法，杂质的定量试验和限度试验。此外还有溶出度试验和粒径分析试验。
2.5 The results of analytical procedures should be reliable, accurate and reproducible. The characteristics that should be considered during valida-tion of analytical methods are discussed in paragraph 6.
使用分析方法得到的结果应当可靠、准确、可再现。第 6 段就验证分析方法时应考虑的方法的特征参数展开了讨论。
2.6 Verification or revalidation should be performed when relevant, for example, when there are changes in the process for synthesis of the drug sub-stance; changes in the composition of the finished product; changes in the analytical procedure; when analytical methods are transferred from one labo-ratory to another; or when major pieces of equipment instruments change.
出现原料药的合成工艺变更、成品的配方变更、分析方法变更、主要设备变更时，应执行确认或再确认；将分析方法从一个实验室移交到另一个实验室时，也需要执行确认或再确认。
2.7 The verification or degree of revalidation depend on the nature of the change(s).
根据变更的性质，确定确认或再验证的程度。

2.8 There should be evidence that the analysts, who are responsible for certain tests, are appropriately qualified to perform those analyses (“analyst proficiency”).
负责某项实验的检验员应当有执行这些分析的资格证明（“检验员资格证”）。

3. Pharmacopoeial methods

药典方法

3.1 When pharmacopoeial methods are used, evidence should be avail-able to prove that such methods are suitable for routine use in the laboratory (verifi cation).
如使用了药典中记载的分析方法，应证明该方法适合实验室日常使用，且该证明过程应有据可查。
3.2 Pharmacopoeial methods used for determination of content or impurities in pharmaceutical products should also have been demonstrated to be specific with respect to the substance under consideration (no placebo interference).
应证明所使用的药品含量或杂质的药典测定方法对待测物具专一性（对照实验对实验无干扰）。

4. Non-pharmacopoeial methods

非药典方法

4.1 Non-pharmacopoeial methods should be appropriately validated.
如使用了药典未记载的方法，应验证。

5. Method validation

方法验证

5.1 Validation should be performed in accordance with the validation pro-tocol. The protocol should include procedures and acceptance criteria for all characteristics. The results should be documented in the validation report.
应严格按照验证方案实施验证。方案中，应阐明验证程序和所有方法的特征参数的合格标准。验证结果应记录在验证报告中。
5.2 Justification should be provided when non-pharmacopoeial methods are used if pharmacopoeial methods are available. Justification should in-clude data such as comparisons with the pharmacopoeial or other methods.
在有药典方法可用的情况下，如使用了非药典的方法，应就此给出采用后者的合理证明；在证明文件中，应给出药典方法和非药典方法的比较。
5.3 Standard test methods should be described in detail and should provide sufficient information to allow properly trained analysts to perform the analysis in a reliable manner. As a minimum, the description should include the chromatographic conditions (in the case of chromatographic tests), reagents needed, reference standards, the formulae for the calculation of results and system suitability tests.
应详细说明标准实验方法，同时给出实验资料，以保证培训后的检验员能可靠地完成分析实验。对实验进行说明时，至少应阐明色谱条件（如采用了色谱分析方法）、实验试剂、对照标准品、结果计算公式和系统适应性实验。

6 Characteristics of analytical procedures

分析方法的特征

6.1 Characteristics that should be considered during validation of analytical methods include:
验证分析方法时，应考虑的方法的特征参数有：

— specifi city
专属性
— linearity
线性
— range
范围
— accuracy
准确度
— precision
精确度
— detection limit
检测限
— quantitation limit
定量限
— robustness.
耐用性。

6.1.1 *Accuracy* is the degree of agreement of test results with the true value, or the closeness of the results obtained by the procedure to the true value. It is normally established on samples of the material to be examined that have been prepared to quantitative accuracy. Accuracy should be estab-lished across the specified range of the analytical procedure.
*准确度*系指测量值与真实值的偏离程度，或指根据分析方法获得的结果与真实值之间的接近程度。确定准确度时，通常需要特地针对该目的制备待测物样品，然后测量样品，从而确定该方法的特征参数。对于指定的分析方法的所有范围，最终确定的准确度应都适用。

Note: it is acceptable to use a “spiked” placebo where a known quantity or concentration of a reference material is used.
*注：*分析时，可向对照品中添加已知量或已知浓度的对照品。

6.1.2 *Precision* is the degree of agreement among individual results. The complete procedure should be applied repeatedly to separate, identical samples drawn from the same homogeneous batch of material. It should be measured by the scatter of individual results from the mean (good group-ing) and expressed as the relative standard deviation (RSD).
*精确度*系指测量值之间的偏离程度。确定精确度时，应先对同一个均匀的产品批取样，然后再对同一样品重复、完整地实施整个分析程序，最后比较单个测量值与平

均值（要精确分类）。一般用相对标准偏差（RSD）表示精确度。

6.1.2.1 *Repeatability* should be assessed using a minimum of nine determi-nations covering the specified range for the procedure e.g. three concentra-tions/three replicates each, or a minimum of six determinations at 100% of the test concentration.
确定*重复性*时，至少要评估代表了规定的分析范围的9个测量值，如三种浓度/每种浓度三个样品；或在不稀释供试品的情况下取同一浓度的6个样品，而后分析测试。

6.1.2.2 *Intermediate precision* expresses within-laboratory variations (usually on different days, different analysts and different equipment). If reproducibility is assessed, a measure of intermediate precision is not required.
*中间精密度*指的是实验室内的偏差（往往指在不同测试时间、不同的检验员和使用不同的仪器时出现的偏差）。如已评估了方法的再现性，可不必再测量中间精密度。

6.1.2.3 *Reproducibility* expresses *precision* between laboratories.
*再现性*指的是实验室之间的*精确度*。

6.1.3 *Robustness* (or *ruggedness*) is the ability of the procedure to provide analytical results of acceptable accuracy and precision under a variety of conditions. The results from separate samples are infl uenced by changes in the operational or environmental conditions. Robustness should be considered during the development phase, and should show the reliability of an analysis when deliberate variations are made in method parameters.
*耐用性（或重现性）*指在不同测量条件下，分析方法提供合格的准确度和精密度的分析结果的能力。如测量条件的不同，单个样品的测量结果会受到不同的操作或环境的影响。应当在方法研发阶段确定耐用性；方法的特征参数发生改变时，应能证明分析方法的可靠性。

6.1.3.1 Factors that can have an effect on robustness when performing chromatographic analysis include:
使用色谱方法分析时，对耐用性产生影响的因素有：

— stability of test and standard samples and solutions;
实验、对照品和溶液的稳定性；
— reagents (e.g. different suppliers);
试剂（如不同的供应商）；
— different columns (e.g. different lots and/or suppliers);
不同的色谱柱（如色谱柱分属不同的小批和/或供应商）
— extraction time;
萃取时间；
— variations of pH of a mobile phase;
流动相的pH的变化；
— variations in mobile phase composition;
流动相的组成的变化；
— temperature; and
温度；
— fl ow rate.
流速。

6.1.4 *Linearity* indicates the ability to produce results that are directly proportional to the concentration of the analyte in samples. A series of samples should be prepared in which the analyte concentrations span the claimed range of the procedure. If there is a linear relationship, test results should be evaluated by ap-propriate statistical methods. A minimum of five concentrations should be used.
*线性*系指测量值与样品中待测物的浓度成比例的能力。确定方法的线性时，需制备一系列待测物浓度可代表分析方法的规定范围的样品（至少应准备5种浓度）。如存在线性关系，就能用适当的统计学方法评估分析测量值。

6.1.5 *Range* is an expression of the lowest and highest levels of analyte that have been demonstrated to be determinable for the product. The speci-fied range is normally derived from linearity studies.
*范围*系指在已证明的现有测量能力下，可测得的供试品中待测物的量的上限和下限。研究线性时，通常即可确定方法的范围。

6.1.6 *Specifi city* (*selectivity*) is the ability to measure unequivocally the desired analyte in the presence of components such as excipients and impu-rities that may also be expected to be present. An investigation of specifi city should be conducted during the validation of identification tests, the deter-mination of impurities and assay.
*专属性（选择性）*系指在存在其它成分（如辅料和杂质）的情况下，分析方法测量某一特定待测物的能力。应当在验证鉴别试验、杂质测定和含量测定方法时，研究方法的专属性。

6.1.7 *Detection limit* (*limit of detection*) is the smallest quantity of an ana-lyte that can be detected, and not necessarily determined, in a quantitative fashion. Approaches may include instrumental or non-instrumental proce-dures and could include those based on:
*检测限*是不一定需要被测定的参数，它指的是以定量形式给出的可检出的待测物的最小量。确定检测限时，可用仪器或非仪器的方法，其方法依据如：

— visual evaluation;
目检；
— signal to noise ratio;
信噪比；
— standard deviation of the response and the slope;
响应值和斜率的标准偏差；
— standard deviation of the blank; and
空白对照试验组的标准偏差值；
— calibration curve.
校准曲线。

6.1.8 *Quantitation limit* (*limit of quantitation*) is the lowest concentration of an analyte in a sample that may be determined with acceptable accuracy and precision. Approaches may include instrumental or non-instrumental procedures and could include those based on:
*定量限（量的限度）*指可测量的样品中待测物最低浓度，该值具备合格的准确度和精确度。确定定量限的方法可以是使用仪器的，也可以是不使用仪器的，其方法依据有：

— visual evaluation;
目检；
— signal to noise ratio;
信噪比；
— standard deviation of the response and the slope;
响应值和斜率的标准偏差；
— standard deviation of the blank; and
空白对照试验组的标准偏差值；
— calibration curve.
校准曲线。

6.2 Characteristics (including tests) that should be considered when using different types of analytical procedures are summarized in Table 1.
选用不同的分析方法时，需要考虑的特征参数（包括试验）总结见表1。

Table 1
表1
Characteristics to consider during analytical validation
分析验证中需靠考虑的特征参数

Type of analytical procedure	Identification	Testing for impurities	Testing for impurities	Assay — dissolution (measurement only) — content/potency
Characteristics		Quantitative tests	Limit tests	
Accuracy	–	+	–	+
Precision				
Repeatability	–	+	–	+
Intermediate precision[a]	–	+	–	+
Specificity	+	+	+	+
Detection limit	–	–[b]	+	–
Quantitation limit	–	+	–	–
Linearity	–	+	–	+
Range	–	+	–	+

分析方法类型	鉴别试验	杂质分析试验	杂质分析试验	含量测定 - 溶出度 （仅指测定试验） - 含量/效价
特征参数		定量分析试验	限度分析试验	
准确度	–	+	–	+
精确度				
重复性	–	+	–	+
中间精密度a	–	+	–	+
专属性	+	+	+	+
检测限	–	–b	+	–
定量限	–	+	–	–
线性	–	+	–	+
范围	–	+	–	+

– Characteristic is normally not evaluated;

+ Characteristic should normally be evaluated.

[a] In cases where a reproducibility study has been performed, intermediate precision is not needed.

[b] May be needed in some cases.

- 通常不予评估分析的特征参数；

+ 通常要求评估分析的特征参数；

[a]如已开展了重现性研究，则无需再再评估中间精密度。

[b]某些情况下需要。

6.3 System suitability testing

系统适应性试验

System suitability testing is an integral part of many analytical procedures. The tests are based on the concept that the equipment, electronics, analyti-cal operations and samples to be analysed constitute an integral system that can be evaluated as such. System suitability test parameters that need to be established for a particular procedure depend on the type of procedure be-ing evaluated, for instance, a resolution test for an HPLC procedure.

系统适应性试验是许多分析程序不可或缺的组成部分。之所以需要开展系统适应性试验，是因为设备、电子系统、分析操作和供试品共同构成了需要分析评估的整体。针对不同的分析方法，根据评估的具体程序的类型，需要分别建立系统适应性参数，如HPLC方法所要求的分辨率试验。

Appendix 5

附录 5

Validation of computerized systems

计算机化系统的验证

1. General

概述

1.1 Computer systems should be validated at the level appropriate for their use and application. This is of importance in production as well as in quality control.
应根据计算机系统的具体使用和应用，对该系统进行验证。该系统的验证在生产中扮演的角色与质量控制具同等重要性。

1.2 The use of a computer system includes different stages. These are planning, specification, programming, testing, commissioning, document operation, monitoring and modifying.
可将计算机系统的使用分成不同的阶段，即计划、规范、编程、测试、试运行、文件操作、监控和更新。

1.3 The purpose of validation of a computer system is to ensure an ac-ceptable degree of evidence (documented, raw data), confi dence (dependability and thorough, rigorous achievement of predetermined specifi ca-tions), intended use, accuracy, consistency and

reliability.
计算机系统验证的目的是确保证明系统的资料（引证、原始数据）、置信度（可信赖度和彻底、严格实现既定标准的能力）、用途、准确度、持续性和可靠性均合格。

1.4 Both the system specifications and functional specifi cations should be validated.
系统规范和功能技术标准均需验证。

1.5 Periodic (or continuous) evaluation should be performed after the initial validation.
初次验证过后，应定期（或持续）评估。

1.6 There should be written procedures for performance monitoring, change control, programme and data security, calibration and maintenance, personnel training, emergency recovery and periodic re-evaluation.
应有针对性能监控、变更控制、工程计划和数据安全、校准和维护、人员培训、紧急状况的恢复措施和定期再验证的书面规程。

1.7 Aspects of computerized operations that should be considered during validation include:
验证过程中，需考虑的与计算机化操作有关的方面有：

— networks
网络
— manual back-ups
手动备份
— input/output checks
输入/输出检查
— process documentation
工艺证明文件
— monitoring
监控
— alarms
警报
— shutdown recovery.
停电后的恢复

2. System specifi cation

系统规范

2.1 There should be a control document or system specifi cation. The control document should state the objectives of a proposed computer sys-tem, the data to be entered and stored, the flow of data, how it interacts with other systems and procedures, the information to be produced, the limits of any variable and the operating programme and test programme. (Examples of each document produced by the programme should be included.)
应有控制文件或系统规范。在控制文件中，应阐明计算机系统的使用对象、录入和储存的数据、数据流向、与其它系统和程序之间的作用、产生的信息、所有变量的

限度、运行程序和测试程序等。（应对程序产生的所有文件举例）

2.2 System elements that need to be considered in computer validation include hardware (equipment), software (procedures) and people (users).

计算机验证过程中需要考虑的系统要素有硬件（设备）、软件（程序）和人员（操作人）。

3. Functional specifi cation

功能技术规范

3.1 A functional or performance specification should provide instructions for testing, operating, and maintaining the system, as well as names of the person(s) responsible for its development and operation.

应有功能或性能技术规范说明，以供系统测试、操作和维护使用，并说明系统研发和操作的负责人的姓名。

3.2 The following general aspects should be kept in mind when using computer systems:

使用计算机系统时，应注意以下几个方面：

— location
安装位置
— power supply
动力供应
— temperature, and
温度
— magnetic disturbances.
磁场干扰。

Fluctuations in the electrical supply can influence computer systems and power supply failure can result in loss of memory.

电力供应的波动会影响计算机系统的运作，而动力供应的故障能导致存储资料的丢失。

3.3 The following general good manufacturing practice (GMP) require-ments are applicable to computer systems.

下面给出的是适用于计算机系统的药品生产管理规范（GMP）。

- *Verifi cation and revalidation.* After a suitable period of running a new system it should be independently reviewed and compared with the sys-tem specification and functional specifi cation.
  *核查确认*和*再验证*。当新系统运行了一段时间后，应对它单独审查，并将它的运行情况与系统规范和功能技术规范进行比较。
- *Change control.* Alterations should only be made in accordance with a defi ned procedure which should include provision for checking, approv-ing and implementing the change.
  变更控制。应根据既定程序实施变更。变更程序中应就变更的核查、审批和实施有说明。
- *Checks.* Data should be checked periodically to confirm that they have been

accurately and reliably transferred.
检查。应定期检查数据，以确认数据转移准确可靠。

4. Security

安全

4.1 This is of importance in production as well as in quality control.
对生产而言，计算机安全与质量控制具有同等的重要性。

4.2 Data should be entered or amended only by persons authorized to do so. Suitable security systems should be in place to prevent unauthorized entry or manipulation of data. The activity of entering data, changing or amending incorrect entries and creating back-ups should all be done in ac-cordance with written, approved standard operating procedures (SOPs).
仅有经授权的人员方可输入或修改数据。应有适当的安全系统来防止未经授权的数据输入或数据处理行为。应针对数据输入、数据变更、修改错误的数据输入和数据备份，建立经过审批的书面标准操作规程（SOP），并严格执行。

4.3 The security procedures should be in writing. Security should also extend to devices used to store programmes, such as tapes, disks and magnetic strip cards. Access to these devices should be controlled.
应制订安全程序的书面文件。程序的储存形式（如磁带、磁盘和磁卡等）的安全也应得到保证，这些储存形式的访问也应受到限制。

4.4 Traceability is of particular importance and it should be able to iden-tify the persons who made entries/changes, released material, or performed other critical steps in manufacture or control.
数据的可追溯性的重要性尤其突出。追溯时，应能确定输入数据/变更数据、物料放行、执行生产和控制措施活动的关键步骤的人员。

4.5 The entry of critical data into a computer by an authorized person (e.g. entry of a master processing formula) requires an independent verifi -cation and release for use by a second authorized person.
由经过授权的人员输入的关键数据（如主工艺配方）应得到另一个获得授权的人员的核实方可放行。

4.6 SOPs should be validated for certain systems or processes, e.g. the procedures to be followed if the system fails or breaks down should be de-fined and tested. Alternative arrangements should be made by the validation team, and a disaster recovery procedure should be available for the systems that need to be operated in the event of a breakdown.
某些系统或工艺的SOP也需要验证，如因系统故障或不合格而需要调查和检验时，所需遵循的那些规程。出现故障时，应有可用的灾难恢复程序，验证小组也应针对故障安排其它的备用方法。

5. Back-ups

备份

5.1 Regular back-ups of all files and data should be made and stored in a secure location to prevent intentional or accidental damage.
应定期备份所有文件和数据；为防止意外事故，应将备份储存在安全的场所。

6. Validation

验证

6.1 Planning, which should include the validation policy, project plan and SOPs, is one of the steps in the validation process.
包括验证方针、工程计划和SOP在内的计划是验证过程的一个组成部分。
6.2 The computer-related systems and vendors should be defi ned and the vendor and product should be evaluated. The system should be designed and constructed, taking into consideration the types, testing and quality as-surance of the software.
应详细说明与计算机有关的系统和供应商，并对供应商和产品进行评估。设计和构筑系统时，应将系统类型、系统测试和质量保证措施考虑在内。
6.3 After installation of the system it should be qualifi ed. The extent of the qualification should depend on the complexity of the system. The system should be evaluated and performance qualification, change control, mainte-nance and calibration, security, contingency planning, SOPs, training, per-formance monitoring and periodic re-evaluation should be addressed.
安装之后，应当对系统展开确认活动，确认活动实施的程度视系统的复杂性而定。确认活动的内容包括系统评估、性能确认、变更控制、维护和校准、系统安全、意外事故的应急措施的计划、SOP、培训、性能监控、和定期再验证的计划。

7. Validation of hardware and software

硬件和软件验证

Table 1 indicates aspects of computer systems that should be subjected to validation.
表1的内容指出了需要验证的计算机系统的各个方面。

Table 1
表 1
Summary of validation requirements for computer systems
计算机系统的验证要求总览

Hardware 硬件	Software 软件
1. Types 类型	1. Level 级别
1.1 Input device 输入设备	1.1 Machine language 机器语言
1.2 Output device 输出设备	1.2 Assembly language 汇编语言
1.3 Signal converter	1.3 High-level language

信号转换器 1.4 Central processing unit (CPU) 中央处理器（CPU） 1.5 Distribution system 系统配置 1.6 Peripheral devices 外围设备	高级语言 1.4 Application language 应用语言
2. Key aspects 重要方面 2.1 Location environment distance input devices 安装位置、环境、距离和输入设备 2.2 Signal conversion 信号转换 2.3 I/O operation I/O 操作 2.4 Command overrides 命令清除 2.5 Maintenance 维护	2. Software identification 软件的鉴定 2.1 Language 语言 2.2 Name 名称 2.3 Function 功能 2.4 Input 输入 2.5 Output 输出 2.6 Fixed set point 固定的设置点 2.7 Variable set point 可变的设置点 2.8 Edits 编辑 2.9 Input manipulation 输入操作 2.10 Programme overrides 程序的清除
3. Validation 验证 3.1 Function 功能 3.2 Limits 限度 3.3 Worst case 最差状况 3.4 Reproducibility/consistency 重现性/持续性 3.5 Documentation 文件 3.6 Revalidation 再验证	3. Key aspects 重要方面 3.1 Software development 软件研发 3.2 Software security 软件安全

	4. Validation 验证 4.1 Function 功能 4.2 Worst case 最差状况 4.3 Repeats 重复 4.4 Documentation 文件 4.5 Revalidation 再验证

I/O, Input/output.
I/O：输入/输出。

7.1 Hardware
硬件

7.1.1 As part of the validation process appropriate tests and challenges to the hardware should be performed.
适当的测试和对硬件的挑战试验应作为验证过程的一部分而执行。

7.1.2 Static, dust, power-feed voltage fluctuations and electromagnetic interference could influence the system. The extent of validation should de-pend on the complexity of the system. Hardware is considered to be equip-ment, and the focus should be on location, maintenance and calibration of hardware, as well as on validation/qualifi cation.
静电、灰尘、输入电压的波动和电磁干扰都对系统有影响。验证实施的程度由系统的复杂性而定。应将硬件作为设备看待，因此，对它们进行验证/确认时，应将重点放在安装位置、维护和软件校准上。

7.1.3 The validation/qualification of the hardware should prove:
硬件的验证/确认活动应能证明：

- that the capacity of the hardware matches its assigned function (e.g. foreign language);
  硬件的性能能满足所指定任务的需要（如外国语言）；
- that it operates within the operational limits (e.g. memory, connector ports, input ports);
  硬件的运行不超出运行限度（如记忆储存、连接器端口、输入端口）
- that it performs acceptably under worst-case conditions (e.g. long hours, temperature extremes); and
  在最差状况（如长时间、温度极值）下运行时，系统也可正常运行；
- reproducibility/consistency (e.g. by performing at least three runs under different conditions).
  重现性/持续性（如在不同情况下至少运行三次）。

7.1.4 The validation should be done in accordance with written qualifi ca-tion protocols and the results should be recorded in the qualifi cation reports.
应按照确认方案的书面文件，严格执行验证；并将验证结果记录在确认报告中。

7.1.5 Revalidation should be performed when significant changes are made.
发生重大变更后，应执行再验证。

7.1.6 Much of the hardware validation may be performed by the computer vendor. However, the ultimate responsibility for the suitability of equip-ment used remains with the company.
虽然许多硬件的验证应由计算机的供应商执行，但企业应对设备使用的适用性负主要责任。

7.1.7 Hardware validation data and protocols should be kept by the com-pany. When validation information is produced by an outside fi rm, e.g. computer vendor, the records maintained by the company need not include all of the voluminous test data; however, such records should be sufficiently complete (including general results and protocols) to allow the company to assess the adequacy of the validation. A mere certifi cation of suitability from the vendor, for example, will be inadequate.
硬件的验证数据和方案应由企业保管。如果这些验证资料来自企业外部，如计算机供应商，在这种情况下，企业不需要保存所有的测试数据，但应保证记录的完整和充分（包括总体结果和方案）足以使企业评估验证的充分性。例如，如仅有供应商提供的适应性资料，是不符合要求的。

7.2 Software
软件

7.2.1 Software is the term used to describe the complete set of programmes used by a computer, and which should be listed in a menu.
软件这个词在这里用来描述计算机使用的所有程序。应有软件清单。

7.2.2 Records are considered as software; focus is placed on accuracy, security, access, retention of records, review, double checks, documentation and accuracy of reproduction.
记录在这里亦被视为软件，因此，它们的验证重点放在准确度、安全、访问、记录保存、审核、双人检查、存档和复制的准确度上。

Identifi cation
鉴定

7.2.3 The company should identify the following key computer pro-grammes: language, name, function (purpose of the programme), input (determine inputs), output (determine outputs), fixed set point (process variable that cannot be changed by the operator), variable set point (entered by the operator), edits (reject input/output that does not conform to limits and minimize errors, e.g. four- or five-character number entry), input manipulation (and equations) and programme overrides (e.g. to stop a mixer before time).
企业应鉴定下列关键的计算机程序：语言、名称、功能（程序的目的）、输入（确定输入）、输出（确定输出）、固定的设置点（操作者不可更改的过程变量）、可变的设置点（由操作者输入）、编辑（拒绝不合限度要求的输入/输出和最小的错误，如四或五位数的输入）、输入控制（及方程式）和程序清除（如在设定时间达

到之前停止搅拌机的运转）。

7.2.4 The personnel who have the ability and/or are authorized to write, alter or have access to programmes should be identifi ed.
应鉴定有能力和/或有权编写、变更或访问程序的人员。

7.2.5 Software validation should provide assurance that computer pro-grammes (especially those that control manufacturing and processing) will consistently perform as they are supposed to, within pre-established limits.
软件的验证应能保证计算机程序（特别是控制生产和工艺的程序）的运行能够持续完成它们的设计要求，程序的运行结果符合既定限度。
When planning the validation, the following points should be considered.
设计验证时，应考虑下列问题。

- Function: does the programme match the assigned operational function (e.g. generate batch documentation, different batches of material used in a batch listed)?
  功能：程序是否能满足所需完成任务的要求（如得到批文件、列出一次批生产中用到的不同物料批）？
- Worst case: perform validation under different conditions (e.g. speed, data volume, frequency).
  最差状况：在不同条件下实施验证（如速度、数据量、频率）。
- Repeats: sufficient number of times (replicate data entries).
  重复：重复次数应足够（重复数据输入）。
- Documentation: protocols and reports.
  文件：方案和报告。
- Revalidation: needed when significant changes are made.
  再验证：需要在发生重大变更后执行。

Appendix 6

附录 6

Qualification of systems and equipment

系统和设备确认

1. Principle

基本原理

1.1 Systems and equipment should be appropriately designed, located, installed, operated and maintained to suit their intended purpose.

系统和设备的设计、安装位置的确定、安装、运行和维护都应符合它们的用途的需要。

1.2 Critical systems, i.e. those whose consistent performance may have an impact on the quality of products, should be qualified. These may in-clude, where appropriate, water purification systems, air-handling systems, compressed air systems and steam systems.

对关键系统，如连续运行可能会对产品质量产生影响的的设备，需要进行确认。这些系统可能有水纯化系统、空气处理系统、压缩空气系统和蒸汽系统。

1.3 The continued suitable performance of equipment is important to ensure batch-to-batch consistency. Critical equipment should therefore be qualifi ed.

为保证持续生产出满足质量要求的不同批次的产品，设备的正常运转应具备持续性。

因此，需要对关键设备进行确认。

2. Scope

范围

2.1 These guidelines describe the general aspects of qualifi cation for systems and equipment.
这些指南阐述了一般情况下，系统和设备确认活动所涉及的方面。
2.2 Normally qualification would be applicable to critical systems and equipment whose performance may have an impact on the quality of the product.
关键系统和设备的性能往往对产品质量有影响，因此，它们也往往需要确认。

3. General

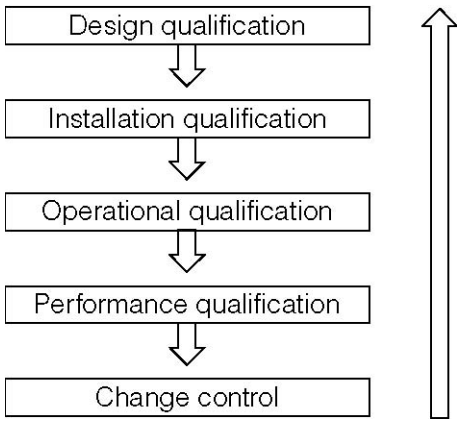
概述

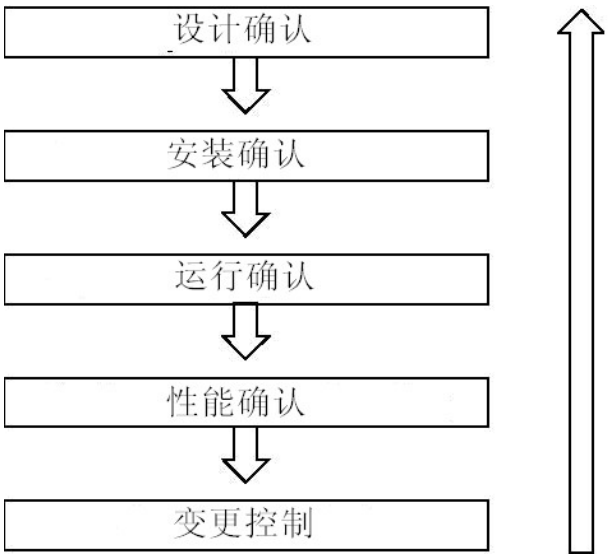
3.1 The manufacturer should have a qualification policy for systems and equipment.
生产商应针对系统和设备制定确认活动的方针。

3.2 Equipment (including instruments) used in production and quality control should be included in the qualification policy and programme.
生产和质量控制中使用的设备（包括仪器）应在确认方针和确认项目中有说明。

3.3 New systems and equipment should pass through all stages of quali-fication including design qualification (DQ), installation qualifi cation (IQ), operational qualification (OQ) and performance qualification (PQ) as ap-propriate (Fig. 1).
对新的系统和设备，需要实施全部的确认，包括设计确认（DQ）、安装确认（IQ）、运行确认（OQ）和性能确认（PQ）（见图1）。

Figure 1
图 1
Stages of qualifi cation
确认的阶段





3.4 In some cases, not all stages of qualification may be required. See also the guidelines on the qualification of water purification systems in Appendix 2 and heating, ventilation and air-conditioning (HVAC) in Appendix 1.
某些情况下，并不需要实施所有阶段的确认。见附录2中的水纯化系统确认指南和附录1中对采暖、通风和空气净化（HVAC）系统的说明。

3.5 Systems should be qualified before equipment.
系统确认的完成应先于设备确认。

3.6 Equipment should be qualified prior to being brought into routine use to provide documented evidence that the equipment is fit for its in-tended purpose.
在设备投入使用前，应对之确认，以得到该设备可满足预期使用目的的文件化证明。

3.7 Systems and equipment should undergo periodic requalifi cation, as well as requalification after change.
应定期对系统和设备确认，发生变更后，还应执行再确认。

3.8 Certain stages of the equipment qualification may be done by the supplier or a third party.
设备确认的某些步骤可由供应商或第三方完成。

3.9 The relevant documentation associated with qualifi cation including standard operating procedures (SOPs), specifications and acceptance crite-ria, certificates and manuals should be maintained.
应保存与确认活动有关的文件，如标准操作规程（SOP）、技术规范和合格标准、证书和使用手册。

3.10 Qualification should be done in accordance with predetermined and approved qualifi cation protocols. The results of the qualifi cation should be recorded and reflected in qualifi cation reports.
应按照既定的获准确认方案实施确认，记录确认结果，并将确认结果体现在确认报告中。

3.11 The extent of the qualification should be based on the criticality of a system or equipment (e.g. blenders, autoclaves or computerized systems).
根据系统或设备的关键性，确定确认活动的实施程度（如搅拌机、高压灭菌器或计算机化系统等）。

4. Design qualifi cation

设计确认

Note: see also "Supplementary guidelines on good manufacturing practices (GMP): validation".
*注：*见"药品生产管理规范（GMP）的补充指南：验证"。

4.1 User requirements should be considered when deciding on the spe-cific design of a system or equipment.
决定具体系统或设备的设计时，应考虑用户的需求。

4.2 A suitable supplier should be selected for the appropriate system or equipment (approved vendor).
针对具体的系统或设备，应选择合适的供应商。

5. Installation qualifi cation

安装确认

Note: see also "Supplementary guidelines on good manufacturing practices (GMP): validation".
*注：*见"药品生产管理规范（GMP）的补充指南：验证"。

5.1 Systems and equipment should be correctly installed in accordance with an installation plan and installation qualifi cation protocol.
应根据安装计划和安装确认方案，正确安装系统和设备。

5.2 Requirements for calibration, maintenance and cleaning should be drawn up during installation.
安装时，应注意满足校准、维护和清洁的要求。

5.3 Installation qualification should include identification and verifi ca-tion of all system elements, parts, services, controls, gauges and other com-ponents.
安装确认活动应包括所有系统组件、部件、维护、控制、仪表和其他配件的鉴定和核查确认。

5.4 Measuring, control and indicating devices should be calibrated against appropriate national or international standards, which are traceable.
应根据国家或国际标准，校准测量、控制和指示设备；这些校准应当可追踪。

5.5 There should be documented records for the installation (installation qualification report) to indicate the satisfactoriness of the installation, which should include the details of the supplier and manufacturer, system or equipment name, model and serial number,

date of installation, spare parts, relevant procedures and certifi cates.
应有可说明安装活动的结果的满意程度的文件记录（安装确认报告）。记录的内容应说明供应商和制造商的详细情况、系统或设备名称、型号和序列号、安装日期、零部件、相关程序和证书。

Format for an installation qualification protocol and report[a]

安装确认方案和报告格式[a]

Validation protocol _____ Installation Qualifi cation _____ Page _____ of _____

Title: _____ Name and address of site: _____

验证方案_____安装确认_____第___页，共___页；标题：_____

名称和地址：_____

Validation Protocol #/验证方案编号 _____

IQ Protocol number/IQ方案号: _____ Title/标题:

_____

Protocol written by/方案起草人: _____ Protocol approved by/方案审批人: _____ Date/日期: _____

QA Approval/QA审批: _____ Date/日期: _____

Objective

To ensure that _____ (system/equipment) installed conforms to the purchase specifications and the manufacturer details and literature, and to document the information that _____ (system/equipment) meets its specifications.

目的

为确保_____（系统/设备）的安装符合采购说明和制造商提供的说明书描述的要求，以及证明_____（系统/设备）本身亦符合要求。

Equipment inventory number/设备清单号:

_____

Scope

To perform installation qualification as described in this IQ protocol at the time of installation, modification and relocation.

范围

在安装、变更和改变安装位置的阶段，按照IQ方案实施安装确认。

Responsibility

_____ (post/person) overseeing the installation will perform the qualifica-tion and records results. _____ (post/person) will verify results and write the report. Quality Assurance will review and approve the IQ protocol and report.

责任

由_____（岗位/人员）负责监督安装确认的实施和结果记录；_____（岗位/人员）负责复核结果和起草报告，质量保证部负责IQ方案和报告的审核和批准。

[a] This format is used for training purposes and refl ects some of the possible contents for an installation qualifi ca-tion protocol.

本格式仅供培训用，其内容体现了安装确认方案中可能出现的内容。

Format for an installation qualification protocol and report (continued)[a]

安装确认和报告的格式（续）[a]

Validation protocol _____ Installation Qualifi cation _____ Page _____ of _____

Title: _____ Name and address of site: _____

验证方案_____安装确认_____第___页，共___页；标题：_____

名称和地址：_____

System/Equipment _____ Code no.: _____

系统/设备_____ 设备编号：_____

a. Description of the system/equipment being installed: general description of the func-tion and the main components.

安装中的系统/设备的说明：功能和主要部件的总体说明

b. List of the main components:

主要部件清单：

1._____Code no./编号: _____

2. _____ Code no./编号: _____

3. _____ Code no./编号: _____

4. _____ Code no./编号: _____

c. Description of supporting utilities (e.g. piping, connections, water supply)

支持工程设施的说明（如管道系统、连接系统、水供应系统等）

1. _____Code no./编号: _____

2. _____Code no./编号: _____

3. _____Code no./编号: _____

4. _____Code no./编号: _____

Procedure

步骤

1. Prepare a checklist of all components and parts, including spare parts according to the purchase order and manufacturer's specifications.

根据订购单和制造商提供的说明书准备所有配件和零部件的清单。

2. Record the information for each actual part, component, item of auxiliary equipment, supporting facilities, and compare with the manufacturer's specifications.

记录每个实际使用的零件、配件、辅助设备、支持设施的信息，并将之与制造商提供的说明书比较。

3. Record any deviations to the system/equipment.

记录系统/设备的所有偏差。

4. Prepare a deviation report including justification of acceptance and impact on the function.

起草偏差报告，说明接受偏差的原因和对功能的影响。

5. Prepare an IQ report.[b]

准备IQ报告。[b]

6. Submit the report to QA for review and approval.

将报告递交给QA，等待审核和批准。

[a] This format is used for training purposes and refl ects some of the possible contents for an installation qualification protocol.

本格式仅供培训用，其内容体现了安装确认方案中可能出现的内容。

[b] As a minimum, the IQ report should include the date of initiation of the study, date completed, observations made, problems encountered, completeness of information collected, summary of deviation report, results of any tests, sample data (if appropriate), location of original data, other information relevant to the study, and the conclusion on the validity of the installation.

IQ 报告的内容至少应包括：研究的启动日期和完成日期、执行的观察、研究过程中遇到的问题、资料收集的完整性、偏差报告总结、所有测试结果、样品数据（可选）、原始数据的存储路径、与研究有关的其他资料、以及安装效果的结论。

Format for an installation qualification protocol and report (continued)[a]

安装确认和报告的格式（续）[a]

Validation protocol _____ Installation Qualifi cation _____ Page _____ of _____ Title: _____ Name and address of site: _____

验证方案_____安装确认_____第___页，共___页；标题：_____

名称和地址：_____

Checklist for component no./部件编号清单 _____

Name/名称: _____Code no./编号: _____

Component function/部件功能：_____

		Require/order 需求/订单说明	Actual 实际情况	Deviations 偏差
1	Model/serial no./型号/序列号			
2	Specifi cation /技术规范			
3	Manual /手册			
4	Drawing /图纸			
5	Wiring/cabling /线路			
6	Power, fusing /动力、保险丝			
7	SOP (operation) /（操作） SOP (maintenance) /（维护） SOP (calibration) /（校准）			
8	Input/output control /输入/输出控制			
9	Environment /环境			
10	Test equipment or instruments / 试验设备或仪器			
11	Utilities and service /公用工程和维护			
12	Spare parts list, part number and supplier / 零部件清单、零件编号和供应商			
13	Other /其它			

Performed by: _____ Date: _____

实施人：_____日期：_____

Deviations: _____ Date: _____

偏差：_____日期：_____

Verifi ed by: _____ Date:_____

复核人：_____日期：_____

[a] This format is used for training purposes and refl ects some of the possible contents for an installation qualifi ca-tion protocol.

本格式仅供培训用，其内容体现了安装确认方案中可能出现的内容。

Format for an installation qualification protocol and report (continued)[a]

安装确认和报告的格式（续）a

Validation protocol _____ Installation Qualification _____ Page _____ of _____ Title: _____ Name and address of site: _____

验证方案_____安装确认_____第___页，共___页；标题：_____

名称和地址：_____

Deviation report

偏差报告

Deviations/偏差:_____

_____

Justification for acceptance/接受偏差的理由

_____

_____

_____

_____

_____

_____

Impact on operation/对操作的影响:

_____

_____

_____

_____

_____

_____

Report written by: _____ Date: _____

报告起草人：_____日期：_____

[a]This format is used for training purposes and reflects some of the possible contents for an installation qualifica-tion protocol.

本格式仅供培训用，其内容体现了安装确认方案中可能出现的内容。

Format for an installation qualification protocol and report (continued)[a]

安装确认和报告的格式（续）[a]

Validation protocol _____ Installation Qualification _____ Page _____ of _____ Title: _____ Name and address of site: _____ 验证方案_____安装确认_____第___页，共___页；标题：_____ 名称和地址：_____
Installation qualification report 安装确认报告 Results/结果:_____ Conclusions/结论: _____ _____
Report written by: _____ Date: _____ 报告起草人：_____日期：_____ QA approved by: _____ Date: _____ QA审批人：_____日期：_____

[a] This format is used for training purposes and reflects some of the possible contents for an installation qualifi-cation protocol.
本格式仅供培训用，其内容体现了安装确认方案中可能出现的内容。

6. Operational qualification

运行确认

Note: see also “Supplementary guidelines on good manufacturing practices (GMP): validation”.
*注：*见“药品生产管理规范（GMP）的补充指南：验证”。

6.1 Systems and equipment should operate correctly and their operation should be verified in accordance with an operational qualification protocol.
系统和设备应能正常运行，并按照运行确认方案实施确认。

6.2 Critical operating parameters should be identified. Studies on the crit-ical variables should include conditions encompassing upper and lower oper-ating limits and circumstances (also referred to as “worst case conditions”).
应确定关键运行参数。研究关键变量时，应考虑运行的上限和下限，以及环境（参见“最差状况”）。

6.3 Operational qualification should include verification of operation of all system elements, parts, services, controls, gauges and other components.
运行确认活动应包括所有系统组件、零件、维护、控制、仪表和其他配件的核实确认。

Format for an operational qualifi cation protocol[a]

运行确认方案的格式[a]

Validation protocol _____ Operational Qualifi cation _____ Page _____ of _____ Title: _____ Name of Facility: _____ 验证方案_____运行确认_____第___页，共___页 标题：_____设施名称：_____
Validation Protocol #/验证方案编号：_____ Operational Qualification/运行确认 ____ Title/标题_____ Protocol written by /方案起草人 _____ Departmental Approval by/ 审批部门_____ Date/日期 _____ QA Approval by /QA 批准_____Date/日期 _____
Objective 目的 To determine that the system/equipment operates according to specifications, and to record all relevant information and data to demonstrate that the system/equipment func-tions as expected. 确定系统/设备的运行合乎标准，记录可证明系统/设备的功能符合要求的相关资料和数据。
Scope 范围 To be performed after installation, modification or relocation, after the Installation Qualifi-cation has been completed. 完成安装确认之后，实施之后的安装、修改或更改安装地点。
Responsibility 责任 Person responsible for operating the system/equipment will perform the qualification and record the information. The supervisor will supervise the study, verify the completion of the records, write the deviation report and the Operational Qualification (OQ) Report. Qualify Assurance will review and approve the OQ protocol and report. 系统/设备的操作人负责确认活动的执行和记录。监督人员负责监督该研究、核实记录的完成情况、起草偏差报告和运行确认（OQ）报告。质量保证部门负责审核和审批OQ方案和报告。

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6.4 There should be documented records for the verification of operation (operational qualification report) to indicate the satisfactory operation.
应记录运行确认活动（运行确认报告），以证明确认活动的结果符合要求。

6.5 Standard operating procedures for the operation should be fi nalized and approved.
应完成并审批操作的标准操作规程。

6.6 Training of operators for the systems and equipment should be pro-vided, and training records maintained.
应对系统和设备的操作人员培训，并保留培训记录。

6.7 Systems and equipment should be released for routine use after completion of operational qualification, provided that all calibration, clean-ing, maintenance, training and related tests and results were found to be acceptable.
在所有校准、清洁、维护、培训、相关测试和测试结果均符合要求的前提下，完成运行确认之后，可将系统和设备投入日常使用。

Format for an operational qualification protocol (continued)[a]

运行确认方案的格式（续）[a]

Validation protocol _____ Operational Qualifi cation _____ Page _____ of _____ Title: _____ Name of Facility: _____ 验证方案_____运行确认_____第___页，共___页 标题：_____设施名称：_____
Materials, Equipment, Documents List of calibration equipment required (Chart 1). 仪器校准所需的物料、设备、文件清单（表1） Materials or supplies needed to perform the Operational Qualification 实施运行确认所需的物料或其它资源。 1 _____Code # /编号_____ 2 _____Code # /编号_____ 3 _____Code # /编号_____ 4 _____ _ Code # /编号_____ 5 _____ Code # /编号_____ 6 _____ Code # /编号_____ SOPs and datasheets for normal operations of the system under test (Chart 2). 受试系统正常运行所需的SOP和数据（表2）。 Training records documenting that operators have been trained (Chart 2). 操作人员的培训记录（表2）。 Manuals for equipment (Chart 2). 设备手册（表2）。
Procedure 步骤 Test and record calibration data for calibrating apparatus and instruments (Chart 1). 仪表和仪器的校准试验和校准数据记录（表1）。 Test and record operative condition of control points and alarms (Chart 3). 测试和记录控制点和警报的运行条件（表3）。 Test and record outputs (Chart 4). 输出测试和记录（表4）。 List of calibration requirements for the system under test and records of the calibration of the system (Chart 5). 受试系统的校准要求清单和系统的校准记录（表5）。 Measure and record the results of specific challenge to the system in normal and worst case situation where appropriate (Chart 6). 正常条件和最差状况下运行的系统的挑战试验的结果测量和记录（表6）。（可选） Record any deviations to the procedures performed. 记录已实施规程的偏差。 Prepare a Deviation Report including the justification of acceptance and impact on the operation. 起草偏差报告，其内容需包括接受偏差的理由和对操作的影响。 Prepare an Operational Qualification Report. This should include date study initiated; date completed; observations made; problems encountered; completeness of informa-tion

collected; summary of deviation report; results of control/alarm tests; sample data if appropriate; location of original data; other information relevant to the study; and conclu-sions on the validity of the equipment/system operations. Submit QA for review and approval.
起草运行确认报告，其内容需包括研究的开始日期、完成日期、执行的观察、研究过程中遇到的问题、资料收集的完整性、偏差报告总结、所有测试结果、样品数据（可选）、原始数据的存储路径、与研究有关的其他资料、以及系统/设备运行效果的结论。报告完成后，将之递交给QA审核并等待批准。

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Format for an operational qualification protocol (continued)[a]

运行确认方案的格式（续）[a]

Validation protocol _____ Operational Qualifi cation _____ Page _____ of _____ Title: _____

Name of Facility: _____

验证方案_____运行确认_____第___页，共___页

标题：_____设施名称：_____

Preparation

准备工作

Chart 1: Calibrating apparatus and instruments.

表1：校准仪表和仪器。

Apparatus/Instrument 仪表/仪器	Calibration method 校准方法	Calibration date 校准日期

Performed by: _____ Date _____

执行人：_____日期：_____

Deviations/偏差: _____

Verifi ed by: _____ Date _____

复核人：_____日期_____

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Format for an operational qualification protocol (continued)[a]

运行确认方案的格式（续）[a]

Validation protocol _____ Operational Qualifi cation _____ Page _____ of _____ Title: _____

Name of Facility: _____

验证方案_____运行确认_____第___页，共___页

标题：_____设施名称：_____

Preparation/准备工作

Chart 2: Document check

表2：文件检查

SOP Title and number SOP标题及编号	File location 储存路径	QA/QC approval date QA/QC审批日期

Training Records

培训记录

Course on SOP # 培训SOP#	Staff name 参加培训人员	Date 日期

Equipment Make and Model 设备制造商及设备型号	Manual Available 是否有手册可用？
	Y[ ] N[ ]
	Y[ ] N[ ]
	Y[ ] N[ ]

Performed by: _____ Date _____

执行人：_____日期_____

Deviations/偏差: _____

Verifi ed by: _____ Date _____

复核人：_____日期：_____

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Format for an operational qualification protocol (continued)[a]

运行确认方案的格式（续）[a]

Validation protocol _____ Operational Qualifi cation _____ Page _____ of _____ Title: _____

Name of Facility: _____

验证方案_____运行确认_____第___页，共___页

标题：_____设施名称：_____

Results /结果

Chart 3: Control points and alarms.

表3：控制点和警报。

Control point/Alarm 控制点/警报	Results 结果	Date 日期

Performed by: _____ Date _____

执行人：_____日期_____

Deviations/偏差: _____

Verifi ed by: _____ Date _____

复核人：_____日期：_____

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Format for an operational qualification protocol (continued)[a]

运行确认方案的格式（续）[a]

Validation protocol _____ Operational Qualifi cation _____ Page _____ of _____ Title: _____

Name of Facility: _____

验证方案_____运行确认_____第___页，共___页

标题：_____设施名称：_____

Results/结果

Chart 4: Outputs

表4：输出

Outputs 输出	Results 结果	Date 日期

Performed by: _____ Date _____

执行人：_____日期_____

Deviations/偏差: _____

Verifi ed by: _____ Date _____

复核人：_____日期：_____

[a]This format is used for training purposes and reflects some of the possible contents for an operational qualifi-cation protocol.

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Format for an operational qualification protocol (continued)[a]

运行确认方案的格式（续）[a]

Validation protocol _____ Operational Qualifi cation _____ Page _____ of _____ Title: _____

Name of Facility: _____

验证方案_____运行确认_____第___页，共___页

标题：_____设施名称：_____

Chart 5: Calibration of Equipment/System

表5：设备/系统校准

Calibration SOP(short title and #) 校准SOP（简要标题及#）	Result 结果	Date 日期

Performed by: _____ Date _____

执行人：_____日期_____

Deviations/偏差: _____

Verifi ed by: _____ Date _____

复核人：_____日期：_____

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Format for an operational qualification protocol (continued)[a]

运行确认方案的格式（续）[a]

Validation protocol _________ Operational Qualifi cation ________ Page _____ of _____ Title: ______________ Name of Facility: ____ 验证方案__________________________运行确认__________________第___页，共___页 标题：__________________设施名称：____
Chart 6: Specific challenge of the equipment or system 表6：设备或系统专属的挑战试验 Test in normal conditions: 正常条件下的试验： Test of worst case situation/最差状况下的试验: (e.g. start-up after shutdown, temperature recovery time, centrifuge imbalance) （如停电后的启动、温度恢复是集纳、离心失衡）
Performed by: ____ Date ____________ 执行人：____日期_____________ Deviations/偏差: ____ Verifi ed by: ____ Date ____________ 复核人：____日期：___________

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Format for an operational qualification protocol (continued)[a]

运行确认方案的格式（续）[a]

Validation protocol _____ Operational Qualifi cation _____ Page _____ of _____ Title: _____ Name of Facility: _____ 验证方案_____运行确认_____第___页，共___页 标题：_____设施名称：_____
Deviation Report 偏差报告 Deviation(s)/偏差: Justification for acceptance/接受偏差的理由: Impact on operation/对操作的影响:
Written by: _____ Date _____ 填写人：_____日期_____

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Format for an operational qualification protocol (continued)[a]

运行确认方案的格式（续）[a]

Validation protocol _____ Operational Qualifi cation _____ Page _____ of _____ Title: _____ Name of Facility: _____ 验证方案_____运行确认_____第___页，共___页 标题：_____设施名称：_____
Operational Qualifi cation Report 运行确认报告 Results/结果： Conclusions/结论：
Written by: _____ Date _____ 填写人：_____日期_____ QA approved by: _____ Date _____ QA审批：_____日期_____

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7. Performance qualifi cation

性能确认

Note: see also “Supplementary guidelines on good manufacturing practices (GMP): validation”.
*注：*见“药品生产管理规范（GMP）的补充指南：验证”。

7.1 Systems and equipment should consistently perform in accordance with design specifications. The performance should be verified in accordance with a performance qualifi cation protocol.
系统和设备的运行应满足设计标准的要求，并按照性能确认方案实施性能确认。

7.2 There should be documented records for the verification of perfor-mance (performance qualification report) to indicate the satisfactory per-formance over a period of time. Manufacturers should justify the selected period over which performance qualification is done.
应有可表示系统和设备在长期运行时，性能仍满足要求的确认工作的记录（性能确认报告）。生产商应证明指定时间段内的性能确认工作已实施。

Format for a performance qualifi cation protocol[a]

性能确认方案的格式[a]

Validation protocol _____ Performance Qualifi cation _____ Page _____ of _____ Title: _____ Name of facility: _____ 验证方案_____性能确认_____第___页，共___页 标题：_____设施名称：_____
Validation Protocol # /验证方案# _____ Performance Qualification/性能确认 Title/标题 _____ Protocol written by/起草人_____ Departmental Approval by _____ Date _____ 审批部门_____日期_____ QA Approval by _____ Date _____ QA审批_____日期_____
Objective 目的 To determine that the systems/equipment perform as intended by repeatedly running the system on its intended schedules and recording all relevant information and data. Results must demonstrate that performance consistently meets pre-determined specifications under normal conditions, and where appropriate for worst case situations. 按照规定的使用时间安排，重复运行系统，以确定系统/设备的性能符合预期效果，并记录所有相关信息和数据。 得到的结果应能证明在正常条件和最差状况下，系统/设备的性能持续、稳定地满足既定要求。
Scope 范围 To be performed after the Installation and Operational Qualification have been completed and approved. 在完成和批准安装确认和运行确认之后，实施性能确认。 To be performed after installation, modification or relocation and for re-validation at appropriate intervals. 在安装、更改系统/设备之后，或改变系统/设备安装地点之后，实施性能确认；定期实施再验证时，也需要执行性能确认工作。 Each piece of equipment must be validated before it serves another piece of equipment/ system during validation of the latter (e.g. water system before steam generator; steam generator before autoclave). 在验证某设备之前，必须验证为该设备的工作服务的所有设备（如在验证蒸汽系统之前验证水系统，在验证高压灭菌器之前验证蒸汽发生器）。

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本格式仅供培训用，其内容体现了性能确认方案中可能出现的内容。

Format for a performance qualification protocol (continued)[a]

性能确认方案的格式[a]

Validation protocol _____ Performance Qualifi cation _____ Page _____ of _____ Title: _____ Name of facility: _____ 验证方案_____性能确认_____第___页，共___页 标题：_____设施名称：_____
Responsibility 责任 Person responsible for operating the system or equipment will perform the qualification and record the information. 系统或设备的操作人负责实施并确认确认活动。 The supervisor will supervise the study, verify the completion of the records and write the Deviation Report and the Performance Qualification Report. 确认工作的监督人员应监督确认研究过程、核实记录的完成、起草偏差报告和性能确认报告。 Qualify Assurance will review and approve the Performance Qualification Protocol and Report. 质量保证部门负责审核和审批性能确认方案和报告。
Materials, Equipment, Documents 物料、设备、文件 SOPs for normal operations of the equipment or system under test (including data record forms, charts, diagrams materials and equipment needed). Attach copies. 与受试设备或系统的正常运行有关的SOP（包括数据记录表、图表、表格、所需物料和设备）。在附件中附上SOP的复印件。 SOP list: SOP清单 _____ _____ _____ SOPs specific for performance tests (including data record forms, charts, diagrams, ma-terials and equipment needed, calculations and statistical analyses to be performed, and pre-determined specifications and acceptance criteria). Attach copies. 性能测试专属的SOP（包括数据记录表、图纸、表格、所需物料和设备、需要的计算和统计分析、既定标准和验收标准）。在附件中附上SOP的复印件。 SOP list: SOP清单 _____ _____ _____

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Format for a performance qualification protocol (continued)[a]

性能确认方案的格式[a]

Validation protocol _____ Performance Qualifi cation _____ Page _____ of _____ Title: _____ Name of facility: _____ 验证方案_____性能确认_____第___页，共___页 标题：_____设施名称：_____
Procedure /步骤 Equipment: Run normal procedure three times for each use (configuration or load) and record all required data and any deviations to the procedure. 设备：每次使用设备时（空载或负载），运行正常程序三次，并记录要求记录的数据和所有程序偏差。 Systems: Run for 20 consecutive working days, recording all required data and any deviations to the procedure. 系统：连续运行20天，记录要求记录的数据和程序偏差。 Prepare the Summary Data Record Form(Chart 1). 完成数据记录总结表（表1） Evaluation /评估 Attach all completed, signed data record forms. 在附件中给出所有完成的签名数据记录表。 Complete the Summary Data Record Form (Chart 1). 完成数据记录总结表（表1）。 Perform all required calculations and statistical analyses (Chart 2). 执行所有要求的计算和统计分析（图2）。 Compare to acceptance criteria (Chart 3). 比较结果和合格标准（图3）。 Prepare Deviation Report including the justification of acceptance and impact on the performance. 完成偏差报告，其内容须包括接受偏差的理由和对性能的影响。 Prepare a Performance Qualification Report: This should include: date study initiated; date completed; observations made; problems encountered; completeness of information collected; summary of deviation report; results of any tests; do results meet acceptance criteria; location of original data; other information relevant to the study; and conclusions on the validity of the equipment/system. 起草性能确认报告：报告的内容应包括：研究的开始日期、完成日期、执行的观察、遇到的问题、资料收集的完整性、偏差报告总结、所有测试结果、结果是否符合合格标准的说明、原始数据的储存地点、与研究有关的其它资料、设备/系统的性能确认结果的结论等。 Submit Performance Qualification Document to QA for review and approval. 将性能确认文件交给QA，等待审核和批准。

[a]This format is used for training purposes and reflects some of the possible contents for a performance qualifi-cation protocol.

本格式仅供培训用，其内容体现了性能确认方案中可能出现的内容。

Format for a performance qualification protocol (continued)[a]

性能确认方案的格式[a]

Validation protocol _____ Performance Qualifi cation _____ Page _____ of _____ Title: _____ Name of facility: _____ 验证方案_____性能确认_____第___页，共___页 标题：_____设施名称：_____
Chart 1: Summary Data Record 表1：数据总结记录 (To be prepared for the specific procedure being tested) （根据具体开展的测试制表）
Performed by: _____ Date _____ 执行人：_____日期：_____ Verifi ed by: _____ Date _____ 复核人：_____日期_____

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本格式仅供培训用，其内容体现了性能确认方案中可能出现的内容。

Format for a performance qualification protocol (continued)[a]

性能确认方案的格式[a]

Validation protocol _____ Performance Qualifi cation _____ Page _____ of _____ Title: _____ Name of facility: _____ 验证方案_____性能确认_____第___页，共___页 标题：_____设施名称：_____
Chart 2: Calculations and Statistical Analyses 表2：计算和统计分析
Performed by: _____ Date _____ 执行人：_____日期：_____ Verifi ed by: _____ Date _____ 复核人：_____日期_____

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Format for a performance qualification protocol (continued)[a]

性能确认方案的格式[a]

Validation protocol _____ Performance Qualifi cation _____ Page _____ of _____ Title: _____ Name of facility: _____

验证方案_____性能确认_____第___页，共___页

标题：_____设施名称：_____

Chart 3: Acceptance Criteria vs. Performance Test Results

表3：合格标准 vs. 性能测试结果

Criteria 标准	Results 结果	Pass/Fail 合格/不合格

Performed by: _____ Date _____

执行人：_____日期：_____

Verifi ed by: _____ Date _____

复核人：_____日期_____

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本格式仅供培训用，其内容体现了性能确认方案中可能出现的内容。

Format for a performance qualification protocol (continued)[a]

性能确认方案的格式[a]

Validation protocol _____ Performance Qualifi cation _____ Page _____ of _____ Title: _____ Name of facility: _____ 验证方案_____性能确认_____第___页，共___页 标题：_____设施名称：_____
Deviation Report 偏差报告 Deviation(s) 偏差: Justification for acceptance 接受偏差的理由: Impact on operation, function or process: 对操作、功能和工艺的影响 ：
Written by: _____ Date _____ 填写人：_____日期：_____ Verifi ed by: _____Date_____ 复核人：_____日期：_____

[a]This format is used for training purposes and reflects some of the possible contents for a performance qualifi-cation protocol.

本格式仅供培训用，其内容体现了性能确认方案中可能出现的内容。

Format for a performance qualification protocol (continued)[a]

性能确认方案的格式[a]

Validation protocol _____ Performance Qualifi cation _____ Page _____ of _____ Title: _____ Name of facility: _____ 验证方案_____性能确认_____第___页，共___页 标题：_____设施名称：_____
Performance Qualifi cation Report 性能确认报告 Results: 结果：   Conclusions: 结论
Written by: _____ Date _____ 填写人：_____日期：_____ Verifi ed by: _____Date_____ 复核人：_____日期：_____

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本格式仅供培训用，其内容体现了性能确认方案中可能出现的内容。

8. Requalifi cation

再确认

Note: see also “Supplementary guidelines on good manufacturing practices (GMP): validation”.
*注：*见“药品生产管理规范（GMP）的补充指南：验证”。

8.1 Requalifi cation of systems and equipment should be done in accor-dance with a defined schedule. The frequency of requalification may be determined on the basis of factors such as the analysis of results relating to calibration, verification and maintenance.
应按照既定日程，实施系统和设备的再确认。根据分析、核实确认和维护的相关分析结果，确定再确认的频率。

8.2 There should be periodic requalifi cation.
应定期实施再确认。

8.3 There should be requalification after changes. The extent of requali-fication after the change should be justified based on a risk-assessment of the change. Requalification after change should be considered as part of the change control procedure.
变更后，需要实施再确认。应根据变更的风险评估结果确定再确认的执行程度。应将变更后实施的再确认工作视作变更控制程序的组成部分。

9. Qualification of “in-use” systems and equipment

使用中的系统和设备的确认

9.1 There should be data to support and verify the suitable operation and performance of systems and equipment that have been “in use” for a period of time, and which had not been subjected to installation and or operational qualifi cation.
应有可支持和核实系统和设备已经正常运行一段时间的数据，但要注意的是，不能从安装确认和/或运行确认中获取这些数据。

9.2 These should include operating parameters and limits for critical variables, calibration, maintenance and preventive maintenance, standard operating procedures (SOPs) and records.
应有关键变量、校准、维护、预防维护、标准操作规程（SOP）和记录的运行参数和限度。

10. Reference

参考文献

A WHO guide to good manufacturing practice (GMP) requirements. Part 2: Validation. Geneva, Global Programme for Vaccines and Immu-nization, Vaccine Supply and Quality, Global Training Network, World Health Organization, 1997

(WHO/VSQ/97.02).

Appendix 7

附录 7

Non-sterile process validation

非灭菌工艺的验证

1. Principle

基本原理

1.1 Process validation provides documented evidence that a process is capable of reliably and repeatedly rendering a product of the required quality.
工艺验证文件可证明该工艺能可靠、持续地生产出符合质量要求的产品。

1.2 The principles of planning, organizing and performing process valida-tion are similar to those for qualification. It should be done in accordance with process validation protocols, data should be collected and reviewed against predetermined acceptance criteria, and reflected in process validation reports.
计划、组织和实施工艺验证的基本原理与确认活动相同。应当严格按照工艺验证方案执行，根据既定的合格标准收集、审核数据，并将之体现在工艺验证报告中。

2. Scope

范围

2.1 These guidelines describe the general aspects of process validation for the manufacture

of non-sterile fi nished products.
这则附录中给出的指导原则适用于非灭菌产品生产的工艺验证。

2.2 Normally process validation should cover at least the critical steps and parameters (e.g. those that may have an impact on the quality of the product) in the process of manufacturing a pharmaceutical product.
通常，工艺验证活动至少应覆盖药品生产工艺的关键步骤和参数（如对产品质量有影响的步骤和参数）。

3. General

概要

3.1 The policy and approach to process validation should be docu-mented, e.g. in a validation master plan, and should include the critical pro-cess steps and parameters.
应在验证主计划等文件中给出工艺验证的方针和方法的证明，并在其中说明关键工艺步骤和参数。

3.2 Process validation should normally begin only once qualifi cation of support systems and equipment is completed. In some cases process valida-tion may be conducted concurrently with performance qualifi cation.
一般情况下，只有在支持系统和设备的确认工作已经完成的前提下，方可开始工艺验证。某些时候，工艺验证与性能确认可同时进行。

3.3 Process validation should normally be completed prior to the manu-facture of finished product that is intended for sale (*prospective validation*). Process validation during routine production may also be acceptable (*con-current validation*).
应在产品商业化生产之前完成工艺验证（*前验证*），也可在日常生产过程中开展工艺验证（*同步验证*）。

4. Prospective validation

前验证

4.1 Critical factors or parameters that may affect the quality of the fi n-ished product should be identified during product development. To achieve this, the production process should be broken down into individual steps, and each step should be evaluated (e.g. on the basis of experience or theoretical considerations).
应在产品研发阶段，确定可能会对成品质量产生影响的关键因素和参数。为了这个目的，应将生产工艺分成单独的步骤并分别进行评估（如在经验和理论的基础上对此评估）。

4.2 The criticality of these factors should be determined through a “worst-case” challenge where possible.
可行时，可通过“最差状况”挑战试验确定这些因素的重要性。

4.3 Prospective validation should be done in accordance with a valida-tion protocol. The protocol should include:
应按照验证方案实施前验证。前验证包括：

— a description of the process;
工艺说明；

— a description of the experiment;
试验说明；
— details of the equipment and/or facilities to be used (including measur-ing or recording equipment) together with its calibration status;
详细说明验证过程中将使用到的设备和/或设施及其校准状态；
— the variables to be monitored;
需要监控的变量；
— the samples to be taken — where, when, how, how many and how much (sample size);
需要采集的样品 – 说明自何处、何时、如何、采集多少（样品量）；
— the product performance characteristics/attributes to be monitored, together with the test methods;
需要监控的产品性能特征参数/性质和试验方法；
— the acceptable limits;
合格限；
— time schedules;
时间表；
— personnel responsibilities; and
人员职责；以及
— details of methods for recording and evaluating results, including statis-tical analysis.
说明记录和评估结果的方法，包括统计学方法。

4.4 All equipment, the production environment and analytical testing methods to be used should have been fully validated (e.g. during installation qualification and operational qualifi cation).
应全面验证将使用的设备、生产环境和分析测试方法（可在安装确认和运行确认阶段实施）。

4.5 Personnel participating in the validation work should have been appropriately trained.
参与验证工作的人员应事先接受相应的培训。

4.6 Batch manufacturing documentation to be used should be prepared after these critical parameters of the process have been identifi ed, and machine settings, component specifications and environmental conditions have been determined and specifi ed.
在鉴定了工艺的关键参数、确定并说明了机器设置、部件标准和环境条件之后，应准备将用到的批生产文件。

4.7 A number of batches of the final product should then be produced. The number of batches produced in this validation exercise should be suf-ficient to allow the normal extent of variation and trends to be established and to provide sufficient data for evaluation.
接下来，应生产几批终产品。验证过程中生产的产品批的数量应能满足正常验证的需要，并足以建立趋势分析和为评估提供所需数据。

4.8 Data within the finally agreed parameters, from at least three consecutive batches, giving product of the desired quality may be considered to constitute a proper validation of the process.
由至少三个连续生产的产品批次的得到的数据应满足最终核准的参数的要求，从而证明产品达到设计质量要求，这也是一个恰当的工艺验证过程的组成部分。

4.9 The batches should be of the same size, and should be the same as the batch size intended in full-scale production. Where this is not possible, the reduced batch size should be considered in the design of the protocol and when full-scale production starts, the validity of any assumptions made should be demonstrated.
验证批的批量应一致，并等同于正式大规模生产的批量。如果不能做到这一点，应在方案设计中说明验证批的批量小于正式生产规模；当正式生产时，应证明验证过程作出的假设均有效。

4.10 Extensive testing should be performed on the product at various stages during the manufacturing process of the batches, including on the final product and its package.
生产验证批时，应在生产的不同阶段展开全面测试，包括对成品和包装的测试。

4.11 The results should be documented in the validation report. As a min-imum, the report should include:
结果应记录在验证报告中。验证报告至少应包括如下内容：

- a description of the process: batch/packaging document, including details of critical steps;
  工艺说明：批/包装文件，包括关键步骤的细节；
- a detailed summary of the results obtained from in-process and final testing, including data from failed tests. When raw data are not in-cluded, reference should be made to the sources used and where it can be found;
  包括失败的试验数据在内的过程测试和最终测试结果的总结。如果没能在总结中给出原始数据，那么则应说明参考资料的来源及如何获取这些资料。
- any work done in addition to that specified in the protocol, or any deviations from the protocol should be formally noted along with an explanation;
  应正式说明方案没有说明的工作和偏差，并给出解释。
- a review and comparison of the results with those expected; and
  实际结果和预期结果的审核和比较；以及
- formal acceptance or rejection of the work by the team or persons des-ignated as being responsible for the validation, after completion of any corrective action or repeated work.
  完成了纠偏措施或重复工作之后，受指派对验证负责的人员或团队对验证工作的最终正式验收或拒收。

4.12 A conclusion and recommendation should be made on the extent of monitoring and the in-process controls necessary for routine production, on the basis of the results obtained.
立足于所获得的结果，对常规生产的监控和必要的过程控制做出结论，并给出建议。

4.13 The conclusion and recommendation should be incorporated into the batch manufacturing and batch packaging documents and/or standard operating procedures (SOPs) for routine use. Limits and frequencies of test-ing and monitoring should be specified. Actions to be taken in the event of the limits being exceeded should be specifi ed.
上述结论和建议应整合在批生产和批包装文件、和/日常使用的标准操作规程（SOP）中，并说明测试和监控的限度和频率和超出限度时所采取的措施。

4.14 Batches manufactured as part of the validation exercise, and intend-ed to be sold or supplied, should have been manufactured under conditions that comply fully with the

requirements of good manufacturing practice and the marketing authorization (where applicable).
验证批、销售批或供应批的生产条件应符合药品生产管理规范和市场销售文件（可行时）的要求。

5. Concurrent validation

同步验证

5.1 In certain cases, it may be appropriate to validate a process during routine production, e.g. where the product is a different strength of a previ-ously validated product, a different tablet shape or where the process is well understood.
某些时候，可在日常生产过程中开展工艺验证，如待验证产品与之前验证过的产品仅有规格上的差别、或仅在药片形状上有差别、或该生产工艺已了解透彻时。

5.2 The decision to carry out concurrent validation should be made by appropriately authorized personnel.
应由经授权的人士决定是否适合开展同步验证。

5.3 It is essential that the premises and equipment to be used during concurrent validation have been previously qualifi ed.
需要特别注意的是，同步验证期间使用的厂房设施和设备应已确认过。

5.4 Prospective validation should be done in accordance with a validation protocol.
应严格按照验证方案实施前验证。

5.5 The results should be documented in the validation report.
应将验证结果记录在验证报告中。

6. Retrospective validation

回顾性验证

6.1 Retrospective validation is based on a comprehensive review of his-torical data to provide the necessary documentary evidence that the process is doing what it is believed to do. This type of validation also requires the preparation of a protocol, the reporting of the results of the data review, a conclusion and a recommendation.
回顾性验证系指在仔细审核历史数据的基础上，证明工艺的实施满足预期要求过程。这类验证也要求准备验证方案、报告数据审查的结果、给出结论和建议。

6.2 Retrospective validation is not the preferred method of validation and should be used in exceptional cases only. It is acceptable only for well-estab-lished processes and will be inappropriate where there have been changes in the composition of the product, operating procedures or equipment.
回顾性验证不属于推荐使用的验证方法，它仅在特殊情况下使用。只有在工艺已经建立完善的基础上，产品成分、操作规程或设备发生了变更时，才适合实施这种验证。

6.3 Sufficient data should be reviewed to provide a statistically signifi cant conclusion.
审核大量数据，以获取重要的统计学结论。

6.4 When the results of retrospective validation are considered satisfac-tory, this should serve only as an indication that the process does not need to be subjected to validation

in the immediate future.
如回顾性验证的结果令人满意，这只说明眼下，该工艺在不需要验证。

7. Revalidation

再验证

Note: see main text on "Validation". The need for periodic revalidation of non-sterile processes is considered to be a lower priority than for sterile processes.
*注：*见"验证"中的内容。灭菌工艺比非灭菌工艺更需要定期再验证。

7.1 In the case of standard processes using conventional equipment, a data review similar to that which would be required for retrospective validation may provide an adequate assurance that the process continues to be under control. The following points should also be considered:
就使用常规设备的标准工艺而言，也要求实施回顾性验证，以证明该工艺受控的持续性。验证时，应考虑以下几点：

— the occurrence of any changes in the master formula, methods, starting material manufacturer, equipment and/or instruments;
主配方、方法、起始物料供应商、设备和/或仪器的变更
— equipment calibrations and preventive maintenance carried out;
实施的设备校准和预防性维护
— standard operating procedures (SOPs); and
标准操作规程（SOP）；以及
— cleaning and hygiene programme.
清洁和卫生计划

8. Change control

变更控制

Note: see main text on "Validation".
*注：*见"验证"的正文。

8.1 Products manufactured by processes that have been subjected to changes should not be released for sale without full awareness and consid-eration of the change and its impact on the process validation.
在没有详细了解和研究变更和变更对工艺验证的影响之前，不应放行由变更后的工艺生产的销售用产品。

8.2 Changes that are likely to require revalidation may include:
要求实施再验证的变更有：

— changes in the manufacturing process (e.g. mixing times, drying temperatures);
生产工艺的变更（如混合时间、干燥温度）；
— changes in the equipment (e.g. addition of automatic detection systems);
设备变更（如添加自动监测系统）；
— production area and support system changes (e.g. rearrangement of ar-eas or a new

water treatment method);

生产区和支持系统的变更（如对区域重新布局或新的水系统处理方法）

— transfer of processes to another site; and

工艺转移到其它生产地点；以及

— unexpected changes (e.g. those observed during self-inspection or during routine analysis of process trend data).

意料之外的变更（如在自检或工艺趋势数据常规分析时发现的变更）