WHO-937-Appendix 3 Cleaning validation
附录3 清洁验证

1. Principle 原则

1.1 The objectives of good manufacturing practices (GMP) include the prevention of possible contamination and cross-contamination of pharmaceutical starting materials and products.
GMP的目标包括了对药品起始物料和产品可能发生的污染和交叉污染进行预防。

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:
许多物质都可能对药品造成污染，如微生物污染物、前个产品（包括活性药物成分API和辅料残留物）、清洗剂残留、空气物质如粉尘和颗粒物、润滑油和辅助材料如消毒剂、以及以下情况的分解产物：

— product residue breakdown occasioned by, e.g. the use of strong acids and alkalis during the cleaning process; and
如在清洁过程中使用强酸强碱引起的产品残留分解；和
— breakdown products of the detergents, acids and alkalis that may be used as part of the cleaning process.
可能用于清洁过程的洗涤剂、酸碱等的分解产物。

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.
恰当的清洁程序能有效预防污染和交叉污染。清洁方法的验证可以作为书面证据，证明已批准的清洁程序将提供符合自身用途的洁净设备。

1.4 The objective of cleaning validation is to prove that the equipment is consistently cleaned of product, detergent and microbial residues to an acceptable level, to prevent possible contamination and cross-contamination.
清洁验证目的在于证明设备始终符合产品、清洗剂和微生物残留验收要求，以预防可能的污染和交叉污染。

1.5 Cleaning validation is not necessarily required for non-critical cleaning 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 floors, walls, the outside of vessels, and following some intermediate steps.
非关键的清洗不一定需要清洁验证，如同一产品不同批次间的清洁（或原液生产过程中同一中间品的不同批次间的清洁）、地板墙壁清洁、容器外部清洁、遵循某些中间步骤的清洁。

1.6 Cleaning validation should be considered important in multiproduct facilities and should be performed among others, for equipment, sanitization procedures and garment laundering.
清洁验证对多产品生产设施来说非常重要，尤其需要对设备、消毒程序和服装洗涤进行清洁验证。

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 manufacturing industry.
指南介绍了清洁验证的通用性质，不包含如制药行业要求的消除病毒或支原体污染等的专门清洁或钝化。

2.2 Normally cleaning validation would be applicable for critical cleaning such as cleaning between manufacturing of one product and another, of surfaces that come into contact with products, drug products and API.
清洁验证通常适用于关键清洁，如不同产品生产之间的清洁、与产品、药品和API接触表面的清洁。

3. General 概述

3.1 There should be written SOPs detailing the cleaning process for equipment and apparatus. The cleaning procedures should be validated.
应有书面的SOP来规范设备和仪器的清洁过程。清洁程序必须经过验证。

3.2 The manufacturer should have a cleaning policy and an appropriate procedure for cleaning validation, covering:
生产商应制定清洁政策以及合适的清洁验证程序，包括对以下程序：

- surfaces that come into contact with the product;
  与产品接触表面的清洁
- cleaning after product changeover (when one pharmaceutical formulation is being changed for another, completely different formulation);
  更换产品后的清洁(一种药品配方将被另一种完全不同配方的药品取代时)
- between batches in campaigns (when the same formula is being manufactured over a period of time, and on different

days);
阶段性生产批次间的清洁（相同配方产品在经过一段时间后的生产）

- bracketing products for cleaning validation. (This often arises where products contain substances with similar properties (such as solubility) 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 “families” of products which differ slightly as to actives or excipients.); and
清洁验证的括入产品（多发生于当产品含有相似特性（如溶解度）或含有不同浓度的相同物质。可采取的策略为，先生产较稀释的类型（不一定是最稀的），然后再生产浓度最高的类型。有时则会产生“家族”产品，只在活性成分或辅料上有轻微差别。）
- periodic evaluation and revalidation of the number of batches manufactured between cleaning validations.
对在进行清洁验证时生产的批次进行的周期性评估和再验证。

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.
清洁验证过程中，至少应进行连续三次清洁程序并保证结果成功，以证明该方法已进行了验证。

4. Cleaning validation protocols and reports 清洁验证方案和清洁验证报告

4.1 Cleaning validation protocols 清洁验证方案

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.
清洁验证应有书面的清洁验证方案，且必须经过如质量控制或质量保证部门的正式批准。

4.1.2 In preparing the cleaning validation protocol, the following should be considered:
制定清洁验证方案时应考虑：
— disassembly of system;
系统可拆卸性
— precleaning;
预清洁
— cleaning agent, concentration, solution volume, water quality;
清洗剂、浓度、溶液体积、水质
— time and temperature;
时间和温度
— flow rate, pressure and rinsing;
流量、压力和冲洗
— complexity and design of the equipment;
设备复杂性和设计
— training of operators; and
操作人员的培训，和
— size of the system.
系统大小

4.1.3 The cleaning validation protocol should include:
清洁验证方案应包含：
• the objectives of the validation process;
验证目的
• the people responsible for performing and approving the validation study;
验证研究的执行人员和批准人员
• the description of the equipment to be used, including a list

of the equipment, make, model, serial number or other unique code;
所使用设备的描述，包括设备名称、品牌、型号、序列号或其它专用代码

- the interval between the end of production and the commencement of the cleaning procedure (interval may be part of the validation challenge study itself)
  生产结束和清洁开始之间的间隔（间隔也可以是验证挑战研究的一部分）
  — 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;
  设备开始清洁前处于污染的最长期间，以及设备清洁后至下次使用前所经过时间的间隔确定。
- the levels of microorganisms (bioburden);
  微生物（生物负载）级别
- the cleaning procedures (documented in an existing SOP, including definition of any automated process) to be used for each product, each manufacturing system or each piece of equipment;
  用于每种产品、每种生产系统或每个设备的清洁规程（书面SOP形式，应包含任何自动化过程的定义）
- all the equipment used for routine monitoring, e.g. conductivity meters, pH meters and total organic carbon analysers;
  日常监控使用的所有设备，如电导率仪、pH计、TOC分析仪
- the number of cleaning cycles to be performed consecutively;
  连续执行的清洁验证循环次数
- the sampling procedures to be used (direct sampling, rinse sampling, inprocess monitoring and sampling locations) and the rationale for their use;
  所采用的取样程序（直接取样、冲洗取样、在线监控和取样位

置）及其选择原理

- the data on recovery studies (efficiency of the recovery of the sampling technique should be established);
  恢复性研究数据（应确定取样技术恢复的效率）
- the analytical methods (specificity and sensitivity) including the limit of detection and the limit of quantification;
  分析方法（专属性和灵敏度），包括检测限LOD和定量限LOQ
- the acceptance criteria (with rationale for setting the specific limits) including a margin for error and for sampling efficiency;
  验收标准（及特定限度的设置原理），包括误差限度和取样效率限度
- the choice of the cleaning agent should be documented and approved by the quality unit and should be scientifically justified on the basis of, e.g.
  清洗剂的选择应有文件证明，必须通过质量部门批准；且应经过基于以下情况的科学验证：
  — the solubility of the materials to be removed;
  要清除物质的溶解度
  — the design and construction of the equipment and surface materials to be cleaned;
  设备的设计和构成以及需要清洁的表面物质
  — the safety of the cleaning agent;
  清洗剂的安全性
  — the ease of removal and detection;
  清除和检测的方便性
  — the product attributes;
  产品属性
  — the minimum temperature and volume of cleaning agent and rinse solution; and
  清洗剂和冲洗溶液的最低温度和体积，和
  — the manufacturer's recommendations;

生产商的建议

- revalidation requirements.
  验证要求

4.1.4 Cleaning procedures for products and processes which are very similar 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.
类似产品和类似工艺的清洁程序是不需要逐个进行验证的。可行的方法是为这些类似产品和类似工艺选择一个有代表性的范围，然后根据所选产品、设备和工艺的相关关键问题确定一合理的验证方案。再考虑相关合格标准的基础上，则单独开展“最坏情况”的验证研究。这类验证也被称之为“括号法”。

4.1.5 Where “bracketing” of products is done, consideration should be given to type of products and equipment.
若对产品进行“括号法”验证，应考虑产品和设备的类型。

4.1.6 Bracketing by product should be done only when the products concerned are similar in nature or property and will be processed using the same equipment. Identical cleaning procedures should then be used for these products.
只有当所涉及的产品在本质或特性上类似且由相同设备生产，才可以进行产品“括号法”验证。对这些产品的清洁验证，也应当采用相同的验证程序。

4.1.7 When a representative product is chosen, this should be the one that is most difficult to clean.
选择具有代表性的最难以清洁的产品。

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.
设备“括号法”验证必须为相似设备或不同尺寸的相同设备（如，300升、500升、1000升罐子）。也可采用替代的方法，即分别验证最大和最小尺寸的设备。

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 presented in cleaning validation reports stating the outcome and conclusion.
保存相关清洁记录（操作人员签字，生产部人员检查，质量保证部人员审核）和源数据（原始结果）。在清洁验证报告中记录清洁验证结果，并给出最终结果并进行总结。

5. Personnel 人员

5.1 Personnel or operators who perform cleaning routinely should be trained and should be effectively supervised.
应对执行日常清洁的人员或操作者进行培训并有效监督。

6. Equipment 设备

6.1 Normally only procedures for the cleaning of surfaces of the equipment that come into contact with the product need to be validated. Consideration should be given to “non-contact” parts of the equipment into which product or any process material may migrate. Critical areas should be identified (independently from method of cleaning), particularly in large systems employing semi-automatic or fully automatic clean-in-place systems.
一般情况下，只需对用于和产品接触设备表面的程序进行验证。

同时还应考虑非接触部分，因为产品或工艺物料可能移动到这些部分。应对关键区域进行鉴别（独立于清洁方法），尤其是采用半自动或全自动CIP系统的在线系统。

6.2 Dedicated equipment should be used for products which are difficult 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 acceptance limits using a validated cleaning procedure.
难以清洁的产品、设备，或者具有高安全风险不容易达到要求清洁验收标准的产品，应采用专用设备。

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.
理论上说，每个设备或系统应有一套清洁工艺。这取决于所生产的产品，是否是相同产品（如大型阶段性生产）批次间的清洁，或是否是不同产品批次间的清洁。

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 filling lines.
设备的设计也可能影响清洁工艺的效果。因此在制定清洁验证方案时应考虑设备的设计，如V型搅拌器、输送泵或灌装线。

7. Detergents 清洗剂

7.1 Detergents should facilitate the cleaning process and be easily removable. Detergents that have persistent residues such as

cationic detergents which adhere very strongly to glass and are difficult to remove, should be avoided where possible.
清洗剂应有助于清洁工艺并易于消除。诸如阳离子清洁剂（强力粘附在玻璃上且难以清除）等产生持续残留物的清洁剂，如果可以的话应避免使用。

7.2 The composition of the detergent should be known to the manufacturer and its removal during rinsing, demonstrated.
生产商应知晓清洗剂的成分，并了解如何冲洗去除这些清洗剂。

7.3 Acceptable limits for detergent residues after cleaning should be defined. The possibility of detergent breakdown should also be considered when validating cleaning procedures.
确定清洁后清洗剂残留的可接受限度。在进行清洁程序的验证时，还要考虑清洗剂分解的可能性。

7.4 Detergents should be released by quality control and, where possible, should meet local food standards or regulations.
清洗剂由质量控制部门放行，必要时，应符合当地食品标准或规定。

8. Microbiology 微生物学

8.1 The need to include measures to prevent microbial growth and remove contamination where it has occurred should be considered.
应考虑是否需要制定预防微生物生长和消除污染的措施。

8.2 There should be documented evidence to indicate that routine cleaning and storage of equipment does not allow microbial proliferation.
应有文件证明设备的例行清洁和保存不会滋生微生物。

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.
清洁前不洁净设备的保存时间和条件，以及设备清洁和再使用之间的时间间隔，应作为清洁程序验证的一部分。

8.4 Equipment should be stored in a dry condition after cleaning. Stagnant water should not be allowed to remain in equipment after cleaning.
设备清洁后应保存在干燥的环境中，且设备上不允许存有死水。

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.
通过充分的设备清洁和恰当的设备保存来控制生物负载，对于保证后续灭菌或消毒程序达到必要的无菌保证及无菌处理中热原的控制非常重要。设备无菌处理不一定能够达到热原的有效钝化或消除。

9. Sampling 取样

9.1 General 概述

9.1.1 Equipment should normally be cleaned as soon as possible after use. This may be especially important for operations with topical products, suspensions and bulk drug or where the drying of residues will directly affect the efficiency of a cleaning procedure.
一般情况下，设备一使用完应立即进行清洁。对于生产局部药品、

悬浮液和原料药，或者残留物的烘干将直接影响到清洗过程的效率，即时清洁更是尤为重要。

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.
有两种可行的取样方法，即表面直接取样和冲洗取样。两者方法的结合使用通常被认为是最理想的。

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.
清洁及操作前或过程中的重新取样不应进行，这种操作只有鲜少案例可接受。立即进行重新测试或重新取样可能会显示清洁工艺没有验证，因为这些重新测试实际证明了因无效的验证工艺导致的不可接受残留物和污染物的存在。

9.2 Direct surface sampling (direct method) 表面直接取样（直接方法）

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：这种取样方法最为常用，是在一个表面上系统地摩擦探头终端（称为拭子）上的惰性材料（如脱脂棉）。所采用的取样材料

类型及其对测试数据的潜在影响非常重要，因为取样材料可能对测试产生干扰。（例如，拭子上的粘合材料已被发现会干扰对样品的分析。）

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.
以下因素也应被考虑在内，包括拭子供应商、擦拭区域、使用的拭子数量、使用是的湿润拭子还是干燥拭子、拭子处理及擦拭技巧。

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.
选择取样点位置时应考虑设备的材质（如玻璃或钢结构）以及位置（如叶片、罐壁或配件）。还应考虑最差状态位置。方案中应体现取样位置。

9.2.3 Critical areas, i.e. those hardest to clean, should be identified, particularly in large systems that employ semi-automatic or fully automatic clean-in-place systems.
应确定关键区域，如难以清洁的区域，特别是应用了半自动或全自动CIP系统的大型系统。

9.2.4 The sampling medium and solvent used should be appropriate to the task.
应确保取样媒介和溶剂的适用性。

9.3 Rinse samples (indirect method) 冲洗取样（间接方法）

Note: This method allows sampling of a large surface, of areas that

are inaccessible 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 sampling, and may be useful for checking for residues of cleaning agents, e.g. detergents.
注：冲洗取样可以对较大表面进行取样，也可以对不易到达的区域和设备平时不可拆卸的部分进行取样。冲洗取样证明了清洁的充分性，也有利于检测清洁剂残留。

9.3.1 Rinse samples should be used in combination with other sampling methods such as surface sampling.
冲洗取样应和其他取样方法结合使用，如表面取样方法。

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.
应有文件证明样品正确回收。例如，80%回收率为良好，50%为合理，低于50%可疑。

9.4 Batch placebo method 批对照方法

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：这种方法是指，生产出一个批次作为对照，稍后用于检查前个产品的残留物。这是个代价昂贵且费力的过程。且难以保证能够均匀地将污染物从设备表面消除。此外，若污染物颗粒或残留足够大，它们不一定会均匀地散布在对照批次上。

9.4.1 The batch placebo method should be used in conjunction with rinse and/or surface sampling method(s).
批对照方法应和冲洗和/或表面取样方法结合使用。

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.)
应对整个生产过程进行取样，并在这些样品中寻找前个产品的痕迹。（应注意的是，分析的灵敏度可能因污染物的稀释而大大降低。）

10. Analytical methods 分析方法

10.1 The analytical methods should be validated before the cleaning validation is performed.
在进行清洁验证之前，要验证所采用的分析方法。

10.2 The methods chosen should detect residuals or contaminants specific for the substance(s) being assayed at an appropriate level of cleanliness (sensitivity).
用于检测残留和污染物的分析方法应当对待测物质有选择性，并要有良好的洁净度（灵敏度），能检测出公司认为合格的清洁程度。

10.3 Validation of the analytical method should include as appropriate:
— precision, linearity and selectivity (the latter if specific analytes are targeted);
分析方法验证应适当考虑精确度、线性和选择性（后者适用于明确了特定供试物的情况下）
— limit of detection (LOD);
检测限

— limit of quantitation (LOQ);
定量限
— recovery, by spiking with the analyte; and
添加供试物样品的复原率，和
— reproducibility.
再现性

10.4 The detection limit for each analytical method should be sufficiently sensitive to detect the established acceptable level of the residue or contaminants.
每一种分析方法的检测限度应该足够灵敏来检测出符合可接受标准要求的残留物或污染物。

10.5 Suitable methods that are sensitive and specific should be used where possible and may include chromatographic methods (e.g. high pressure 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 immunosorbent assay (ELISA).
必要时应采用合适的敏感特异的分析方法，可包含层析法（如高压液相色谱HPLC）、气相色谱法（GC）和高压薄层色谱法（HPTLC）。其它方法包括（单独或结合）TOC测量、pH或电导率，紫外光谱法，酶联免疫吸附试验（ELISA）。

11. Establishing acceptable limits 确定验收限度

Note: uniform distribution of contaminants is not guaranteed.
注：不保证污染物的均匀分布。

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.
样品中污染物程度的验收标准应当是根据实际确定的、切实可行而且能够进行验证。残留物限度的确定应当基于对涉及物料的合理了解。

11.2 Each situation should be assessed individually. The manner in which limits are established should be carefully considered. In establishing residual limits it may not be adequate to focus only on the principal reactant, because other chemical variations may be more difficult to remove.
每个情况应单独评估。并慎重考虑确定限度的方式。在确定残留物限度时，仅仅强调主要反应物是不够的，因为其它化学变异产物可能更难去除。

11.3 Where necessary, screening using thin-layer chromatography should be performed in addition to chemical analyses.
除化学分析外，必要时还应采用薄层色谱扫描。

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. detergents or solvents).
前个产品、反应副产品和清洗剂，或清洁过程本身（如清洗剂或溶剂）不允许产生残留物。

11.5 The limit-setting approach can:
限度设定方法可以：

- be product-specific;
  根据产品而定；
- group products into families and choose a worst case product;

将产品归类，选择最差状况产品；

- group products into groups according to risk, e.g. very soluble products, products with similar potency, highly toxic, or difficult to detect products;
  按风险将产品分组，如易溶性产品、效价相似产品、剧毒性产品、或难以检测产品；
- use different safety factors for different dosage forms based on physiological response (this method is essential for potent materials).
  基于生理反应的不同剂型采用不同安全系数(该方法对强效物料非常重要）。

11.6 Limits may be expressed as a concentration in a subsequent product (ppm), limit per surface area (mcg/cm2), or in rinse water as ppm.
限度可表示为后续产品中的浓度（ppm）、每单位表面积浓度（mcg/cm2）或冲洗用水中的浓度（ppm）。

11.7 The sensitivity of the analytical methods should be defined to enable reasonable limits to be set.
对分析方法灵敏度的确定应保证能够界定合理的限度。

11.8 The rationale for selecting limits for carry-over of product residues should meet defined criteria.
对产品残留物遗留污染限度的选择应符合既定的标准。

11.9 The three most commonly used criteria are:
三种最常用的标准为：

- visually clean. (No residue should be visible on equipment after cleaning.) Spiking studies should determine the concentration at which most active ingredients are visible. This criterion may not be suitable for highpotency,

low-dosage drugs;
目视清洁（设备清洗后不允许有可见的残留）。加样研究应确定在河浓度下大部分活性成分是可见的。该标准不适用于高效价低剂量的药品；

- no more than 10 ppm of one product will appear in another product (basis for heavy metals in starting materials); and
甲产品出现在乙产品的量，不能多过10ppm（作为起始原料中重金属的基础）；和
- no more than 0.1% of the normal therapeutic dose of one product will appear in the maximum daily dose of a subsequent product.
一个产品残留在其后续产品最大日剂量中的水平，不能超过其正常治疗剂量的0.1%

11.10 The most stringent of three options should be used.
应采用上述三个标准中最为严格的一个。

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.)
对于某些过敏性物质（如青霉素和头孢菌素）以及高效价物质（如类固醇和细胞毒素），应无法被现有最好分析方法检出。（这意味着在实际操作中，需要采用专门的生产设施生产和加工这些产品。）

Appendix 4 Analytical method validation
附录4 分析方法验证

1. Principle 原则
2. General 概述
3. Pharmacopoeial methods 药典方法
4. Non-pharmacopoeial methods 非药典方法
5. Method validation 方法验证
6. Characteristics of analytical procedures 分析方法指标

1. Principle 原则

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.
本附录介绍了分析方法验证过程中需要考虑的指标信息。除本附录列举方法外，其它方法也可采用并接受。生产商应选择最适合自己产品的验证方案和方法。

1.2 The manufacturer should demonstrate (through validation) that the analytical procedure is suitable for its intended purpose.
生产商应（通过验证）证明分析方法能够达到预期目的。

1.3 Analytical methods, whether or not they indicate stability, should be validated.
无论是否与稳定性有关，分析方法均应该进行验证。

1.4 The analytical method should be validated by research and development before being transferred to the quality control unit when appropriate.
适当时，应在移交质量控制部门前通过研究开发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.
应分别建立物料和产品的质量标准。所执行测试应在标准测试方

法文件中予以描述。

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.
可以采用药典规定的质量标准和标准测试方法（"药典方法"），或者经国家药品管理部门批准的质量标准和测试方法（"非药典方法"）。

2.3 Well-characterized reference materials, with documented purity, should be used in the validation study.
验证研究应当使用具有良好性能的且有文件证明纯度的参考物料。

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.
最常见的分析方法包括鉴别测试、原料药和药品分析试验、杂质含量定量测试以及杂质的限度检测。其它分析方法包括溶出度试验和例子大小测定。

2.5 The results of analytical procedures should be reliable, accurate and reproducible. The characteristics that should be considered during validation of analytical methods are discussed in paragraph 6.
分析方法结果应准确可靠，重现性好。分析方法验证过程中应考虑的指标见6描述。

2.6 Verification or revalidation should be performed when relevant, for example, when there are changes in the process for synthesis of the drug substance; changes in the composition of the finished product; changes in the analytical procedure; when analytical methods are transferred from one laboratory to another; or when major pieces of equipment instruments change.
任何需要的情况下应进行检验或验证，如当原料药合成工艺改变时、成品成分改变时；分析程序改变时、当分析方法从一个实验室转移到另一个实验室、或者当主要设备仪器发生更换时。

2.7 The verification or degree of revalidation depend on the nature of the change(s).
检验或验证程度取决于变更性质。

2.8 There should be evidence that the analysts, who are responsible for certain tests, are appropriately qualified to perform those analyses (“analyst proficiency”).
应有文件证明，负责测试的分析员具有执行分析试验的资格（“分析员资格认定”）。

3. Pharmacopoeial methods 药典方法

3.1 When pharmacopoeial methods are used, evidence should be available to prove that such methods are suitable for routine use in the laboratory (verification).
若采用药典方法，应有文件证明这些方法适合实验室常规使用（检验）。

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).

用于测定药品中含量或杂质的药典方法须经过验证是否适用于需要进行检测的物质（无对照剂干扰）。

4. Non-pharmacopoeial methods 非药典方法

4.1 Non-pharmacopoeial methods should be appropriately validated.
非药典方法应适当验证。

5. Method validation 方法验证

5.1 Validation should be performed in accordance with the validation protocol. The protocol should include procedures and acceptance criteria for all characteristics. The results should be documented in the validation report.
验证应根据验证方案开展。验证方案应包含所有指标的分析方法和验收标准。验证结果记录在验证报告中。

5.2 Justification should be provided when non-pharmacopoeial methods are used if pharmacopoeial methods are available. Justification should include data such as comparisons with the pharmacopoeial or other methods.
若药典方法已存在，则需要对采用的非药典方法进行检验。检验应包含诸如与药典或其他方法的对比等数据资料。

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.
应对标准测试方法进行详细描述，以便对分析员进行培训使之开

展可靠的分析。对标准测试方法的描述应至少包括色谱条件（在色谱测试情况下）、所需试剂、参考标准品、结果计算公式和系统适用性测试。

6. Characteristics of analytical procedures 分析方法指标

6.1 Characteristics that should be considered during validation of analytical methods include:
分析方法验证过程中应考虑的指标包括：

— specificity 专属性
— linearity 线性
— range 范围
— accuracy 准确度
— precision 精密度
— detection limit 检测限
— quantitation limit 定量限
— robustness. 稳固性

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 established across the specified range of the analytical procedure.
准确度是指测试结果与真实值的一致程度，或者方法测得结果与真实值的接近程度。准确性通常建立在用于定量准确性分析的物料样品上。应确定整个分析方法规定范围的准确度。

Note: it is acceptable to use a “spiked” placebo where a known quantity or concentration of a reference material is used.
注：当使用某个参考物料的一个已知数量或浓度时， “加标”对照剂的使用可以接受。

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 grouping) and expressed as the relative standard deviation (RSD).

精密度是指单个结果之间彼此的符合程度。从同一均匀批次物料中抽取的完全相同的单个样品，应分别进行完整的分析程序。精密度通过判断单个结果与平均值的分散测得，表示为相对标准差（RSD）

6.1.2.1 *Repeatability* should be assessed using a minimum of nine determinations covering the specified range for the procedure e.g. three concentrations/three replicates each, or a minimum of six determinations at 100% of the test concentration.

重复性是指在规定范围内，至少用 9 次测定结果进行评价，如制备3个不同浓度的试样，各测定3次；或100％的浓度水平，用至少测定6次的结果进行评价。

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.

中间精密度是在同一实验室、不同时间由不同分析人员用不同设备测定结果的精密度。若对重现性进行了评估，则不再需要测量中间精密度。

6.1.2.3 Reproducibility expresses precision between laboratories.

重现性是指在不同实验室中使用此种分析方法的精密度

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 influenced 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.

稳固性（或耐用性）是指利用相同的方法在各种正常实验条件下对同一样品进行分析得到可接受准确度和精密度的能力。单个样品测得的结果受操作或环境条件变化的影响。稳固性在分析方法的开发阶段就应该考虑。并且当故意更改程序参数时，稳固性能够显示分析的可靠性。

6.1.3.1 Factors that can have an effect on robustness when performing chromatographic analysis include:

进行色谱分析时影响稳固性的因素有：

— stability of test and standard samples and solutions;

测试和标准样品以及溶液稳定性

— reagents (e.g. different suppliers);

试剂（如来源于不同供应商）

— different columns (e.g. different lots and/or suppliers);

不同层析柱（如来源于不同批次和/或不同供应商）

— extraction time;

提取时间

— variations of pH of a mobile phase;

流动相的pH变异数

— variations in mobile phase composition;

流动相组成变化

— temperature; and

温度，和

— flow rate.

流量

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 appropriate statistical methods. A minimum of five concentrations should be used.

线性是在给定范围内获取与样品中供试物浓度成正比的试验结果的能力。应准备一系列样品，因为供试物浓度跨越了整个程序的范围。若为线性关系，使用恰当的统计方法评估测试结果。应至少采用五种浓度进行分析。

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 specified range is normally derived from linearity studies.

范围是指产品证实可检测的供试物最高和最低水平的表达方式。规定的范围通常通过线性研究得出。

6.1.6 *Specificity* (*selectivity*) is the ability to measure unequivocally the desired analyte in the presence of components such as excipients and impurities that may also be expected to be present. An investigation of specificity should be conducted during the validation of identification tests, the determination of impurities and assay.

专属性（选择性）是指在样品介质中有其他组分共存时该分析方法对供试物质准确而专属的测定能力。在鉴别测试、杂质测定和试验验证过程中，应对专属性进行调查研究。

6.1.7 *Detection limit* (*limit of detection*) is the smallest quantity of an analyte that can be detected, and not necessarily determined, in

a quantitative fashion. Approaches may include instrumental or non-instrumental procedures and could include those based on:
检测限（LOD）指能够检测出的样品中药物的最低浓度，无需定量测定。测试可采用仪器或非仪器程序方法，以及以下方法：

— visual evaluation;
目视评估

— signal to noise ratio;
信噪比

— standard deviation of the response and the slope;
反应和斜率的标准偏差

— standard deviation of the blank; and
空白值的标准偏差，和

— 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（LOQ）是指在保证具有一定准确度和精密度的前提下，分析方法能够测定出的样品中药物的最低浓度。测试可采用仪器或非仪器程序方法，以及以下方法：

— visual evaluation;
目视评估

— signal to noise ratio;
信噪比

— standard deviation of the response and the slope;
反应和斜率的标准偏差

— standard deviation of the blank; and
空白值的标准偏差，和

— 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.

表1概括了采用不同类型分析方法时应考虑的指标（包括测试）。

Table 1 Characteristics to consider during analytical validation

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	–	+	–	+

– 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.

表1　分析验证应考虑的指标

分析程序类型	鉴定	杂质检测	杂质检测	分析试验 — 溶解（仅指测量） — 含量/效价
指标		**定量测试**	**限度测试**	
准确度	–	+	–	+
精密度				
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;
一般不需评估的指标

\+ Characteristic should normally be evaluated.
必须评估的指标

a In cases where a reproducibility study has been performed, intermediate precision is not needed.
若已执行了重复性研究，则不再需要中间精密度。

b May be needed in some cases.
在某些情况下可能需要。

6.3 System suitability testing 系统适用性测试

System suitability testing is an integral part of many analytical procedures. The tests are based on the concept that the equipment, electronics, analytical 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 being evaluated, for instance, a resolution test for an HPLC procedure.

系统适用性测试是许多分析程序必不可少的组成部分。测试基于如此理念：设备、电子元件、分析运算和被分析样品组成了一个整体系统，所以也应该作为一个整体进行评估。为某个特定程序确定的系统适用性测试参数，取决于被评估程序的类型。例如，用于HPLC程序的分辨率测试。