APIC publishes Guidance on Cleaning Validation in Active Pharmaceutical Ingredients Plants

APIC 颁布原料药工厂清洁验证指南

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1.0 FOREWORD

The original version of this guidance document has now been updated by the APIC Cleaning Validation Task Force on behalf of the Active Pharmaceutical Ingredient Committee (APIC) of CEFIC.

本指南文件的原版本已经由 APIC 清洁验证工作组代表 CEFIC 委员会进行了更新。

The Task Force members are:- 以下是一些工作组的成员：

Annick Bonneure, APIC, Belgium
Tom Buggy, DSM Sinochem Pharmaceuticals, The Netherlands
Paul Clingan, MacFarlan Smith, UK
Anke Grootaert, Janssen Pharmaceutica, Belgium
Peter Mungenast, Merck KGaA, Germany.
Luisa Paulo, Hovione FarmaCiencia SA, Portugal
Filip Quintiens, Genzyme, Belgium
Claude Vandenbossche, Ajinomoto Omnichem, Belgium
Jos van der Ven, Aspen Oss B.V., The Netherlands
Stefan Wienken, BASF, Germany.

With support and review from:-

Pieter van der Hoeven, APIC, Belgium
Anthony Storey, Pfizer, U.K.
Rainer Fendt, BASF, Germany.

The subject of cleaning validation in active pharmaceutical ingredient manufacturing plants has continued to receive a large amount of attention from regulators, companies and customers alike.

原料药生产工厂的清洁验证一致是法规人员、公司和客户等关注的重点问题。

The integration of Cleaning Validation within an effective Quality System supported by Quality Risk Management Processes should give assurance that API Manufacturing Operations are performed in such a way that Risks to patients related to cleaning validation are understood, assessed for impact and are mitigated as necessary.

原料药生产企业应将清洁验证与有效的质量体系相结合，由质量风险管理来支持，了解与清洁验证相关的患者风险，评估其影响，并在必要时降低风险。

It is important that the requirements for the finished manufacturing companies are not transferred back in the process to active pharmaceutical ingredient manufacturers without consideration for the different processes that take place at this stage.

重要的是，不能将对制剂生产企业的要求直接用于原料药生产商，而不考虑在此阶段所用生产工艺的差别。

For example, higher limits may be acceptable in chemical production compared to pharmaceutical production because the carry-over risk is much lower for technical and chemical manufacturing reasons

例如：与制剂生产相比，化学生产可以接受较高的残留限度，因为技术原因，化学生产所带入后续产品的残留风险会低很多。

The document reflects the outcome of discussions between APIC member companies on how cleaning validation requirements could be fulfilled and implemented as part of routine operations.

本文件反映 APIC 成员公司之间关于如何满足 CV 的要求及作为日航操作来实施进行讨论的结果。

In addition, APIC is aligning this guidance with the ISPE Risk MaPP Guide 1 that follows the 1 ISPE Baseline® Pharmaceutical Engineering Guide, Volume 7 – Risk-Based Manufacture of PharmaceuticalProducts, International Society for Pharmaceutical Engineering (ISPE), First Edition, September 2010,www.ispe.org.5Quality Risk Management Processes as described in the ICH Q9 Guidance on Quality RiskManagement.

另： APIC 将本指南与 ISPE 基于风险的要生产指南保持一致，遵守 ICHQ9 质量风险管理中的质量风险管理流程。

The criteria of Acceptable Daily Exposure (ADE) is now recommended to be used by companies to decide if Dedicated Facilities are required or not and to define the Maximum Acceptable Carry Over (MACO) of API's in particular, in Multi-Purpose Equipment.

目前推荐公司使用“可接受日暴露水平”标准来决定是否专用设施界定原料药“最大可接受残留 MACO”，特别是针对多用于设备。

A new chapter is introduced to define factors that should be considered in Controls of The Cleaning Process to manage the Risks related to potential chemical or microbiological contamination.

加入了一个新的章节，对“清洁工艺的控制”中药考虑的因素进行了定义，以管理与潜在化学和微生物污染有关的风险。

The PDA Technical Report No. 29 – Points to Consider for Cleaning Validation 2 is also recommended as a valuable guidance document from industry.

也推荐企业将“PDA 低 29 号技术报告—清洁验证中应考虑的问题”作为有用的指南文件进行参考。

The following topics are discussed in the PDA document: Cleaning process (CIP/COP): design and qualification

一下问题在 PDA 文件中进行了讨论：清洁工艺（CIP/COP）：涉及和确认

- Types of residues, setting acceptance criteria, sampling and analytical methods
  残留类型、设定可接受标准、取样和分析方法
- Maintenance of the validated state: critical parameters measurements, process alarms, change control, trending & monitoring, training and periodic review
  维护状态：关键参数测量、工艺警示、变更控制、趋势& 监控，培训和周期性评估
- Documentation
- 文件记录

2.0 Objective

This document has been prepared to assist companies in the formulation of cleaning validation programmes and should not be considered as a technical standard but a starting point for internal discussions. The document includes examples on how member companies have dealt with specific areas and issues that arise when performing cleaning validation.
目的：本文件的目的是版主公司制定清洁验证程序，不能作为是一个技术标准。只应作为内部讨论的出发点，本文包括了成员公司如何处理特殊领域的例子，以及在实施清洁验证时提出的问题点。

3.0 Scope

Six specific areas are addressed in this Guidance document:
本指南文件包括了 6 个方面

- Acceptance Criteria 接受标准
- Levels of Cleaning 清洁水平
- Control of the cleaning process 清洁工艺的控制
- Bracketing and Worst Case Rating 分类法和最差情况分级
- Determination of the amount of residue 残留量的检测
- Cleaning Validation Protocol 清洁验证方案

Finally, the most frequently asked questions are answered to give further guidance on specific points related to cleaning validation.
最后是一些常见问题及回答，对一些清洁验证有关的特殊情况给予指导。

4.0 Acceptance Criteria 科接受标准

4.1. Introduction 概述

Companies must demonstrate during validation that the cleaning procedure routinely employed for a piece of equipment limits potential carryover to an acceptable level. That limit established must be calculated based on sound scientific rational.
公司在验证时要证明各设备日常所使用的清洁程序能将带入下一个产品的潜在残留限限制在一个可以寄售的水平，所以建立的限度必须进行科学合理的计算。

This section provides practical guidance as to how those acceptance criteria can be calculated. It is important that companies evaluate all cases individually. There may be specific instances where the product mix in the equipment requires further consideration.
本部分提供实用的指南，知道如何计算这些可接受标准。公司对个案进行个案评估是非常重要的，有时候还需要考虑产品从那部开始混入设备中。

The acceptance criteria preferably should be based on the Acceptable Daily Exposure (ADE) calculations whenever this data is available. The Acceptable Daily Exposure defines a limit at which a patient may be exposed every day for a lifetime with acceptable risks related to adverse health effects. Calculations of Acceptable Daily Exposures of API's and intermediates are usually done with involvement of industrial hygienists and toxicologists, who review all available toxicology and clinical data to set the limits. The justification of the calculation should be documented.
如果可以获得可接受日暴露（ADE）值，最好依据其计算可接受标准。可接受日暴露定义的是患者终身每天暴露于该浓度，但对健康的不良影响仍处于可接受风险水平，原料药和中间体的 ADE 一般由企业的微生物专家和毒理学家来制定，他们会审核各种可以获得的毒性和临床数据来设定限度。计算的合理性要进行记录。

In many cases Occupational Exposure Limits (OEL) will be defined for API's, Intermediates and Industrial Chemicals by Industrial Hygienists and toxicologists and the OEL data is then

used to define containment measures such that operators are adequately protected while working with the chemicals.

The OEL data can also be used to calculate the ADE for cleaning of equipment.

在很多情况下，会有行业微生物专家和毒理学专家对原料药、中间体和工业级化学品的执业暴露限度（OEL）值进行界定，这时应使用 OEL 数据来制定限度的措施，例如，操作人员在操作化学物质时需要受到的充分保护。OEL 数据也可以用于计算设备清洁的 ADE 值。

In certain cases where availability of pharmacological or toxicological data is limited, for example for chemicals, raw materials, intermediates or API's in early phase clinical trials, cleaning limits based on fraction of clinical doses, LD 50 or general cleaning limits may be calculated. In these cases, carcinogenic, genotoxic and potency effect of these structures should be evaluated by toxicologists.

在特定情况下，如果药性或毒性数据有限，例如,化学物质、原料、中间体或处于早期临床试验的原料药，其清洁限度是可以基于临床剂量，半数致死量或一般清洁限度来计算，在这种情形下，需要有毒理学的专家对其结果的致癌性、基因毒性和效价影响进行评估。

The acceptance criteria for equipment cleaning should be based on visually clean in dry conditions and an analytical limit.

合并清洁的可接受标准应依据干燥状态下目视清洁及分析限度。

Unlike in pharmaceutical production, where residues on the surface of equipment may be 100 % carried over to the next product, in API production the carry-over risk is much lower for technical and chemical manufacturing reasons. Therefore all the following examples for calculating the limits can be adapted to the suitable situation by using different factors. A competent chemist with detailed knowledge about the equipment and the chemical processes and the properties of the chemicals involved such as solubility should justify this factor by evaluating the specific situation.

在制剂生产中，设备表面残留会 100%被带入下一产品，而在原料药中，由于技术和化学生产原因，带入风险要低很多，因此，以下现付计算距离可以采用不同安全银子后用于适当的情形，应有一名具备化学工艺知识的人对其安全系统进行评估。

4.2. Methods of Calculating Acceptance Criteria 计算可接受标准的方法

4.2.1 Acceptance criteria using health-based data 采用健康基础数据的可接受标准

The Maximum Allowable Carryover (MACO) should be based upon the Acceptable Daily Exposure (ADE) when this data is available. The principle of MACO calculation is that you calculate your acceptable carry-over of your previous product, based upon the ADE, into your next product

在可获得可接受日暴露水平（ADE）值时，最大允许残留（MACO）应基于 ADE 计算。MACO 计算的原则是基于 ADE 值，计算允许从上一个产品带入下一个产品中的残留量。

Procedure 程序

Calculate the ADE (Acceptable Daily Exposure) according to the following equation and use the result for the calculation of the MACO.

根据以下公式计算 ADE 值，将结果用于 MACO 值的计算：

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

From the ADE number, a MACO can be calculated according to:

根据以下公式从 ADE 值计算 MACO 值：

$$MACO = \frac{ADE_{previous} \times MBS_{next}}{TDD_{next}}$$

MACO Maximum Allowable Carryover: acceptable transferred amount from the previous product into your next product (mg) 允许最大残留：从上一品种带入下一品种的最大可接受量

ADE Acceptable Daily Exposure (mg/day) 可接受日暴露水平

NOAEL No Observed Adverse Effect Level (mg/kg/day) 未观察到副反应的水平

BW Is the weight of an average adult (e.g. 70 kg) UFc 平均成人体重

Composite Uncertainty Factor: combination of factors which reflects the inter-individual variability, interspecies differences, sub-chronic-to-chronicextrapolation, LOEL-to-NOEL extrapolation, database completeness. 组分不确定因子：反映单个变量之间、不同品种差异、亚急性折算为急性外推、LOEL 折算为 NOEL 外推、数据完整性等补偿因素的系数

MF Modifying Factor: a factor to address uncertainties not covered by the other factors 修正因子：用于表达未被其它因子覆盖的不确定因素

PK Pharmacokinetic Adjustments 药动学调整

TDDnext Standard Therapeutic Daily Dose for the next product (mg/day) 下一产品的标准治疗日服用剂量

MBSnext Minimum batch size for the next product(s) (where MACO can end up) (mg) 下一产品的最小批量（MACO 全部带入其中）

The draft EMA/CHMP/CVMP/SWP/19430/2012 makes reference to the Permitted Daily Exposure (PDE). The PDE uses the no observed effect level (NOEL) instead of the no observed adverse effect level (NOAEL) used in the ADE calculation. The PDE may also be used as alternative to the ADE to calculate the MACO.

EMA/CHMP/CVMP/SWP/19430/2012 草案中引用了允许日暴露(PDE)值，PDE 采用了无可见影响水平（NOEL）代替无可见不良反应水平（NOAEL）用于 ADE 值的计算，PED 值也可以用于代替 ADE 值来计算 MACO 值。

Instead of calculating each potential product change situation, the worst case scenario can be chosen. Then a case with most active API (lowest ADE) is chosen to end up in the following API with the smallest ratio of batch size divided with TDD (MBS/TDD ratio).

If OEL data is available, the ADE can be derived from the OEL.

可以选择最差情况方案来代替每个可能的产品更换情况下的残留计算。这时，可以选择活性最强的原料药（ADE 最低）作为上一个产品，选择批量 TDD 比值（MBS/TDD 比值）最小的原料药作为后续产品。如果可以获得 OEL 值，则可以从 OEL 值计算 ADE 值。

4.2.2. Acceptance criteria based on Therapeutic Daily Dose

基于日治疗剂量的可接受标准

When limited toxicity data is available and the Therapeutic Daily Dose (TDD) is known, this calculation may be used. It is used for final product changeover API Process —A to API Process —B.

如果可以获得有限毒性数据和日治疗剂量（TDD）值，可以采用本计算方式，它可以用在原料药生产工艺 A 更换到原料药生产工艺 B。

Procedure 程序：

Establish the limit for Maximum Allowable Carryover (MACO) according to the following equation. 根据以下公式建立允许最大残留（MACO）值：

TDD previous(上一产品) x MBS next（下一产品）

MACO = ----------

SF x TDD next （下一产品）

MACO Maximum Allowance Carryover: acceptable transferred amount from the previous product into your next product (mg)允许最大残留：从上一产品中可以接受转入下一产品的数量（mg）

TDDprevious Standard Therapeutic Daily Dose of the investigated product (in the same dosage from as TDD next) (mg/day) 讨论的产品的日标准治疗剂量（以下一产品 TDD 的同样剂量）

TDDnext Standard Therapeutic Daily Dose for the next product (mg/day)下一产品的日标准质量剂量

MBSnext Minimum batch size for the next product(s) (where MACO can end up (mg) 下一产品的最小批量（MACO 带入的出产品）

SF Safety factor (normally 1000 is used in calculations based on TDD).安全系数（一般基于 TDD 值采用 1000 来计算）

4.2.3. Acceptance criteria based on LD 50 半数致死量的可接受标准

In cases where no other data is available (e.g. ADE, OEL, TDD,…) and only LD 50 data is available (e.g. chemicals, intermediates, detergents, …), the MACO can be based upon LD 50 data.如果没有办法获得其他数据(e.g. ADE, OEL, TDD,…)，只能获得半数致死量数据（例如化学物质、中间体、清洁剂。。。。。。。。），MACO 可以基于半数致死量数据来计算

Procedure 程序

Calculate the so called NOEL number (No Observable Effect Level) according to the following equation and use the result for the establishment of MACO (See [3] œ page 53 - for reference).

根据以下公式，计算 NOEL 值（无可见影响水平），用于建立 MACO 值（page 53 - for reference)

LD 50 x BW

NOEL = ----------

2000

From the NOEL number a MACO can be calculated according to:从 NOEL 值，用以下公式计算 MACO：

NOEL previous NOEL（上一产品）x MBS next （MBS 下一产品）

MACO = ----------

SF next（SF 下一产品） x TDD next（TDD 下一产品）

MACO Maximum Allowance Carryover: acceptable transferred amount from the previous product into your next product (mg) 允许自大残留

NOEL previous No Observed Effect Level (mg/day) 无可见影响水平

LD50 Lethal Dose 50 in mg/kg animal. The identification of the animal (mouse, rat etc.) and the way of entry (IV, oral etc.) is important

(mg/kg) 50%的动物致死量，单位 mg/kg.动物种类（大鼠、小老鼠等）和摄入途径（注射、

口服等）也很重要（mg/kg）

BW　Is the weight of an average adult (e.g. 70 kg) (kg)　成年人平均体重（例如：70kg）

2000　2000 is an empirical constant　　经验常数

TDDnext　Standard Therapeutic Daily Dose for the next product (mg/day)　下一产品的目标准治疗剂量(mg/day)

MBSnext　Minimum batch size for the next product (s) (where MACO can end up)下一产品的最小批量（MACO 会带入的产品）（mg）

SFnext　Safety factor　　安全系数

The safety factor (SF) varies depending on the route of administration (see below). Generally a factor of 200 is employed when manufacturing APIs to be administered in oral dosage forms.

安全系数（SF）根据摄入途径不同而不同（如下）。一般系数 200 用于口服剂型原料药的生产。

Safety factors:安全系数

Topicals　10 – 100　局部给药

Oral products　100 – 1000　口服给药

Parenterals　1000 – 10 000　注射给药

4.2.4 General Limit as acceptance criteria　　可接受标准的一般限度

If MACO calculations result in unacceptably high or irrelevant carryover figures, or toxicological data for intermediates are not known, the approach of a general limit may be suitable. Companies may choose to have such an upper limit as a policy. The general limit is often set as an upper limit for the maximum concentration (MAXCONC) of a contaminating substance in a subsequent batch.

如果 MACO 计算结果太高，不能接受，或者与带入数字不相关，或中间体毒性数据未知，则使用通用限度方法。公司可以选择例如一个最高限度作为原则，通用限度一般设定为一种污染物质在后续批次中最大浓度上限（MAXCONC）

Procedure 程序

Establish MACOppm, based on a general limit, using the following equations.

利用以下公司，基于一个通用限度建立 MACO 限度，PPM 为单位。

MACO ppm = MAXCONC x MBS

MACOppm　Maximum Allowable Carryover: acceptable transferred amount from the investigated product ("previous"). Calculated from general ppm limit.允许最大残留：所讨论的产品（上一产品）被带入下一产品的可接受值，一般表达为 ppm 限度

MAXCONC　General limit for maximum allowed concentration (kg/kg or ppm) of "previous" substance in the next batch.允许上一产品在下一产品中的最大浓度通用限度(kg/kg or ppm)

MBS　Minimum batch size for the next product(s) (where MACO can end up)　下一产品的最小批量

E.g. for a general limit of 100 ppm: MACO = 0.01% of the minimum batch size (MBS), and for a general limit of 10 ppm: MACO = 0.001% of the minimum batch size (MBS).

例如：对于通用限度为 100ppm,MACO=最小批量（MBS）的 0.01%，对于通用限度为 10ppm，MACO=最小批量（MBS）的 0.001%

Remarks: The ICH impurity document (Q 3) indicates that up to 0.1% of an individual

unknown or 0.5% total unknowns may be present in the product being tested.
注意：ICH 杂质文件 Q3 指出，在被测试的产品中，单个未知杂质可以达到 0.1%，总未知杂质可以达到 0.5%。
A general upper limit for the maximum concentration of a contaminating substance in a subsequent batch (MAXCONC) is often set to 5-500 ppm (100 ppm in APIs is very frequent) of the previous product into the next product depending on the nature of products produced from the individual company (e.g. toxicity, pharmacological activity, …).
根据各个公司所生产产品的属性不同（例如：毒性、药物活性等），从上一产品带入下一产品中的污染物最大浓度通用上限通常设定为 5-500ppm（原料药中 100ppm 是较常见）。
The Threshold of Toxicological Concern (TTC) concept could be applied to intermediates or API's with no clinical (e.g. early development) or toxicological data. This concept includes three categories of products with limited or no data:
毒性关注值（TTC）概念可以应用于没有临床（例如早期开发阶段）或毒性数据的中间体或原料药。这个概念将数据有限或没有数据的产品分为三个类别。

Products that are likely to be carcinogenic; 可能致癌的产品
Products that are likely to be potent or highly toxic; 可能具有效价或高毒性的产品
Products that are not likely to be carcinogenic, potent or highly toxic.可能致癌、具有效价或高毒性的产品

The corresponding ADE's recommended for these three categories are 1, 10, 100 µg/day, respectively.对应此三类所推荐的 ADE 值分别为 1.10 个 100ug/day。
Another possibility to calculate your ADE for intermediates or API's, with no clinical or toxicological data (e.g. early development), is based upon the exposure duration of your next product. The values of the CHMP guideline on the Limits of Genotoxic Impurities (ref. EMEA/CHMP/SWP/431994/2007) can be used for your ADE.
在没有临床或毒性数据（如早期开发）时，计算中间体或 API 的 ADE 还有一个方法，就是基于下一产品的暴露时间长短，可以将 CHMP 指南“基因毒性杂质”（(ref. EMEA/CHMP/SWP/431994/2007）限度至可以用于 ADE 计算。
Note - If you decide to employ the concept of levels of cleaning (ref. section 5), then different safety factors (ppm limits) may be used for different levels. Especially if the product cleaned out is within the same synthetic chain and covered by the specification of the API, much higher (qualified) levels are acceptable.
注意：如果你决定采用清洁水平概念（ref. section 5）则对不同水平可以采用不同的安全系数（ppm 限度）。特别是如果被清洁的产品是在同一条合成链中，且其限度包括在原料药的质量标准中，则残留水平较高是如果进行过确认也是可以被接受的。

4.2.5 Swab Limits 擦拭限度
If homogeneous distribution is assumed on all surfaces, a recommended value can be set for the content in a swab. The maximum allowable carry over from one batch to another can be established based on e.g. ADE, NOEL or TDD (see above). If the total direct contact surface is known, the target value for contamination per square meter can be calculated according equation 4.2.5-I. This can be used as basic information for preparation of a method of analysis and detection limit.
如果假定所有表面上残留的恩不是均匀的，可以个擦拭样品设定一个推荐值，可以根据例如 ADE 值、NOEL 或 TDD（如上）设定一批到另一批的最大允许残留值。如果知道直接接触产

品的总面积，则可以根据 4.2.5-1 公式计算单位面积上的污染目标值，改制可以在制定方法验证方案和监测限值时参考。

$$\text{Equation 4.2.5-I Target value [µg/dm2]} = \frac{\text{MACO [µg]}}{\text{Total surface [dm2]}}$$

$$\text{公式 4.2.5-I 目标值[µg/dm2]} = \frac{\text{MACO[µg]}}{\text{总表面积[dm2]}}$$

Also other methods with different swab limits for different surfaces in a piece of equipment and/or equipment train can be used. If the equipment can be divided in several parts, different swab limits may be taken for the different parts building up the equipment train. If the result of one part is exceeding the target value, the whole equipment train may still be within the MACO limit. The Carry Over is then calculated according equation 4.2.5-II (see below).

也可以对同一设备或设备链不同的表面使用不同的擦拭限度。如果设备被分为几个部分，对可以针对设备链不同部分采用不同的擦拭限度。如果一个部件的结果超出了目标值，整个设备链的残留值扔可能是在 MACO 的限度内。这时，可以按公式 4.2.5- II (see below).

During equipment qualification and cleaning validation hard to clean parts can be determined. Rather than declaring the hard to clean part as the worst case swab limit for the whole equipment train, it could be separated and dealt with as mentioned above. It should be noted that different types of surfaces (e.g. stainless steel, glass lined, Teflon) may show different recoveries during swabbing. In those cases it may be beneficial to divide the equipment train in several parts, and combine the results in a table or matrix. The total calculated amount should be below the MACO, and the individual swab results should not exceed the maximum expected residues established during cleaning validation / equipment qualification. Recovery studies and method validation are necessary when applying swabbing as a method to determine residues.

在设备确认和清洁验证中可以确定那个部件是难以清洁的，其实可以用采用上述的方法来将难以清洁的部件分开来，而不需要采用最难清洁的部件作为最差擦拭情况的限度用于整个设备链。要注意不同材质表面（例如：不锈钢、搪玻璃、ptfe）可能有不同的擦拭回收率。在这种情况下，如果把设备链划分为几个部分，将结果在一份表或类别中合并可能会比较好。合计数量应低于 MACO 值，单个擦拭结果不应超过在清洁验证/设备确认中所设立的最大或者最高的期望值。在使用擦拭方法测定残留量时，要进行回收率研究和方法验证。

Equation 4.2.5-II 公式

$$CO\ \mu g = \Sigma\,\Sigma(\,Ai\,[dm2\,] \times mi\,[\,\mu g\,/dm2\,]\,)$$

CO True (measured) total quantity of substance (possible carryover) on the cleaned surface in contact with the product, calculated from results of swab tests.采用擦拭监测结果计算出的与产品直接接触的已清洁表面实际总残留量

A i Area for the tested piece of equipment # i. 所测试的 I 设备的面积

m I Quantity in µg /dm 2 , for each swab per area of swabbed surface (normally 1 dm 2)单位擦拭面积的残留数量

4.2.5.1. Setting Acceptance Criteria for Swab Limits 对擦拭限度设定可接受标准

For each item tested, the following acceptance criteria (AC) apply.以下可接受标准适用于各测

试项目

AC1. The cleaning result of an individual part should not exceed the maximum expected residue. 单个设备清洁结果应不超过最大可接受残留量。

AC2. For the total equipment train the MACO must not be exceeded.总设备链的 MACO 不得超过。

In determining acceptance limits, all possible cases of following products in the relevant equipment shall be taken into account. It is proposed that a matrix be set up in which the limits for all cases are calculated. Either acceptance criteria for each product in the equipment can be prepared or the worst case of all product combinations may be selected.

在制订可接受限度时，要考虑在相关设备中可能生产的所有后续产品。建议画出矩阵图，在其中所有情况下的限度进行计算，然后针对在该设备中生产的每个产品分布制订可接受标准，也可以对所产品选择最差情况下的可接受标准。

4.2.5.2. Evaluation of results 结果评估

When all surfaces have been sampled and the samples have been analyzed, the results are compared to the acceptance criteria. Companies may find it easier to evaluate against the MACO. However, it is advisable to have a policy for swab limit as well. Especially because analytical methods are validated within a certain range for swab results. Another reason is that some pieces could be very contaminated, and it is not good practice to clean certain pieces very thoroughly in order to let others be dirty. Thus, limits for both MACO and swabs should be set.

在对所有表面取样后，对样品进行分析，将结果与可接受标准进行比较。公司可以发现采用 MACO 来评估会比较容易。但是，还是建议对于擦拭限制订一个原则，主要是因为擦拭样品分析方法的验证是在一定的浓度范围内进行的。另一个原因是有一些部件的污染可能会比较严重，没有理由让一些部件清洁的非常彻底而让玲一些部件很脏。因此，应同时设定 MACO 限度和擦拭限度。

4.2.6. Rinse Limit 淋洗限度

The residue amount in equipment after cleaning can also be determined by taking rinse samples. During equipment qualification it should be established that all direct content parts of the equipment is wetted / reached by the rinsing solvent. After the last cleaning cycle (last rinse), the equipment should be assessed as 'clean'. In some cases it may be advisable to dry the equipment in order to do a proper assessment. Thereafter, the rinse cycle can be executed, and a sample taken (sampling rinse). The procedure for the rinse cycle and sampling should be well established and described to assure repeatability and comparability (cycle times, temperatures, volumes, etc.). The choice of the rinse solvent should be established during cleaning validation, taking into account solubility of the contaminations, and reactivity of the rinse solvent towards the contaminants (saponification, hydrolyses, etc). Method validation is needed。

设备清洁后的残留量也可以采用淋洗样来检测。在设备确认时，应该识别出设备中所有可以被淋洗溶剂淋到的部件，在最后清洁（最后淋洗）结束后，设备状态应评估为“清洁”方可取样。有时，需要对烘干设备以便进行适当的评估。之后，对设备进行淋洗、取样（淋洗样）。应制订书面程序描述淋洗和取样操作，以保证其可重复性和可比较性（重复次数、温度、体积等）。在清洁验证时应对淋洗用溶剂作出选择，选择时应考虑污染物的溶解度，以及淋洗用溶剂与污染物之间的反应活性（皂化反应、水解反应等。）淋洗方法要进行验证。

In a worst case approach, the amount of the residue in the equipment can be assumed to be

equal to the amount determined by analysis of the rinse sample. This can be supported by rinse studies that show a strong decay of a residue in a piece of equipment.
如果采了最差情形方法，可以假定设备中的残留量对淋洗样品的检测结果相等。这个假设可以通过对一个设备部件上淋洗前后残留物急剧减少来支持。
The MACO is usually calculated on each individual product change over scenario according to the procedures outlined above and individual acceptance criteria are established using the following equation:
通常根据上述所列的方法，针对各个产品更换的情况计算 MACO。采用以下公式，可以计算出单个可接受标准：
Target value (mg/L) = MACO (mg) / Volume of rinse or boil (L)
目标值=MACO/淋洗溶剂体积
For quantitation a solvent sample (e.g. 1 L) is taken, the residue in the sample is determined by a suitable analytical method and the residue in the whole equipment is calculated according to the following equation:
对于一定的取样体积（例如 1L），采用适当的分析方法，测定样品中的残留量，根据以下公式计算整个设备中的残留量：
M = V*(C-Cb)
M Amount of residue in the cleaned equipment in mg 已清洁设备中的残留总量
V Volume of the last rinse or wash solvent portion in L 最后淋洗或冲洗溶剂的体积
C Concentration of impurities in the sample in mg/L 样品中杂质浓度
Cb Blank of the cleaning or rinsing solvent in mg/L. If several samples are taken during one run, one and the same blank can be used for all samples provided the same solvent lot was used for the whole run.
空白淋洗或冲洗溶剂如果在一个轮次中取了几个样品，则可以采用其中一个空白用于该轮中所有样品的计算
Requirement: M < Target value.
要求：M＜目标值
The requirement is that M < target value. If needed, the sample can be concentrated before analysis.
要求是 M＜目标值。如果需要，样品可以在检测前进行浓缩。
The choice for swab or rinse sampling usually depends on the type of equipment. Areas to be swabbed are determined during equipment and cleaning validation (‘hard to clean areas’), and are preferably readily accessible for operational reasons, e.g. near the manhole. If swabbing of the indicated area is not easy, rinse sampling is the alternative. The advantage is that the whole surface of the equipment is sampled for contamination, being provided that during equipment qualification, surface wetting testing was taken into account. Thus equipment used for milling, mixing, filters, etc. are usually swabbed, whilst reactor systems are usually sampled by rinsing.
选择擦拭样品还是淋洗样品通常取决于设备的类型，擦拭取样点应在设备验证和清洁验证中确定（难以清洁点），最好还要易于操作，例如接受人孔处，如果要取样的地方很难采用擦拭取样，可以采用淋洗水取样。淋表取样的优点是设备的整个表面都能被取样测试来体现出污染程度。淋洗取样时，要考虑表面湿润测试，该测试应在设备确认期间完成，签于此，用于粉碎、混合、过滤等的设备一般采用擦拭取样，而反应釜系统一般采用淋洗取样。
4.2.7 Rationale for the use of different limits in pharmaceutical and

chemical production

在药品和化学生产中使用不同限度的合理性

Unlike in pharmaceutical production, where residues on the surface of equipment may be 100 % carried over to the next product, in API production the carry-over risk is much lower for technical and chemical manufacturing reasons. Thus higher limits may be acceptable in chemical production compared to pharmaceutical production. For example chemical processing steps often include dissolution, extraction and filtration steps that are likely to reduce significantly any residue left from previous production and cleaning operations. A factor of 5-10 could be applied to the MACO calculated using the Acceptable Daily Exposure Limit or the secondary criteria defined in the previous sections.

在药品生产中，设备表面残留可能会 100%被带入下一产品，与之不同的是，在原料生产中，由于技术和化学生产原因，残留带入风险要低很多。因此，在与药品生产相比，在化学生产中采用较高的残留限度是可以接受的，例如，化学工艺步骤经常包括溶出、提取和过滤，这些步骤可能会显著降低上一产品和清洁操作所残留的东西，如果采用 ADEL 值计算 MACO，则可以使用 5-10 的安全系数，或者采用上述部分中界定的中等标准。

In all cases, the limits should be justified by a competent chemist with detailed knowledge about the equipment and the chemical processes, following Quality Risk Management Principles and the limits should be approved by Operations and Quality Assurance Managers.

在所有情况下，所有的限度均应该有具备一定资质的化学专家进行讨论。应该具备关于设备和化学工艺的知识，遵守质量风险管理的原则，所制订的限度应由质量保证部经理批准。

The following description shows an example where the carry-over risk for a residue in chemical production equipment is much lower than in pharmaceutical production equipment.

一下例子说明在化学生产设备中，其残留的带入风险比药品生产设备要低很多。

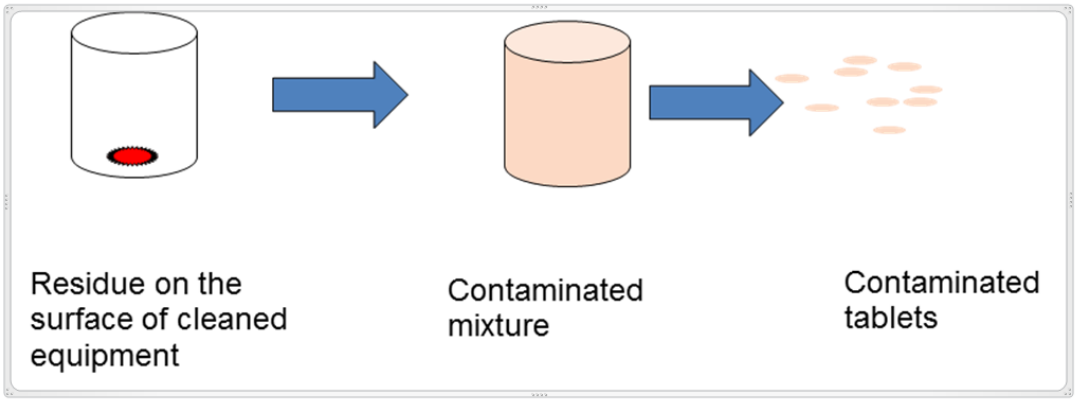
Assuming that the common criteria (ADE, 1/1000 th dose, LD 50 NOEL/ADI with SF 100-1000, 10 ppm) represent the state of the art for pharmaceutical production and are considered sufficiently safe, then the calculation of limits in API manufacture must reflect the different processes in pharmaceutical production and in the chemical production of active pharmaceutical ingredients to allow comparable risk analyses to be undertaken.

假定常用标准（ADE，1000 分之一计量。LD50 NOEL/AEL 安全系数 100-1000,10ppm）代表药品生产理想状态，被认为是足够安全的，这时原料药生产中的限度计算必须反映化学原料药生产与药品生产工艺的不同，是的可以进行风险分析比较。

Pharmaceutical production, Chemical production physical process 药品生产、化学生产的物理处理

In pharmaceutical production a residue remaining on the surface of equipment after cleaning is, in the next production cycle, distributed in a mixture of active substance and excipients if it does not remain on the surface. In the worst case it will be 100 % transferred to the first batch of next product.

在药品生产中，清洁后残留保存在设备表面，在下一个生产循环中，如果这些残留不再停留在设备表面，则会分布在原料药和辅料的混合物中，最差情况是这些残留 100%的被带入到下一产品的第一个批次



清洁后设备表面残留　　受污染的混合物　　受污染的片剂

Chemical production/processing　　化学生产/工艺

In chemical production a 100 % carry-over of residue from the equipment surface to the next product to be manufactured is very unlikely based on the way the process is run and on technical considerations. The residue remaining on the equipment surface can, during the next production cycle, be carried over into the reaction mixture consisting of solvent and raw materials. In most cases, however, any residue in solution will be eliminated from the process together with the solvent, and insoluble residue by physical separation processes (e.g. filtration), so likely carry over into the end-product will be low.

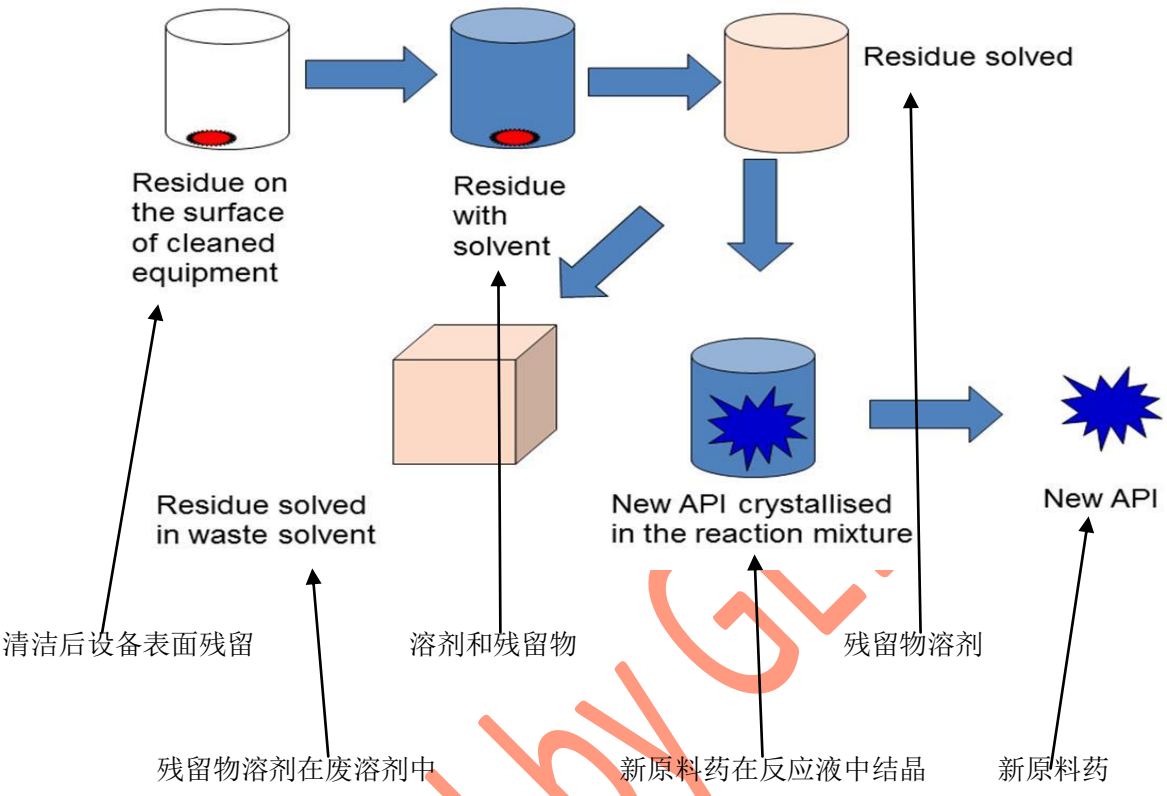
在化学生产中，考虑到工艺运行的方式，以及技术问题，残留物被 100%的从设备表面带入下一产品中的情况不太可能发生。残留在设备里面的东西，在下一生产循环中，会被带入溶剂和原料所组成的混合反应液中。在大多数情况下，所有溶液中的残留都会与溶剂一起被从工艺中去除，不溶性残留会被物理分离工艺（例如过滤）减少，因此，可能被带到最终产品中的残留会很低。

The final step in a multi-step chemical synthesis is selective purification of the API (e.g. by crystallization), during which contaminants are removed from the process and/or insoluble residues are removed by physical separation). From the original reaction mixture of educt, agent and solvent there remains only a fraction of the original mass as API at the end of the chemical process.

在多步化学合成的最后一步，一般是原料药选择性精制（例如，通过结晶方式）。在精制过程中，污染物从工艺中去除，不溶性残留物被物理分离所去除。在经过这些化学工艺后，原来那些由离析物、实际和溶剂所组成的混合反应液值剩下一些原来物质的片断，在最后成为原料药。

It is also to be noted that, during subsequent pharmaceutical production, the API is further diluted through the excipients that are added.

还有要注意的是，在后续的药品生产过程中，原料药通过加入辅料被进一步稀释了。



Conclusion: 结论：

Assuming that there is no intention to impose more stringent yardsticks during API production than in pharmaceutical production but that they should be approximately the same, the logical conclusion is that the limits in chemical production should be set higher than in pharmaceutical production. Based on this rationale, a factor of 5 - 10 compared to the established pharmaceutical production limits is both plausible and, in terms of pharmaceutical risk, acceptable.

假定我们并无意将比药品生产更加严格的标尺强加给原料药生产，而只是要将他们保持大致相同，则从逻辑上德奥的结论就是在化学生产中的限度应该设定得比药品生产中的限度要高。基于此理论，相比于已经建立的药品生产限度，对有原料药生产采用 5-10 的安全系数感觉好像是比较合理的，如果单从药品质量风险的角度来考虑，也是可以被接受的。

Chemical production “physical processes” (drying, mixing, filling, ...)化学生产的“物理处理”（干燥、混合、填充。。。。。。）

Apparatus and equipment that is used for physical end-treatments such as drying, mixing or milling may either be operated together with the previous synthesis equipment or generally be used separately. During separate physical end-treatments of APIs, there is no decrease of contaminants compared to the aforementioned chemical process. Consequently, we recommend in this case that the calculation methods applied should be those normally used in pharmaceutical production, (ADE, 1/1000 th dose, LD 50 NOEL/ADE with SF 100-1000, 10 ppm). The Limits for carry over into the final API should be the same as those calculated in the previous sections.

用于最终物理处理，如干燥、混合或磨粉的设备仪器，可以与之前的合成设备一起使用，通常是单独使用。在原料药单独的物理最终处理过程中，与之前提到的化学过程相比，其污染物不会减少，因此我们推荐在这种情况下，应采用制剂产品中常用的计算方法（ADE、千分之一剂量、半数致死量、NOEL/ADE 和安全系统 100-1000、10ppm）。带入最终原料药的残留量限度英语之前各部分所计算的一致。

ANNEX 1: Examples of MACO calculations.

附录 1：MACO 计算的例子

Example 1: ADE calculation

例 1：ADE 计算

Product A has a NOAEL 70kg of 100 mg/day human oral dose. Uncertainty factors applied to calculate the ADE are an UF S of 3 (extrapolation from an acute dose to subchronic/chronic dosing) and UF H of 8.13 (the inter-individual variability based upon a PK (kinetic component) of 2.54 and PD of 3.2 (dynamic component)). The MF is 10 (extrapolation from a 'generally healthy' population to a more susceptible sick patient population). Product B is an oral product (PK = 1).

$$ADE = \frac{100 \text{ (mg/day)}}{3 \times 8.13 \times 10 \times 1} = 410 \text{ (µg/day)}$$

Result: ADE oral is 410 µg/day

A 产品 NOAEL 70kg 人类口服剂量为 100mg/dag ，用于计算 ADE 的不确定因子 UFS 为 3（从急性剂量到亚慢性/慢性给药外推得到），UFH 为 8.13（根据 PK（动力学组成）为 2.54 和 PD 为 3.2（动力学组成）所得的内在固体变化）。MF 为 10（从“一般健康”人群外推至易感人群），产品 B 为口服产品（PK=1）

结果：口服 ADE 值为 410ug/day。

If product B is a parenteral product and the PK is 62.5 (based upon an oral bio-availability study in human after parenteral).

如果产品 B 是一个注射液产品、PK 值为 62.5(基于人体注射后利用度研究)

$$ADE = \frac{100 \text{ (mg/day)}}{3 \times 8.13 \times 10 \times 62.5} = 6.6 \text{ (µg/day)}$$

Result: ADE parenteral is 6.6 µg/day

结果：注射 ADE 值为 6.6ug/day。

Example 2: Acceptance criteria based on Acceptable Daily Exposure

例 2：根据日治疗剂量计算可接受标准

Product A will be cleaned out. The product has an ADE of 2 mg and the batch size is 200 kg. The next product B has a standard daily dose of 250 mg and the batch size is 50 kg. Calculate the MACO for A in B.

产品 A 要被清洁，其标准日剂量为 10mg，批量为 200kg。下一产品 B 标准日剂量为 250mg，批量为 50kg。A 和 B 都是口服摄入，安全系数 SF 设定为 1000，计算 A 在 B 中的最大允许残留量 MACO。

$$MACO = \frac{0.002\ (mg) \times 50\,000\,000\ (mg)}{250\ (mg)} = 400\ (mg)$$

Result: MACO is 0.4 g (400 mg)

结果：允许最大残留值为 2g（2000mg）

Example 4: Acceptance criteria based on Therapeutic Daily Dose

例 4：

Product A will be cleaned out. The product has a standard daily dose of 10 mg and the batch size is 200 kg. The next product B has a standard daily dose of 250 mg and the batch size is 50 kg. Both A and B are administrated orally and SF is set to 1000. Calculate the MACO for A in B.

$$MACO = \frac{10\ (mg) \times 50\,000\,000\ (mg)}{1000 \times 250\ (mg)} = 2\,000\ (mg)$$

Result: MACO is 2 g (2000 mg)

Example 5: Acceptance criteria based on Therapeutic Daily Dose

Now product B in example 1 will be cleaned out. The following product is product A in example 1. Calculate the MACO for B in A.

$$MACO = \frac{250\ (mg) \times 200\,000\,000\ (mg)}{1000 \times 10\ (mg)} = 5\,000\,000\ (mg)$$

Result: MACO is 5 kg (5 000 000 mg)

5.0 Levels of Cleaning

清洁级别：

5.1 Introduction 介绍

The manufacturing process of an Active Pharmaceutical Ingredient (API) typically consists of various chemical reaction and purification steps followed by physical changes. In general, early steps undergo further processing and purification and so potential carryover of the previous product would be removed

原料药的生产工艺一般由不同化学品经过反应和纯化步骤，在经过一些物料变化组成，一般来说，焦躁的步骤会经过进一步处理和钝化，因此上一产品潜在额残留会被清除掉。

The level of cleaning required in order to ensure that the API is free from unacceptable levels of contamination by previous substances varies depending on the step being cleaned and the next substance being manufactured in the same piece of equipment (train).

保证下一原料药比上一产品污染水平可接受，所需要进行的清洁成都取决于清洁所针对的工艺步骤，以及在同一设备中生产的下一产品。

API`s and related intermediates are often produced in multi-purpose equipment with frequent product changes which results in a high amount of cleaning. To minimize the cleaning effort the concept of using different levels of cleaning as a function of the level of risk related with the possible carryover may be applied without affecting the safety of the API.

原料药和相关的中间体一般会在多用于的设备中生产，频繁的更换产品会导致大量的清洁操作，为了将清洁工作量降至最小，在不影响原料药的安全性的前提下，可以考虑使用不同的

清洁级别来应对与可能的残留相关的不同风险水平。

5.2 Cleaning levels

清洁级别

It is recommended that at least three levels of cleaning in the production of a commercial product may be implemented. This approach is outlined in the table below, however it should be mentioned that additional levels might be necessary depending on the nature of the process and requirements of individual companies but should always be based on risk assessment where the characteristics of the previous and subsequent products such as solubility, recovery studies, nature of residues, process step, etc. should be considered.

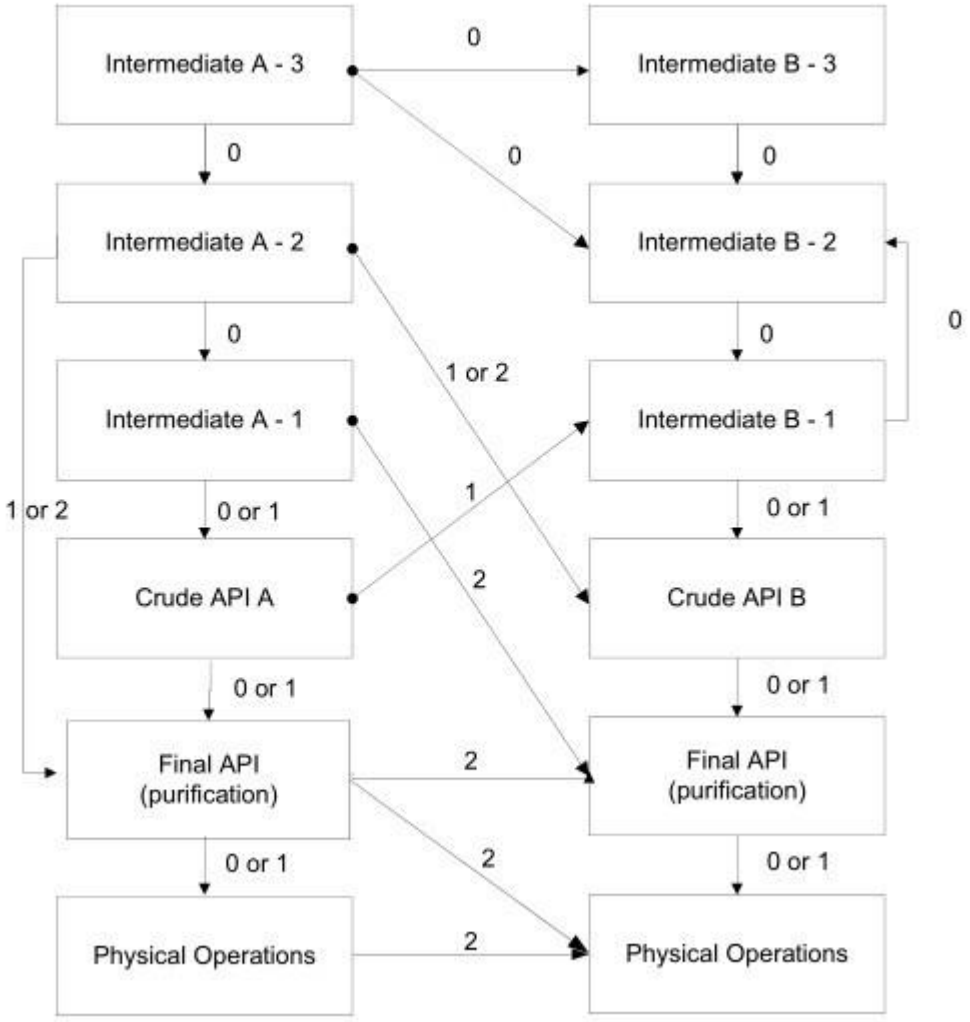
在商业化产品生产中，推荐使用至少 3 个清洁水平，以下表格中列出了该方法，但值得一提的是，根据各公司的工艺特性和要求，可能需要增加更多水平，不管怎么样，要使用基于质量风险评估的原则，考虑上一次产品和下一产品的特性，如溶解度、回收率、残留特性、工艺步骤等来作出决定。

Level	Thoroughness of cleaning	Cleaning verification		Cleaning Validation
		Visual Inspection	Analytical verification	
2	Carryover of the previous product is critical. Cleaning required until predetermined stringent carry over limits are met. High risk	Yes	Yes	Mandatory
1	Carryover of the previous product is less critical. Cleaning should reduce the potential carry over to a less stringent limit as required for level 2. Medium risk	Yes	Yes	Recommended
0	Only gross cleaning if carryover of the previous product is not critical. Low risk	Yes	NO	NO

A general approach how these levels could be established for typical product changeover situations in a multi-purpose API-plant is outlined in the figure below.

下图列出了在一个多用途原料药工厂针对典型的产品更换情况如何建立 3 个水平的通用方法。

Figure 1: Typical Product Changeover Scenarios



The levels established as shown in figure 1 are based on the approach that in general the thoroughness of cleaning will increase and the acceptable carryover of the previous product will decrease from early steps in the route of synthesis to the final API due to the fact that early steps undergo further processing and/or purification and so the potential carry over will be reduced by further processing. Physical operations, which mean e.g. powder handling such as drying, sieving or milling obviously do not reduce the potential carry over. During the risk assessment it should be taken in consideration that the residues may contribute to a degradation of the next product's quality or safety and ultimately have a detrimental effect on the final consumer.

建立图 1 中所示的清洁级别的依据是在一般情况下，随着合成步骤越来越接近原料药成品，清洁的彻底程度会增加，上一产品在下一产品中允许残留量会减少，由于较前面的步骤会经历一步工艺过程和精制，因此潜在的残留物会被后续的工艺过程降低。物料操作，例如粉料处理如干燥，过筛或粉碎，很显然不会降低潜在的残留量。在风险评估过程中，要考虑残留物可能会引起下一产品质量或安全性变化，最终对产品使用的消费者造成不良的影响。

Fig 1 shows examples of several possibilities of equipment usage patterns

图 1 显示了集中可能的设备使用模式。

1) The following product is the next step in the synthetic chain 下一产品是合成链中的下一步骤

A typical manufacturing process applied to production of Active Pharmaceutical Ingredients consists of various chemical reaction and purification steps followed by physical changes, as can be generally illustrated by the sequence of the production line of a product A or B. In this case level 0 may be applied because the previous product is the starting material of the following manufacturing step and the analytical methods applied for the following product are usually suitable to detect the previous product which is covered and limited by the impurity profile.

典型的原料药生产工艺由不同化学放映和精制步骤组成，之后再进行物理变更，因此一般可以由产品 A 或 B 的生产顺序来表示。这种情况下，可以作为 0 级，因为上衣产品是后续生产步骤的起始物料，后续产品所使用的分析方法一般适用于监测上一产品，上一产品实际上包括在杂质谱中，并设定了限度。

2) Between different steps of the same synthetic chain 同一合成链不同步骤之间

In general there is a higher potential for contamination of the API if the following product in a sequence is close to the final API - step. So progression of levels from early steps to later steps in the synthetic chain is expected as outlined in figure 1. In the example of product changeover "A – 2" to "Final API A" level 2 may be chosen if "A – 2" is not specified in the specification of "API A" or "A – 2" is a toxic compound. If it is specified or is purged during the process or harmless, level 1 may be acceptable.

一般来说，如果序列中的后续产品接近于原料药成品步骤，则对原料药产生的潜在污染水平会比较高，因此，从合成路线中较早步骤到较后步骤，其预期水平如图 1 所示，在例子中，生产完 A-2 后，在生产原料药成品 A，如果 A-2 在原料药成品中 A 质量标准中并未作为杂质列明，或者 A-2 为毒性物质，则可以选择水平为 2 级。如果 A-2 作为杂质列明，或在工艺中被清除，或该物质对人体无害，则选择水平为 1 级是可以被接受的。

3) Between batches of different product lines 不同产品线所生产批次之间

The level of cleaning required depends on the stage of manufacture. If the following product is an early stage in the API chain, in general lower levels are required than if it is an intermediate or final stage.

所要求的清洁水平取决于生产的步骤。如果后续产品在原料药工艺路线中为较早的步骤，一般来说相对于中间或最终步骤来说其要求水平更低。

The progression of levels is outlined in figure 1, however an individual risk assessment for each potential product changeover scenario has to be performed to decide which level is applicable. This risk assessment should address the following topics:

分级的层次在图 1 列出，但对每种可能的产品更换情况应进行单独的风险评估，以决定适用哪个水平。风险评估应说明以下情况：

Easiness of cleaning 清洁难易程度

Toxicological / pharmacological activity of the previous product, its side products or degradants 上一产品的毒性/药物活性，其副产物和降解产物

Maximum daily dose of the following product 下一产品的最大日剂量

Microbiological growth 微生物的滋长

Batch size of the following product 下一产品的批量

Solubility, experience, difficult to remove previous product 溶解度、经验、上一产品清除

难度

Chemical interactions 化学相互反应

Campaign lengths should be evaluated and determined as part of the risk assessment. 要评估和确定生产周期的长度，作为风险评估的一部分

Consideration should be given to any heels present and whether they need to be removed on a regular basis.

要考虑所有可能的情况，以及法规是否要求对其清除。

Instead of the investigation of each individual cleaning situation, similar situations could be grouped and classified using bracketing concepts (ref. section 7).

可以对相似的情形划分为同一组，采用分类法的概念进行分类，代替对各种清洁情形所进行的研究(ref. section 7).

5.3 Cleaning Verification/validation 清洁确认/验证

The cleanliness status and validation of cleaning procedures is verified against pre-defined acceptance criteria.

清洁状态和清洁程序的验证要更具预定的可接受标准进行验收

5.3.1 Cleaning verification 清洁确认

The cleaning verification can be made by: 清洁确认可以按以下方式进行：

visual inspection or 目视检查

visual inspection and analytical verification (e.g., swabbing and/or rinsing).

目视检查以及分析确认（例如，擦拭和/或淋洗）

Visual inspection:目视检查

After cleaning procedures performed equipment should be dried to allow the visual inspection. No residue should then be visible. Visual inspection should be performed using the best known capabilities.

对设备进行清洁后，应干燥以便目视检查，这时应目视无残留，应使用一直最好的能力进行目视的检查。

During visual inspection the following situations should be considered:

在目视检查中，需要考虑以下情况：

Discoloured surfaces, worn or torn parts;

部件表面的褪色，磨损或破损

Solid residues (for final product equipment used downstream of last filtration, the residues should be evaluated also by passing the final washing through a rough filter media (e.g. a lint-free cloth));

固体残留（对于最终过滤后所用的设备，残留要通过粗滤介质（如：无纺布）进行最终冲洗进行评价）

Visual inspection is usually applied in Level 0 where no cleaning validation is required.

目视检查一般适用于 0 级，这时不需要进行清洁验证。

Analytical verification 分析确认：

Analytical verification should be performed with scientifically sound methods.

要采用科学合理的方法进行检测验收。

The analytical methods should be validated before use in cleaning validation (see 5.3.2), unless they are compendial methods (see chapter 8.2).

除药典方法外（see chapter 8.2），分析方法在用于清洁验证前，需进行分析方法的验证（see 5.3.2）

5.3.2 Cleaning validation 清洁验证

The cleaning validation involves a series of stages over the lifecycle of the product and cleaning process: cleaning process design, cleaning process qualification and continued cleaning process verification. Details on the work to be performed and acceptance criteria should be defined in a protocol. The cleaning procedure can be prepared per equipment or set of equipment and should include detail enough to reduce operator's variability (see chapter 7.3).

清洁验证所涉及产品和清洁工艺的一系列阶段：清洁工艺设计、清洁工艺确认和持续清洁工艺确认。在方案中应确定要实施的工作细节和可接受标准。清洁程序可以针对各设备单独制订，也可以针对一套设备制订。清洁程序的内容应详细，以便减少操作人员的不确定性(see chapter7.3).

The strategy should be defined and taken in consideration in the validation activities.

要制订验证活动的策略，并在实施时加以考虑。

The validation consists in successive applications of the cleaning procedure complying with the acceptance criteria defined, in a minimum of 3 successful applications. The success of the applications should be consecutive unless the cause of failure is clearly identified as not related to the process or procedure.

验证包括连续至少 3 次成功实施清洁程序，并符合制订的可接受标准。除非清楚的识别出识别的原因与清洁程序不相关，否则验证实施批次必须是连续的。

Depending on the individual product changeover situation it may take some time to finalize the cleaning validation with the third application (see chapter 8 bracketing and worst case rating). In these cases cleaning verification using validated analytical methods has to be performed in the meantime.

根据各产品交替情况，可能需要一定时间来采用第三种工具发起决定是否需要采用此种工具来决定清洁验证，（参见第 8 章分类法和最差情形分级法）。在这些情况下，同事需要采用经过验证的分析方法进行清洁验证确认。

At this stage analytical methods should be validated and suitable to quantify at the acceptance criterion level. The limit of detection must be lower than or equal to the acceptance criterion level. Blanks must be evaluated to ensure that there is no significant interference with the recovery of the analyte. In dedicated facilities, validation of cleaning procedures is not normally required but a risk assessment should be performed to make sure that there is no potential for degradation and or microbial contamination that may adversely impact the quality of the product.

在此阶段，分析方法需要进行验证，且在可接受标准水平应该可以定量。检测限必须低于或等同于可接受标准水平。必须对空白进行评估，以保证对分析物的回收率没有严重的干扰。在专用设施中，清洁程序的验证一般是不需要的，但是应该进行风险评估，以保证没有会对产品的质量有负面影响的降解的可能性或微生物的污染。

For both dedicated and multi-product facilities, the frequency with which the cleaning procedure should be performed should be validated to assess risks related to potential degradation and microbiological contamination。

对于专用和多功能设施，均要验证其相关的清洁程序，评估与潜在降解和微生物污染有关的风险。

The validation of the Dirty Hold Time (DHT) should be an outcome of the cleaning validation. Whenever the DHT is exceeded, analytical verification should be performed and

the extension of the DHT should be handled through change control procedure.
清洁验证还需确认在较脏的情况下可以放置的时长（DHT）。一旦放置时间超过了 DHT，则需要进行分析却热。延长 DHT 应通过变更控制程序来处理。

5.3.2.1. Cleaning process design 清洁工艺设计

Cleaning process design intends to design, develop and understand the cleaning process residues and to establish the strategy for the cleaning process control.
清洁工艺设计的目的是设计、研发和了解清洁工艺的残留，建立清洁工艺的控制策略。
The main activities in this stage are evaluation of the chemical and physical properties of the residue; determination of the most difficult to clean residue; evaluation of residue solubility and stability.
在此阶段的主要活动是评估残留物中的化学和物料特性，评估最难清洁的残留物，评估出残留物的溶解度和稳定性。

5.3.2.2. Cleaning process qualification 清洁工艺确认

In this stage it should be demonstrated that the cleaning procedure works as expected. The following activities are included among others: qualification of specific equipment used in the cleaning such as Clean In Place (CIP) systems, cleaning operational parameters (e.g. temperature, flow rates, pressure, etc.); identification of the most difficult cleaning locations; training of operators.
在此阶段，要证明清洁工艺能起到预期的作用，下列活动包括在其他活动中：在清洁中使用的特定设备的确认，例如在线清洁系统（CIP）、清洁操作参数（例如温度、流苏、压力等）、最难清洁点的识别以及对操作人员的培训。

5.3.2.3 Continued cleaning process verification 持续清洁工艺确认

In this stage it should be demonstrated that the cleaning process remains in control throughout the product lifecycle.
在本阶段，要证明清洁工艺在整个产品生命周期受控。
The following should be considered in this stage: Post validation monitoring; Change control; Periodic management review.
在此阶段要考虑一下内容：验证后监控、变更控制、定期管理评估。

Post validation monitoring 验证后监控

After cleaning validation, the analytical verification may be omitted or replaced by simpler analytical methods (e.g. conductivity; pH; etc.) that have proven to be suitable for the intended use. However, visual inspection should be maintained in the dried equipment and no visible residues should be observed.
在清洁验证后，可以不需要进行分析确认，但可以采用较简单的分析方法替代验证所用的方法（例如：电导率、PH 值等），制药是被证明适用于既定用于即可。但是，对干燥后的设备仍要保留目视检查，且不应有目视可见残留。
The confirmation of the validation status should be performed periodically according to the periodicity defined in the validation report.
验证状态可以根据要争报告中界定的周期进行确认。

Change control 变更控制

Any change to the cleaning procedure, analytical methods, manufacturing process, equipment, etc. during the execution of the cleaning validation protocol or after the validation is concluded should be handling through the change control procedure in place in the organization. The impact on the cleaning validation process should be evaluated.

在清洁验证方案实施期间或在验证完成后，对清洁程序、分析方法、生产工艺、设备等进行变更应根据内部的变更控制程序进行处理。要评估变更对清洁验证工艺产生的影响。

Periodic management review 周期性管理评审

Deviations, non-conformances, changes in the cleaning procedure and/or product manufacturing process, trends should be periodically reviewed with the aim to continuously improve the cleaning process, reduce variability and to assess the validation status of the procedure.

应对偏差、不符合情况、清洁程序变更和/或产品生产工艺趋势进行周期评审，目的是持续提高清洁工艺，减少波动，评估清洁程序的验证状态。

6. CONTROL OF CLEANING PROCESS 清洁工艺的控制

In order to validate a cleaning process, the cleaning process needs to be repeatable and sufficiently robust for the to-be-cleaned load. It should be clear which steps are considered part of the production process/ unit operation and which are part of the cleaning process, for example if the pre-rinse or wash-out which may be routinely applied to bring the equipment in a good starting position is part of the overall cleaning process or not. Another example is the cleaning of chromatography columns, which are typically cleaned with buffers prior to the chromatography skid cleaning.

为了对清洁工艺进行验证，清洁程序应是可重复的，正对将要清洁的负载，具有足够的清洁能力，要清楚说明，那个操作是生产工艺/单元操作的一部分，那个是清洁工艺的一部分。例如，对设备进行前期冲洗或者淋洗，以使其成为一个洗前的起始状态，是否是整个清洁工艺的一个部分。

To assure repeatability and robustness of the cleaning, adequate cleaning instructions are required.

为保证清洁的可重复性和耐用性，要制订充分的清洁指令。

For manual cleaning, this is typically accomplished by sufficiently detailed cleaning instructions, including an unambiguous description of the attributes to be used and how to handle these, together with adequate training.

对于手动清洁，一般是根据详细的清洁指令来完成，其中包括对清洁方法的清楚描述，如何操作，并需要进行详细的培训。

The detailed description should consider:

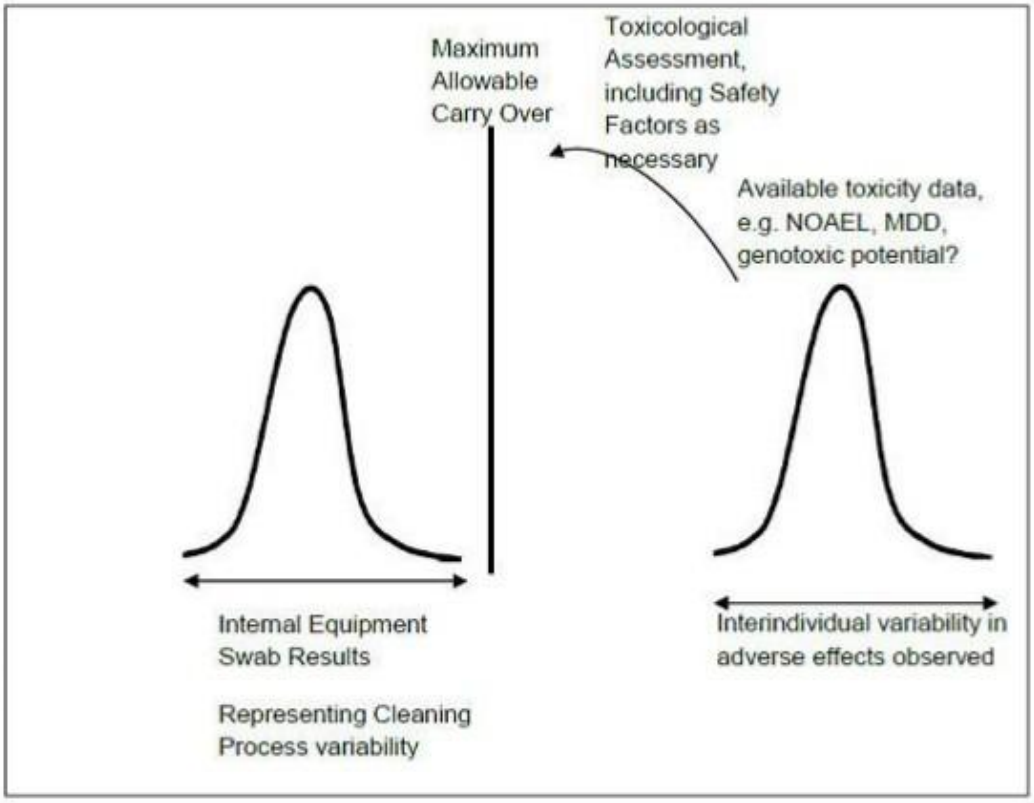
1. the system boundaries
2. cleaning agents/solvents to be used
3. volumes and or concentrations
4. reflux or rinse times, and temperatures
5. the sequence of cleaning steps or pre-defined repeats
6. in process analyses
7. description of pumps used (if needed)
8. sample instructions (if needed)

详细描述需考虑：

1、 系统的界限
2、 使用的清洁剂/情急溶剂
3、 体积和/或浓度
4、 冲洗或淋洗时间、温度

5、 清洁步骤或预定重复顺序
6、 过程中的检测
7、 所用泵的描述（如有需要）
8、 取样指令（如有需要）

For automated cleanings this should be ensured by the equipment design together with the cleaning software, cleaning recipe and built-in control mechanisms.
要保证自动化清洁设备设计中包括了清洁软件、清洁配方、内置控制结构。
For automated systems, it is expected that a cleaning instruction covers:
对于自动化设备，要求清洁指令涵盖以下内容：
1) The applied cleaning phases, for example once-through versus re-circulating versus soak versus reflux-mode rinse/wash phases
所使用的清洁工序，例如——清洗、再循环、浸泡、回流方式淋洗/冲洗工序
2) The sequences of the cleaning phases
清洁工序的顺序
3) Time of each of the cleaning phases
各清洁工序的时间
4) Action applied during the cleaning process. Note that the mechanical action/impact is often flow/pressure related (e.g. if spray balls are being used).
在清洁过程中所执行的操作，注意机械性操作/冲击通常会与流动/压力相关（例如：如采用喷淋球）
5) Used cleaning agents and/or cleaning solvents
所用的清洁剂和/或清洁溶剂
6) The concentrations and/or quality of the used cleaning agents and/or cleaning solvents
所用的清洁剂和/或清洁溶剂的浓度和/或质量
7) Temperatures applied during the various cleaning phases
不同清洁工序的温度
Because of the uncertainties on cleaning parameters, like a.o. flow, time, temperature, detergent concentration and starting conditions (inclusive Dirty Hold Time and soiling), and the geometric aspects of the cleaned system, the cleaning process is susceptible to variability/ spread. The mean effectiveness of the cleaning process together with its spread should be adequately removed from the edge of failure of the cleaning process, which can be established by performing the MACO calculations as discussed in the previous chapters. At minimum, the level of cleaning should support a cleaning result (including the spread) below the obtained MACO level. Schematically, this can be depicted as:
由于清洁参数的不确定性，例如流动情况、时长、温度、清洁剂浓度和起始条件（包括清洁前放置时长 DHT 和污染程度），以及被清洁系统的几何结构，清洁工艺具有很大的不确定度。这些清洁过程的不确定因素加上平均效果应该从清洁工艺的失效边缘中扣除，失效边缘是用过前章节中 MACO 的计算来确定的。至少，清洁级别应该可以获得在 MACO 水平以下的清洁结果（包括其延展区）。下图对此做出了示意：



The level of cleaning should be commensurate to the level of risk that the cleaning process poses in relation to the related production processes. Notice that the cleaning risk can be further reduced either by:

清洁水平应与相关生产工艺所具的清洁工艺风险水平相互适应。应注意可以通过以下方式进一步降低清洁风险。

1) improving the cleaning cycle to improve cleaning effectiveness and shift the mean cleaning result further away from the MACO level, which typically requires cleaning development studies;

改善清洁轮次，以提高清洁效果和转换平均清洁结果，使其远低于 MACO 水平，这一般需要进行清洁研究。

2) reducing process variability, which is typically established by increasing the level of control on the cleaning process parameters. An improved level of control on cleaning parameters such as flow, temperature and time, may not only result in more robust cleaning processes with smaller process variability, but may also create cleaning optimization opportunities (e.g. reduced chemical and water consumption).

减低工艺变数，这一般通过增加对清洁工艺参数的控制来实现。对于清洁参数，例如流动情况，温度和时长的控制水平的提升，不仅可以通过减少工艺波动来增加清洁工艺的耐受性，而且可以创造优化清洁的机会（例如：降低化学物和说的消耗）。

For automated systems, the level of control can often be enhanced by applying in-line measurements together with enhanced controlling capabilities. Improved monitoring capabilities often results into enhanced cleaning process knowledge and may be used in a

Process Analytical Technology (PAT) framework.
对于自动化系统，通过实施在线测量和加强控制能力，可以增强控制水平。提升监控能力通过可以增减对清洁工艺的了解，可以用于工艺分析技术（PAT）框架。

7.0 Bracketing and Worst Case Rating　分组法（括号法）和最差情况分级

7.1 Introduction

The cleaning processes of multiple product use equipment in API facilities are subject to requirements for cleaning validation. The validation effort could be huge. In order to minimize the amount of validation required, a worst case approach for the validation can be used.

By means of a bracketing procedure the substances are grouped.
采用分组法时，物质按照类别进行分组。

A worst case rating procedure is used to select the worst case in each group.
然后在每组中采用最差情形分级法选择各组中最差的情况。

Validation of the worst case situation takes place. However, it is of utmost importance that a documented scientific rational for the chosen worst cases exists.
对最差的情形进行验证，只管重要的是，选择最差情形的科学合理性要进行记录。

This chapter gives an overview of the suggested work to be carried out, the acceptance criteria and the methodology for evaluation of the data. It should be emphasized that this is only an example to give guidance. The equipment, the substances produced and the procedures in place may vary; and this results in other solutions than those given in this example.
本章介绍了所需要进行的工作，可接受标准和数据评估方法。需要强调的是，这只是一个指导性的例子，而实际情况下，设备、生产的物质和清洁程序可能有所不同，在可能需要采用与例子中不同的解决的方案。

The worst case rating priority will then support a conclusion that the cleaning procedures are effective for all drug substances and other chemicals within the bracket, including those not individually tested.

7.2 Bracketing Procedure　分组法

The objective of a bracketing project, is for the company to demonstrate that it has a scientific rationale for its worst case rating of the substances in the cleaning validation program. The first thing to do is to make groups and sub groups - which we will term “bracketing”, from which worst cases will later be selected based on the results from the rating. The bracketing procedure should be included in a company policy, or an SOP or an equivalent document on cleaning validation. A multipurpose facility, Clean Company, is presented as an example we will follow.
分组法的目的就是让公司可以证明清洁验证方案，对原料药进行最差情形分级具有科学合理性，首先要做的是进行分组和分小组~~~~我们成为“分组法（括号法）”，在一个组中，在根据分级结果选择一个最差情形。分组流程应包括在公司方针中或在 SOP 或相当清洁 SOP 的文件中。一下的例子中我们假定一个多功能工厂、一个清洁公司。

a)　Equipment Train

The Clean Company is a multipurpose site for synthesis and isolation of organic substances (see figure 1). It is divided into six equipment trains separated from each other and intended for different use (earlier API steps, final API purification, drying etc.). In TrainA 9 substances can be produced, in TrainB 9 substances can be produced, in TrainC 8 substances

can be produced, in TrainD 8 substances can be produced, in TrainE 10 substances can be produced, and in TrainF 11 substances can be produced. With no bracketing and worst case rating, cleaning validation studies would be required for each of the 55 substances.

设备链：清洁公司是一个多功能场所，生产有机物质合成和分离步骤（参见图 1）。其设备被分为 6 条生产设备链，相互独立，用于不同的用途（较早的原料药步骤、最终原料药精制、干燥等）。在 A 链中，可以生产 9 种物质，在 B 链中，可以生产 9 种物质，在 C 链中，可以生产 8 种物质，在 D 链中，可以生产 8 种物质，在 E 链中，可以生产 10 种物质，在 F 链中，可以生产 11 种物质，如果不采用分组法和最差情形发的话，则需要对 55 中物质分别进行清洁验证。

The first grouping criteria is that the substances in a group are produced in identical equipment trains and cleaned out following the same cleaning procedure/SOP. The ideal with regard to cleaning validation (as will be discussed in 7.3) each train could be considered as a group. Then 6 worst cases would ideally be identified. In reality, the number of worst cases identified will often be something between these two extremes (more than 6, but less than 55).

进行分组的第一个标准时组内的物质是在同一条设备链中生产，并采用同一个清洁程序/SOP 进行清洁，理想状态时每条链可以作为一个组来进行清洁验证（如 7.3 中的讨论一样）。这样，理想状态下需要识别出 6 中最差情形。现实中，最差情形的识别可能会是两个极端情况（多于 6 个，但是少于 55 个）

CleanCompany　清洁公司

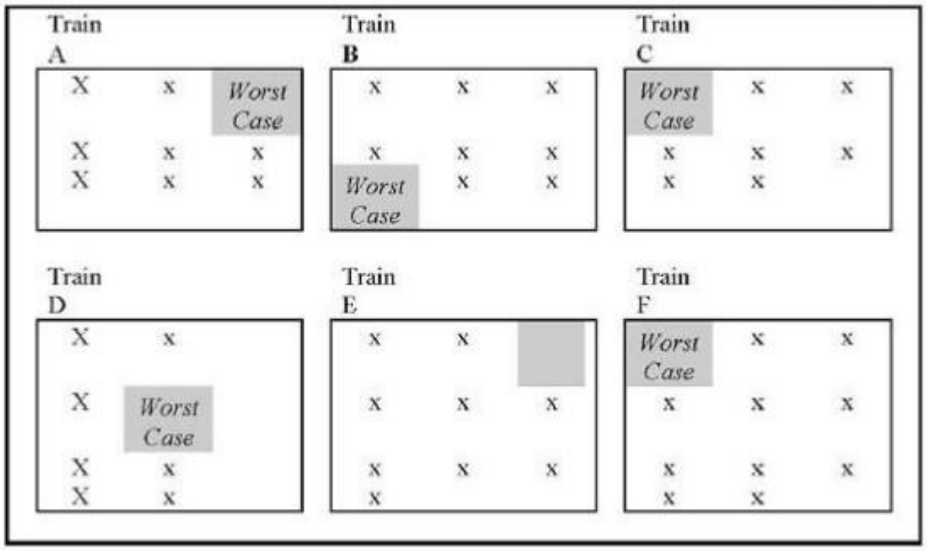


Figure 1 CleanCompany's ideal example (1 train considered as 1 group) gives 6 worst cases .

In this example the main classes in this bracketing are based on the different Trains. The following equipment classes are maintained:

图 1：清洁公司的理想案例（设备链 1 被作为第一组）给出了 6 个最差情形。在此案例中，组内主要级别是基于不同生产链的，以下设备分级不变：

- TrainA
- TrainB

- TrainC
- TrainD
- TrainE
- TrainF

b) Substances 物质

If the company has two or more trains used for the same purpose (such as earlier API steps, final API purification, drying etc.) a choice of which products to be produced in each of the trains used for the same purpose is done. The combination of substances (starting materials, intermediates or APIs) in a train can be chosen based on one or more of the following strategies, or combinations of them:

如果公司有 2 个或更多设备链用于同一个生产目的（例如,更早的原料药生产步骤，最终原料药精制、干燥等），已选好了在每个设备链中生产那个产品。在一个设备链生产那些物质（起始物料、中间体或原料药）可以采用以下策略或联合策略来作出选择：

Produce in the same train substances with the same cleaning procedure;

同一设备里生产可以采用相同的清洁程序的物质

Produce in the same train substances with very low therapeutic doses and/or low batch sizes (and the opposite);

在同一设备中生产治疗剂量很低和/或批量很小（以及相反情况）的物质

Produce in the same train substances with very low ADE values (and the opposite).

在同一设备中生产 ADE 值非常低（以及相反情况）的物质

Also a choice of maximum flexibility can be used, but this could result in low limits for residues (for example if the substance to be cleaned out has a very low therapeutic dose, and the following substance has a small batch size and/or a very high daily dose) and thus longer cleaning times. Advantages and disadvantages with several cleaning procedures, compared to one cleaning procedure, will be discussed in section 7.3. More explanations on effects of different strategies will be evident from section 7.4.

也可以选用具有最大灵活性的方式，但是这样可能会使得残留限度非常低，导致清洁时间会很长，在 7.3 中讨论了选用几个不同的清洁程序相比于选用用一个清洁程序的优缺点，在 7.4 中对不同策略的效果给出了进一步解释。

7.3 Cleaning Procedures

清洁程序

For one train, in which several substances are being produced, several cleaning procedures often exist. In order to be able to defend the bracketing into groups, the second criterion is that the same cleaning procedure (method) shall be used for the substances within a group. Cleaning procedures (before change of products) can for example be considered to be the same if:

1. Same or equivalent issued cleaning batch records/cleaning SOPs;相同或等同情书的清洁批记录、清洁 SOP
2. Same solvent, solubility or similar properties.相同溶剂、溶解度或相似特性

Advantages and disadvantages with several cleaning procedures, compared to one cleaning procedure, are presented in the following table.

下表列除了几个清洁程序与采用同一个清洁程序的优缺点。

The same cleaning procedure for all substances (chosen to clean out the most difficult substance)所有物质（选取最难清洁的物质做验证）采用统一清洁程序

Optimised cleaning procedures for each substance 优化每个物质的清洁程序

+	Minimum number of cleaning validation studies (perhaps only one)	-	Not optimal cleaning procedures for each substance → longer clean out times on average as well as higher consumption of solvents.
		-	Normally a low limit for residues valid for all substances

Optimised cleaning procedures for each substance

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+	Minimum clean out time on average	-	Maximum number of cleaning validation studies (as many as there are cleaning procedures)

减少清洁验证的次数（可能只需进行一次）　　对所有物质都不是最优的清洁方法-平均清洁次数会较多，同时溶剂消耗量大，一般对所有的物质采用同一较低的残留限

In the example the Clean Company has evaluated the cleaning procedures. The cleaning procedures have been examined and categorised into different classes. Substances in the same class are cleaned in the same way, using the same solvents and usually exhibit some chemical similarity with each other (e. g. salts, chemical structure etc.). In this example, totally, four cleaning procedure classes are included:

在案例中，清洁公司评估了清洁程序，通过检查将其分为不同类别，同一类别中的物质采用相同方法清洁，采用相同的溶剂，通常其所含的化学物质相互类似（例如：盐、化学结构等）。在本例中，共包括了四类清洁程序：

- Class I　water soluble substances.一类：水溶性物质
- Class II　methanol soluble substances.　甲醇可溶性物质
- Class III acetone soluble substances.　　丙酮可溶性物质
- Class IV separate class for special substances with defined solubility　更具溶解度制订的特殊物质特定级别

7.4 Investigations and Worst Case Rating (WCR)/Risk assessment 调查和最差情况风险评估

A worst case rating study/Risk assessment, will prioritise existing drug substances, in a cleaning validation program, based on information on applicable criteria chosen by the company. Clean company chose the following criteria which are relevant to the molecule

preparation in their facility (companies should evaluate individual situations):
a) Hardest to clean: experience from production;最难清洁：生产所得的经验
b) Solubility in used solvent;在所用溶剂中的溶解度
c) Lowest Acceptable Daily Exposure(If ADE data are not available, other pharmacological (dose) , OEL or toxicity data (LD 50) may be used (see chapter 4); 可接受最低日暴露（如果不能获得 ADE 数据，可以使用（参见第四章）其他药学（剂量）数据、OEL 或毒性数据（LD50））
d) Lowest therapeutic dose (or toxicity data LD 50); 最低质量剂量（或毒性数据 LD50）
In order to present documented evidence supporting the scientific rating for each criterion, investigations (a formalized Risk assessment) should be carried out and formal reports should be written. For each criterion groups of rating with corresponding descriptive terms should be presented. When available, the descriptive terms can be chosen from the scientific literature on the subject (i. e. for solubility and toxicity). For other cases the rating is based on scientific investigations carried out by the company and collecting experience regarding details on the cleaning processes (i.e. "experience from production").
为了形成书面证据来支持各标准分级的科学性，应进行验证（正式的风险评估）并形成书面的正式报告。每个标准中，要列出分级组所对应的描述性术语。如果可能应从文献中选取相应的术语描述（例如溶解性和毒性）。其他情况下，分类也可以根据公司的科学研究和在清洁工艺方面积累的经验（即“生产经验”）
Clean Company chose to execute the WCR according to a formal protocol, in which the rating system was identified and the rating documented. In a Risk assessment report the results including the WCR were summarised, as well as conclusions.
a) Hardest to Clean out - Experience from Production 难以清洁—生产中得出的经验
One criterion which can be used is, experience from production with regard to how difficult a substance is to clean out. The study is recommended to be in the form of interviews with operators and supervisors. A standardised sheet with questions could be used in which the answers are noted. Hard-to-clean substances are identified and the difficulty of cleaning
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could be rated according to the three categories suggested below. The opinions of the personnel are subjective, and therefore should be supported by a scientific rationale.
Category: 1 = Easy
2 = Medium
3 = Difficult
b) Solubility
A solubility-rating should be carried out based on the solubilities of the substances in the solvents used for cleaning. Suggested rating numbers, with explanations, are presented in the table below. The descriptive terms are given in [1] - page 53 - USP 24 under —Reference Tables (Description and Solubility, 2254)“.
c) ADE concept
The Acceptable Daily Exposure defines a limit at which a patient may be exposed every day for a lifetime with acceptable risks related to adverse health effects (see chapter 4).
An example of rating numbers, with explanations, is presented in the table below.
Group ADE
1 >500 µg

2 100 - 500 µg
3 10 – 99 µg
4 1 – 9 µg
5 <1 µg
If ADE data are not available, other pharmacological (dose), OEL or toxicity data (LD 50) may be used (see chapter 4).

Group	Included descriptive terms	Approximate quantities of solvent by volume for 1 part of solute by weight
1	Very soluble	less than 1 part
	Freely soluble	from 1 to 10 parts
2	Soluble	from 10 to 30 parts
	Sparingly soluble	from 30 to 100 parts
3	Slightly soluble	from 100 to 1 000 parts
	Very slightly soluble	from 1 000 to 10 000 parts
	Practically insoluble	more than 10 000 parts
	Insoluble	-

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d) Therapeutic Doses

An investigation of therapeutic doses is typically base on oral and/or parenteral data. In the cases where the therapeutic doses are not available, corresponding values based on the toxicity could be used (recalculated according to company procedure). An example or rating numbers, with explanations, are presented in the table below.

Group	Include dose intervals (smallest therapeutic dose)
1	>1 000 mg
2	100 - 1 000 mg
3	10 – 99 mg
4	1 – 9 mg
5	<1 mg

7.5. Worst Case Rating

The substances are scientifically matrixed by equipment class (train/equipment) and cleaning class (procedure). Each existing combination of the classes is considered as a group. When this bracketing has been carried out, the - “Worst Case Rating (WCR)”- can start. For at least one worst case in each group, cleaning validation studies shall be carried out. The rating

procedure for CleanCompany presented as an example could be used.

a) Rating Procedure

During a worst case rating, the results of the investigations are summarised for each substance in each equipment class. If the evaluation of the cleaning procedures indicates that some of the substances have unique cleaning procedures, then each of those substances will be considered as a group (with one group member which is the worst case).

If all the substances in a cleaning class (train/equipment) will be tested, then individual limits may be used for each substance. In case of groups, where only some "worst cases" are tested, the strategy described below shall be followed. The following methodology shall normally be applied when a priority based on a worst case shall be used.

Choice of common, general residual limit

Evaluate if the lowest calculated limit is reasonable to apply on all substances. If that is the case, this limit shall be valid as a common general limit for the specific equipment. If the lowest limit is found to be too low as common limit for all substances, then the second lowest limit is evaluated and so on.

Criteria for the validation of the cleaning processes:

1. For the substances with common, general limit, it is required that the substance with the lowest solubility (in the cleaning solvent/solution) shall be tested for each cleaning method. If more than one substance fulfils this criterion, then the substance shall be chosen which, based on experience is most difficult to clean.

2. Any substance which does not fall within this 'bracket' must be validated individually.

b) Evaluation of Rating

The worst case rating can be executed according to an issued protocol in which the methods and procedures for the rating will be identified. The applicable investigations presented in section 7.4 a-d would then be used (and could be enclosed to the protocol or a report, to support the rationales for the rating). A matrix system, for each equipment class (such as a dryer), can be set up as evident from the following table where TrainA of CleanCompany has been chosen. In this case a formal rating matrix has been filled in for TrainA. Altogether two cleaning classes were identified for the substances produced in TrainA. All the categories are introduced as columns in a matrix.

Substance
Cleaning
Method
Class
a):
Hardest to
clean*
b):
Solubility
c):
ADE
d):

Ther.
dose
Esubstance III 2.3 1 4 3
Fsubstance III 2.2 1 2 4
Csubstance III 2.1 1 3 2
Lsubstance III 1.9 1 3 3
Osubstance III 2.8 2 2 3
Msubstance III 2.5 2 2 3
Psubstance I 2.2 1 2 3
Rsubstance I 2.6 2 3 3
Tsubstance I 1.8 1 2 3
* Each figure is the mean value for different questions answered by operators and supervisors.
For the products in this train two cleaning methods (Class I and III) are used.
Therefore two groups have to be validated.
The worst case product (for the validation study) for class III is Osubstance (Solubility 2 and Hardest to clean* 2.8).
The worst case product (for the validation study) for class I is Rsubstance (Solubility 2 and Hardest to clean* 2.6).
In both cases the limit should be calculated with the most active substance (ADE 4).
If ADE data are not available, the limit should be calculated with the most active substance (Therapeutic dose 4).
If the limit calculated with ADE 4 or Therapeutic dose 4 is achievable for all products, this limit can be chosen for both groups.
If the limit calculated with ADE 4 or Therapeutic dose 4 is too low and not achievable for all products, Esubstance and Fsubstance should be considered as separate groups or produced in dedicated equipment.
The limit for the remaining group should be calculated with the most active substance (ADE 3 or Therapeutic dose 3).
In case a substance of top priority is not produced regularly, the substance with the second

highest priority will be tested in order to show that the cleaning procedure is sufficient for all the other substances in that class. The substance of top priority will then be tested at the first possible occasion.
The WCR/Risk assessment could typically result in a report including a priority, based on the rating, for the substances in the cleaning validation program. It is recommended that the applicable background investigations shall be completed, approved and enclosed to the cleaning protocol or the report.

c) Re-rating

Change control should be applied to the WCR. If the conditions for the rating are changed, then a re-rating procedure should be carried out. The following listing gives examples where a formal re-rating procedure may be required:

- Changed cleaning method
- Changed process

- Changed / additional new product
- Changed / new equipment

After re-rating, it is recommended to issue an official controlled document including a worst case listing or table, with the same type of result presented for the involved substances/ equipment/methods, as for the original rating.

8.0 Determination of the Amount of Residue 残留限的检测

8.1 Introduction 介绍

This section provides a practical guidance for the determination of the amount of residue in cleaned equipment based on the requirements from regulatory authorities 3 and current guidelines on analytical validation. 4 Specific requirements for the validation of analytical and sampling methods for cleaning validation purposes are provided in this section, in addition to examples of sampling methods and the appropriate use of analytical methods.

本部分是根据药监局的要求和现行分析方法验证指南，头功了监测已清洁设备中残留物数量的实用指南。在本本份中给出了清洁验证所用的分析方法和取样方法的验证要求，以及取样方法和适当使用分析方法的例子。

The carryover acceptance limit (Mper) is a calculated figure that represents the specification limit for the equipment cleanliness (see Section 4.0, Acceptance Limits), however, the determination of the actual amount of residue (M) remaining in the equipment following cleaning must be achieved using appropriate methods i.e. for both the sampling method and the quantitation of the contaminant in the sample.

允许残留限度（Mper）是一个计算出的数值，代表设备清洁程度的质量标准限度（参见 4.0 部分，可接受限度），但是，对于清洁后设备残留物(M)实际数量的监测必须使用使用的方法来获得，即。针对取样方法和样品中污染物的定量。

Since the decision on the acceptable cleanliness of the equipment bears a potential risk to product quality, the method(s) used for the determination of M must be validated 1 and the specificity, sensitivity and recovery of the method(s) should be determined as a minimum.

由于对设备可接受标准清洁度的决定会对产品质量有潜在的风险，因此用于 M 检测的方法必须要进行验证，至少验证方法的专属性、灵敏度和回收率。

8.2 Validation Requirements

8.2.1 General

The requirements for analytical method validation are defined in ICH Q2(R1), Validation of

3 FDA Guide to Inspections Validation of Cleaning Processes, http://www.fda.gov/ICECI/Inspections/InspectionGuides/ucm074922.htm

4 ICH Q2 (R1), Validation of Analytical Procedures: Text and Methodology, November 2005

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Analytical Procedures: Text and Methodology, November 2005. There are four types of analytical methods with principally different validation requirements; these are identification tests, tests for impurities (both quantitative and limit tests) and assay tests. The validation requirements for each method type are shown Table 1.

The list should be considered typical for the aforementioned analytical procedures, however , exceptions should be dealt with on a case-by-case basis. It should be noted that robustness is not listed in the table and should be considered at an appropriate stage in the development of the analytical procedure.

In practice, it is usually possible to design the experimental work such that the appropriate

validation characteristics can be considered simultaneously to provide a sound, overall knowledge of the capabilities of the analytical procedure, for instance; specificity, linearity, range, accuracy and precision.

The validation of an analytical method should occur in compliance with pre-established acceptance criteria that should be documented in a written general policy or Validation Plan. However, there should be one validation report per validated method that summarises the specific results.

Characteristic
Type of Analytical Procedure
Identification
Testing for Impurities
Assay
Quantitative Limit
Accuracy – + – +
Precision
Repeatability + – +
Intermediate Precision – + 1 – + 1
Specificity 2 + + + +
Detection Limit – – 3 + –
Quantitation Limit – + – –
Linearity – + – +
Range – + – +

Key

– Signifies that this characteristic is not normally evaluated.
+ Signifies that this characteristic is normally evaluated.
1 In cases where reproducibility has been performed, intermediate precision is not needed.
2 Lack of specificity of one analytical procedure could be compensated by other supporting analytical procedure(s).
3 May be needed in some cases.

T ABLE 1 Requirement List for Analytical Validation

The requirements for 'Testing for Impurities' are typically employed for the validation of analytical methods specific to cleaning validation.

The requirements for 'Quantitative Testing for Impurities' can apply, for example, in cases where a method should be suitable for several possible acceptance limits and therefore quantitation of the residue over a certain range may be necessary e.g. the measured amount of residue M must be compared with acceptance limits between 5 and 750 g/equipment. This is possible when the method will be used for several changeovers.

The requirements for 'Limit Testing for Impurities' can apply, for example, in cases where the method should be suitable for one specific acceptance limit e.g. the measured M must be compared with Mper ≤ 105 g/equipment.

8.2.2 Analytical Method Validation for Cleaning Validation

In the following sections, aspects of analytical method validation specific to cleaning

validation are emphasised. For further details refer to ICH Q2 (R1).

Specificity is a basic requirement for all analytical methods (see Table 1), however, in the case of cleaning validation it may occur, that not all potential impurities are clearly specified. It is important to note that in such a situation a specific method may not always detect all impurities. Studies should be performed to characterise the unknown impurities, develop and validate suitable analytical methods. However, this can be an unacceptably time consuming task. In this case a method that detects all potential impurities together can be suitable, even when it is not specific for each of the impurities. For example, in a situation where only non-volatile impurities occur, a dry residue determination method that is specific for the sum of non-volatile impurities could be used, provided that the validation requirements according to Table 1 are satisfied. In order to consider the equipment acceptable for use it must be assumed that the dry residue consists of the worst case impurity (most toxic, most active etc.). In some cases a combination of several methods can achieve the necessary specificity.

After the completion of a cleaning validation study an unspecific method (e.g. dry residue) may be used for the routine verification of equipment cleaned by the validated cleaning procedure provided that it is shown that the unspecific method is suitable for the intended purpose. If possible, the sensitivity of impurity detection for cleaning validation should be determined for both the sampling and analytical methods together (see Section 7.2.4).

8.2.3 Detection and Quantitation Limits

Measured values below limit of quantification (LOQ) should be reported as the LOQ value (worst case approach). For example if the LOQ is 10 mg/l, the measured blank is 7 mg/l and the measured residue amount is 3 mg/l, the reported value for the sample should be equal to the LOQ i.e. 10 mg/l.

Usually it can be assumed that, for quantitative impurity determination, the LOQ should approximately be 0.5 of the specification i.e. for cleaning validation 0.5 of the acceptance limit or lower. LOQ should never be higher than the acceptance limit. In the following sections three methods of LOQ/LOD determination are outlined:

- Based on Visual Evaluation

Visual evaluation may be used for non-instrumental methods but may also be used with instrumental methods. Frequently this approach is used for TLC.

- Based on Signal-to-Noise Approach

This approach can only be applied to analytical procedures which exhibit baseline noise (e.g. GC, HPLC). A signal-to-noise ratio (S/N) between 3 or 2:1 is generally considered acceptable for estimating the detection limit (LOD) and a typical ratio for acceptable quantitation limit is 10:1 (LOQ). The value for S/N can be calculated according to Equation 1 and Figure 1:

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Equation 1:

where: H is the height of the peak from the mean baseline.

h n is the maximum deviation of the baseline within the range of

5 to 20 fold width of peak at half height.

F IGURE 1 Detection Limit Base on Signal to Noise Approach

- Based on the Standard Deviation of the Response and the Slope

The detection limit may be expressed by Equation 2 and the quantitation limit by Equation 3.

Equation 2: LOD =

Equation 3: LOQ =

8.2.4 Determination of Recovery

If possible, the recovery of impurity detection for cleaning validation should be determined for the sampling and analytical methods together at least for recovery and sensitivity (Limit of Quantitation - LOQ, or Limit of Detection - LOD). This can be achieved, for example, by spiking a surface equivalent to the equipment surface (e.g. material, polish grade) with different known amounts of the impurity. The impurity can then be recovered and analysed using the same sampling and analytical methods that will be used for the cleaning validation study. The overall results from this procedure are then compared to criteria for detection or quantitation limits as defined in ICH Q2 (R1). Validation of the limits may be achieved by the analysis of samples known to be near at the limits.

The measured results are then compared to the actual amount applied to the surface. The recovery is typically determined during the accuracy determination and should be reported as a percentage of the known applied amount of the impurity.

As an example, quantitative impurity determination recoveries of ≥ 90 % are usually regarded acceptable. For cleaning validation, recoveries of ≥ 90 % do not need to be taken into account for the calculation of the true value for M. Recoveries of < 90 % must be included in the calculation for M (see Equation 4) and recoveries of < 50 % should be omitted.

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Equation 4: M =

Where: M: True value for the amount of residue remaining in the equipment after cleaning;

M res: The measured amount of residue (sampling and then analytical measurement);

R Recovery in % divided by 100 (e.g. for 75%, 75/100 = 0.75).

8.2.5 Validation Requirements for Quantitative Testing of Impurities

The requirements for the validation of quantitative testing of impurities according to ICH Q2 (R1) are shown in Table 2, including proposed acceptance criteria (as an example only). Alternative acceptance criteria may be established based on sound scientific rationale.

It is important to note, that the summarised requirements should be used for the validation of quantitative testing for impurities during cleaning validation studies. Validation of quantitative testing for impurities is usually applied when the analytical method will be used for several specifications of the residue amount in the equipment.

The lowest foreseen acceptance limit is referred to as M perMin and the highest limit as M perMax

in Table 2. For only one specific acceptance limit normally limit testing for impurities and the corresponding validation of the analytical method is sufficient. If the validation of quantitative testing for impurities will be used for one specific acceptance limit, then M perMin = M perMax = M per .

For the experimental work described in Table 2, the samples can be spiked with appropriate levels of the impurities (when standards are available) or compared with another well-characterised procedure (when standards are not available) to obtain the true value of the analyte concentration.

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Experiments Possible Acceptance Criteria

Accuracy:

Perform a minimum of 9 determinations over a minimum of 3 concentration levels covering the specific range (e.g. 3 concentrations/3 replicates each of the total analytical procedure). Determine analyte with respect to the total amount of residue in the sample (e.g. weight/weight). Report:

Accuracy as percent recovery or 90.00 – 110.00 %

Difference between the mean and the accepted true value. ≤ 10.00 % (P = 95 %)

Confidence intervals.

Precision:

Investigate using homogenous, authentic samples or (if not possible) artificially prepared samples. Perform a minimum of 9 determinations covering the specified range for the procedure (e.g. 3 concentrations/3 replicates each) or a minimum of 6 determinations at 100 % of the test concentration.

Repeatability (intra-assay precision):

Establish precision under the same operating conditions over a short interval of time. Report:

Standard deviation (interdependent with S rel) see S rel

Overall relative standard deviation over the whole range of the method ≤ 10.00 %

Relative standard deviation within one concentration level ≤ 20.00 %

Confidence interval

Intermediate Precision (may include robustness, ruggedness):

Establish precision on different days, for different analysts, on different equipment and after variation of method parameters (= robustness, e.g. stability of solutions, variations of pH, of mobile phase composition, of flow rate, of temperature, of columns etc.). It is not necessary to study these effects individually. Experimental design (matrix) may be applied. Report:

Standard deviation (interdependent with relative standard deviation) see S rel

Relative standard deviation 3 × S rel from repeatability or 10 % whichever is greater

Confidence interval

Specificity:

Demonstrate the discrimination of the analyte in the presence of the other impurities:

Test samples containing the analyte and other impurities.

Obtain positive and correct results for the analyte.

Specify acceptable deviation

Test samples without the analyte. Negative results

For chromatographic procedures use representative chromatograms to document specificity. Label individual components appropriately.

Specify acceptable resolution of peaks

T ABLE 2 Validation Requirements

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8.3 Sampling Methods

In order to demonstrate that the plant equipment is verified clean and meets the pre-defined acceptance criteria, sampling and analysis should be carried out using the methods described in the following sections. Justification should be provided for the selection of the appropriate verification technique on a case by case basis. A combination of the two methods is generally the most desirable. For all methods the sampling points should be fixed in a manner such that the true contamination of the equipment will be reflected.

8.3.1 Swab sampling (Direct Surface Sampling)

Swab sampling of the direct surface is designed to test small sections of the equipment surface for the presence of residues. Samples should be taken from all main equipment items and since swab sampling does not cover the entire equipment surface area, justification should be provided for the choice of the area for swabbing.

Typically a small area of the cleaned equipment is swabbed with a material according to a pre-defined method i.e. swab material, solvent and technique. The swab sample can then be extracted and examined using a suitable analytical method.

The quantified residue obtained from the sample is then extrapolated to the whole equipment (see Equation 6).

Experiments Possible Acceptance Criteria

Linearity:

Measure a minimum of 5 concentrations across the range of the procedure (dilute standard stock solution or prepare synthetic mixtures). Plot the signals as function of concentration. Evaluate the plot:

Visually Linear

Statistically (e.g. regression line by the method of least squares)

correlation coefficient ⩾ 0.99000

y-intercept Confidence band (P = 95 %) contains 0

slope of the regression line

residual sum of squares

Range:

Confirm that the analytical procedure provides an acceptable degree of linearity, accuracy and precision within or at the extremes of the specified range. Minimum specified ranges:

From the reporting level to 120 % of M perMax . The reporting level for cleaning validation reasonably will be the LOQ.

However, the reporting level must be below M perMin and should

be below or at 80% of M perMin .
From LOQ or 80 % of
M perMin to 120 % of
M perMax
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It is important:

That the validation of the swab sampling is performed on the same surface (material, polish grade, area in dm 2) and with the same materials as the routine sampling of the equipment.

That the choice of swabbing material considers extractable materials that could interfere with the expected residue.

To ensure that the sampling points represent the worst case areas of the equipment.

The disadvantage of this sampling method for often complex API equipment is that difficult to reach areas (e.g. sealings, condensers, transfer pipework) may not be accessible by swabbing. Nevertheless these areas may be the critical areas for the determination of the amount of residue in the equipment.

Equation 6: (
) [
∑(
)] = (
) [
∑(
)]

M Amount of residue in the cleaned equipment in mg.
WF Recovery rate for the whole chain swab/analytical method (e.g. 0.8 for 80%).
F tot The entire inner surface of the equipment in dm 2
Mi Amount of residue (e.g. previous product) in the sample i in mg.
C i Gross amount of residue in the sample i in mg.
C Bi Blank of the sample i in mg. To establish the blank, a swab (or several swabs) can be treated in the similar way as a sampling swab except swabbing of the contaminated surface. Usually one and the same blank can be used for all N sampling swabs.
F i Area swabbed by the swab i in dm 2 .
N Number of swab samples.
i Sample identifier (current number from 1 to N).

The first production batch of the following product may be sampled and analysed for impurities (for preceding product) since chromatographic analytical methods will typically be used (e.g. HPLC, GC, TLC).

8.3.2 Rinse or Wash Solvent Sampling

In cases where swabbing is not possible, for example restricted access, swabbing may be substituted by the analysis of final rinse solutions. Rinse samples can be used to determine the carryover of residues over a large surface area and cover all main process items including transfer pipework. In cases where swab sampling is not practical, it is acceptable to analyse only rinse samples, however this should be justified as part of the validation study.

This section outlines the quantitation of the amount of residue remaining in the equipment after cleaning based on the amount of residue in the last rinse of the routinely used cleaning procedure.

The residue amount in the equipment can be assumed to be equal to the amount of residue in the last wash or rinse solvent portion. The assumption is based on the worst case consideration that a further rinse (or any reaction) would not remove more than the same amount of residue present in the analysed rinse sample.

The advantage of the rinse sampling method is the whole equipment will be reached by the

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solvent, including difficult to reach locations that cannot be disassembled. Therefore, if appropriately designed, this method will give the best indication of the amount of residue remaining in the equipment.

For quantitation, a solvent sample (e.g. 1 litre) is removed and the residue in the sample is determined by a suitable analytical method, which can then be extrapolated to the whole equipment according to Equation 5.

Equation 5: $M = V \times (C - C_B)$

Where M Amount of residue in the cleaned equipment in mg.

V Volume of the last rinse or wash solvent portion in litres.

C Concentration of impurities in the sample in mg/l.

C_B Blank of the cleaning or rinsing solvent in mg/l. If several samples are taken during one run, one and the same blank can be used for all samples provided the same solvent lot was used for the whole run.

8.3.3 Stamps

In this exceptionally used sampling method, “coins” (or stamps) are placed on appropriate sampling points in the equipment during the manufacture of the previous product and during cleaning. After cleaning, the contamination on the coins can be analysed and the overall contamination can be calculated by extrapolation to the whole equipment. For quantitation, the coins may be firstly swabbed followed by further analysis of the samples.

8.4 Analytical Methods

A sample isolated by either of the sampling methods discussed in Section 8.3 should be analysed by a suitable analytical method (e.g. HPLC, GC, GC-MS, TLC, dry residue, TOC, UV, titration, conductivity or pH). The suitability of the method can be documented by appropriate validation as detailed in Section 8.2.

A combination of analytical methods can be used if appropriate. For example evaporation of the solvent sample and analysis of the dry residue by another method (e.g. HPLC) can enhance the sensitivity of the final analytical method by a factor 10^6. Alternatively, the use of several methods (e.g. titration, HPLC) can provide the required specificity.

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9.0 Cleaning Validation Protocol

PREPARED BY (DEPT.): _____ DATE:_____

REVIEWED BY (DEPT.) : _____

DATE:_____

APPROVED BY (DEPT.) : _____

DATE:_____

APPROVED BY (DEPT.) : _____

DATE:_____

APPROVED BY (DEPT.) : _____ DATE:_____

TITLE:

PROTOCOL NO:_____

PROTOCOL ISSUE DATE: _____

CLEANING SOP REFERENCE AND ISSUE NO : _____

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TABLE OF CONTENTS

9.1 Background

Equipment X is routinely cleaned after product Y (or group of products*) according to procedure XXX.....

*If group of products describe rational for choosing this grouping strategy.

Describe: Equipment

Cleaning method

Cleaning agents.

9.2 Purpose

The purpose of this study is to demonstrate that remaining product residues previous in a piece of equipment are always within the established acceptance criteria if the equipment is cleaned by a defined cleaning method.

9.3 Scope

A visual test and a chemical evaluation of the equipment will be performed after a clean to demonstrate that product residue(s) (active ingredient, intermediates and / or excipients) and cleaning agent residues (exclude solvents used in process) have been removed to levels within the acceptance criteria.

The equipment cleanliness will be proven by testing and evaluation of samples in accordance with this protocol from Z* consecutive cleans. (*Z: Generally three consecutive cleans are acceptable, however, companies should determine the number adequate for their operation.)

At least a visual revision of the working areas will performed to minimize the risk of cross contamination that results from e.g. contamination on the surface of the process room.

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In order for the cleaning procedure to be deemed valid all data generated during the study should be within the acceptance criteria detailed in section 9.7 of this protocol.

A report will be written assessing the data generated and thus determining the validity of the cleaning process.

The equipment should not be used to process another product until clearance indicating that the equipment is adequately clean has been received from the validation department in accordance with process transfer SOP AAA (or detail whatever system is in-place to ensure that equipment is not used).

9.4 Responsibility

The responsibility for completion of this study lies as follows (for example):

Scheduling: Manufacturing, QA, QC and Engineering.

Cleaning of equipment: Manufacturing

Removal of samples: QA

Testing of samples: QC

Review of data and approval of study: Validation / Manufacturing / QC

9.5 Sampling Procedure

Remove swab and rinse samples from the equipment as detailed in section 8.3 of this guidance document.

SWAB SAMPLES:

See attached equipment sampling diagram (It is important to show clearly where the sampling locations are). Definition of sampling locations should be based on a Risk Assessment.

Swab samples should be removed according to swabbing procedure SOP BBB (or if there is no SOP in place describe in the text the validated sampling technique for the QA sampler).

The swab sampling locations are as follows:

Product residue samples: list of sample locations and no of swabs to be removed.

Cleaning agent samples: list of sample locations and no of swabs to be removed.

Samples should be removed from the locations on the equipment deemed to be ‘worst case’ i.e. most difficult to clean locations and therefore where product is most likely to reside if cleaning has not been adequate. It is important that these locations have been determined scientifically and can be rationalised if necessary.

RINSE SAMPLES:

Rinse samples should be removed according to procedure SOP CCC (or if there is no SOP in place describe the sampling technique for the QA sampler).

The volume of liquid used to rinse the equipment should be detailed. (volume must be shown to be sufficient to cover all product contact surfaces of the equipment).

The volumes of the rinse samples should also be stipulated in the protocol.

MICROBIOLOGICAL TESTING

See attached equipment sampling diagram (It is important to show clearly where the sampling locations are)

Microbiological test samples should be removed according to procedure SOP DDD (or if there is no SOP in place describe the sampling technique for the QA sampler).

The microbiological testing locations are as follows:

List of sample locations and no of microbiological tests samples to be removed
All sampling details (swab, rinse and microbiological) should be referenced in Table
Samples should then be sent to the QC department for analysis. Any relevant
sample transfer conditions should be noted.
9.6 Testing procedure
Rinse samples should be tested for:
- Product residues in accordance with analytical protocol
- Cleaning agent residues in accordance with analytical protocol
Swab samples should be tested for:
- Product residues in accordance with analytical protocol
- Cleaning agent residues in accordance with analytical protocol
Microbiological test samples should be tested for:
Total germ number
Note the limits of quantitation and detection as well as the % recovery for the tests
being performed.
The analytical protocol should include a calculation to convert the amount of
residue detected in the sample to 100% (i.e. if the analytical validation results
indicate that only 50% of spiked active / cleaning agent is recovered using the
swabbing / rinse method of choice, the amount of active cleaning agent recovered
per sample should be multiplied by 2 to bring result to 100%).
All data generated should be attached to this study and returned to the Validation
department where calculations and adherence to acceptance criteria is determined.
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9.7 Acceptance criteria
• The Visual cleanliness of the equipment must be checked and verified after cleaning
according to the procedure xxx:
Equipment is visually clean: Signed (manufacturing): _____ Date: _____
Verified (QA): _____ Date: _____
The swab / rinse sample acceptance criteria for product and cleaning agent residues
as well as the microbiological test acceptance criteria should be detailed along with
a rational for the figures quoted.
(Unlike product residues, it is expected that no (or for ultra sensitive analytical test
methods - very low), detergent levels remain after cleaning. Detergents are not part of
the manufacturing process and are only added to facilitate cleaning. Thus they should
be easily removed. Otherwise a different detergent should be selected.)
Reference: Please see chapter 4 of this guidance document for examples of
calculating acceptance criteria.
In addition a sample calculation detailing how the residual levels of active ingredient /
cleaning agent for the entire equipment are computed should be given.
POINTS TO CONSIDER:
Surface area calculations should be performed, verified and kept on file for all equipment
evaluated (photos may be incorporated into the protocol to ensure samples are taken from the
correct position).
When the worst case result recorded is less than the limit of quantitation but greater than the

limit of detection for the test method, the value denoting the limit of quantitation should be used to perform the calculations.

When the worst case result recorded is less than the limit of detection for the test being performed the value denoting the limit of detection should be used to perform the calculations.

Dirty Hold Times and Clean Hold Times

The period and when appropriate, conditions of storage of equipment before cleaning, commonly referred to as The Dirty Hold Time (DHT) and the time between cleaning and equipment reuse, prior to additional cleaning, commonly referred to as The Clean Hold Time (CHT), should form part of the validation of cleaning procedures. This is to provide confidence that routine cleaning and storage of equipment does not allow potential for build up of degradation products that may not be removed by the standard cleaning procedure and does not allow potential for microbial contamination of equipment and to ensure that these potential risks are properly assessed and controlled.

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TABLE 1: SAMPLE REFERENCE TABLE

Sample	To be tested for	Area swabbed	Total surface area (cm2)	Sample ref.	signed / date
swab sample	Active xxx				
swab sample	Cleaning agent	xxx			
swab sample	Active xxx				
swab sample	Cleaning agent	xxx			
swab sample	Active xxx				
swab sample	Cleaning agent	xxx			

swab
sample
Active xxx
swab
sample
Cleaning agent xxx
swab
sample
Active xxx
swab
sample
Cleaning agent xxx
Sample To be tested
for
Sample
volume
total volume
of rinse
Sample
ref.
signed /
date
rinse
sample
Active
rinse
sample
Cleaning agent
Sample To be tested
for
Sample ref. signed /
date
swab
sample
Microbial
contamination
swab
sample
Microbial
Contamination

9.8 Deviations

Please indicate whether deviations occurred during the completion of this Validation Protocol and give details especially with regard to impact on the effectiveness of the cleaning validation and with regard to corrective and

preventive actions.

.

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9.9 Revalidation

Define the Revalidation strategy for cleaning processes

Signed: _____ Verified: _____

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10.0 Validation Questions

Question 1: When should a company validate/ revalidate cleaning procedures? When is validation not required?

Advice: Ref. Section 7.0 and 10.0

Companies should look at each situation individually and determine the need for validation. Section 7.0 provides a basic template, which may be used as a starting point in this evaluation. The necessity to revalidate cleaning procedures should be determined under change control parameters - See Section 10.0.

If routine verification procedures are used, these should be monitored to ensure that the procedure is in control. Companies should consider a periodic evaluation of cleaning procedures , which are subject to variation (i.e. manual procedures etc.), as an additional precaution to assure that the procedures are still valid.

Question 2: When is it appropriate to use Prospective, Concurrent or Retrospective Validation

Advice: Ref. Section 9.0

Retrospective Validation of cleaning is not condoned by regulatory Authorities

Prospective Validation is the ideal method of validation.

In situations where very few runs are manufactured in any given period and/ or a business decision has been taken to release the next material manufactured after cleaning based on a high level of testing of the equipment (i.e. Validation level,) concurrent release of material may take place.

Question 3: What level of testing is needed after cleaning validation?

Advice: Ref. Section 5.3

The answer to this question depends on individual situations. Typically, companies perform visual inspection and take rinse samples to monitor the effectiveness of the cleaning in pre-defined intervals (time or number of batches).

If after validation company decides to perform always cleaning verification non-specific scientifically sound analytical methods may be used.

A practical approach for monitoring the effectiveness of cleaning after completion of cleaning validation in an effective, scientific sound and inexpensive way is given below:

1.)Visual inspection of the cleaned equipment. Only after this check is considered satisfactory, proceed with the next step.

2.)Take a rinse and/or swab sample (one litre of rinsing liquid is usually

required)

3.)Determine the dry residue by evaporating about 500 ml to dryness in a

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small flask using a rotary evaporator. This unspecific test covers also inorganic salts, known or unknown organic products and will detect the total residues. (this test might be omitted for the drying equipment, in this instance we have a pure API or intermediate and typically no potential for side products, degradation, etc.)

4.)If the result meets the specification, proceed to specific (chromato-graphic) technique. Start with a TLC-limit test (inexpensive and fast to validate, broad detection range – UV and specific derivatisation – if these techniques are combined, the method is very specific for the different impurities potentially present in the sample. Apply 2 samples: the last washing liquid (to see all potential residues), the rinsing liquid (to look for the residue) and two standards: one of the suspected residual product at a concentration that is the limit accepted, and a 1:2 dilution of the standard. If the main spot in the rinsing liquid has lower intensity than the standard, the equipment is clean. The second standard is for confirmation of detection.

5.)If TLC is not the appropriate technique, revert to HPLC or GC.

Question 4: What critical parameters need to be looked at during cleaning validation?

Advice: Ref. Section 8.2 for details

It is vital that the equipment design is evaluated in detail in conjunction with the product residues to be removed, the available cleaning agents and the cleaning techniques. Also the ruggedness and reproducibility of the cleaning procedure should be covered.

Question 5: What number of cleans should be run in order to validate a cleaning procedure?

Advice: Ref. Section 9.0

A validation program generally encompasses three consecutive successful replicates. However, companies should evaluate each situation individually.

Question 6: Is it acceptable for a validated cleaning procedure to be continued until the analytical results demonstrate it is clean?

Advice: Regulatory authorities do not condone this practice.

When the analytical result does not meet the acceptance criteria an investigation to determine the possible root cause should be performed. If needed re-training of the operators should be performed and/or adjustment of the cleaning procedure to solve the issue.

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Question 7: Is it necessary for companies to validate a maximum time allowed for a piece of equipment to be dirty before cleaning?

Advice: Companies should have SOPs in place, which require cleaning to be performed immediately after production has stopped. This scenario should be validated.

However, if for some reason immediate cleaning is not always possible, companies should consider the effect of time on the material deposited on the equipment. It may be possible to 'Group' or 'Bracket' products, and validate a worst case scenario.

Question 8: Is it necessary for companies to validate a maximum time allowed for a piece of equipment to be left clean before re-use?

Advice: Companies should have SOPs in place to ensure that pieces of equipment are adequately protected from any contamination after cleaning has taken place i.e. ensure that the equipment is adequately covered, closed from dust etc. If the company feels that there is any risk of contamination during 'idle time' after cleaning, validation should be considered.

Question 9: Is it necessary to establish time limits for cleaning if equipment is not used frequently?

Advice: Please see previous advice to question 8.

Question 10: What is the maximum time allowed after cleaning with water as last rinse?

Advice: Equipment should not be left with water in it after cleaning. The last step of the cleaning procedure involve drying with solvent or flushing with Nitrogen, thus ensuring that there is no opportunity for microbial growth.

Question 11: Is it possible that a deterioration of equipment may take place over time, thus invalidating the original validation results?

Advice: Materials used to manufacture equipment for the pharmaceutical / chemical industry is of a very high standard. However, equipment materials used should be evaluated to ensure their durability over time as part of the preventative maintenance programme. The possibility of surface roughness and any possible effects that it may have on cleaning should be considered.

Companies employing verification methods after validation should monitor analytical data generated as part of this process.

Question 12: If a company has validated a worst case scenario (grouping or bracketing regime), should they also need to validate a 'less' worst case?

Advice: When grouping products and determining worst case situation scenario for validation, companies should determine whether or not the worst case being

validated is one, which is appropriate for routine manufacture. For operational reasons it may be beneficial to validate a "less" stringent cleaning procedure for some products.

Question 13: In a case of a dedicated plant with no degradants, is there a need to validate?

Advice: Ref. Section 7.0

Companies should consider each situation individually and validate where there is a potential for contamination. In the above situation, there may not be a need. However, consideration should be given to the number of runs being performed prior to full cleaning.

Question 14: Should cleaning validation be part of a development programme?

Advice: While it is not a requirement of ICH that cleaning validation be performed during development phase the following should be considered:

If the equipment being cleaned after the development product in question is used to manufacture commercial product or product for human use for example clinical trials, it is essential to verify the appropriate cleanliness of the equipment prior to re-use.

Development of the Cleaning procedure for the product should take place at development phase for validation when the product becomes commercially available. The cleaning procedure validation should be performed or at least should start with the process validation campaign.

Question 15: Is it necessary to include microbiological testing / aspects in the cleaning validation programme?

Advice: Ref. Section 8.1

Yes, if the following product needs to have a low microbiological load, also depending on the cleaning agent used, if there is any risk for microbiological contamination of the subsequent product (e.g. if water is used for final cleaning).

Question 16: Which analytical methods should be used in cleaning validation studies (is only HPLC -testing acceptable?) and to which extend should these methods be validated?

Advice: Ref. Section8.0 of this “Guidance on Aspects Document”

Any analytical method suitable for its intended use could be used. In general limit tests are performed in cleaning validation studies which result in less stringent validation requirements. (as outlined in ICH-Q2A and Q2B).

However, if a company decides to validate analytical methods, suitable for the determination of the residue over a certain range (e.g. decay-curve, to prove the success of cleaning during proceeding of a defined cleaning procedure consisting

of individual cleaning steps) also less stringent validation requirements for e.g. linearity and accuracy could be established compared with figures typically required in the validation of API release testing methods.

Question 17: Do we have to wait for swab and rinse samples to be approved prior using the equipment for production?

Advice: During cleaning validation studies it is recommended to wait for completion of all planned tests prior to release equipment for further use (to be able to perform an investigation if tests fail). In routine operations (after validation has been completed) the release of equipment pending testing results (verification, monitoring status of the tests) could be done. Responsibilities and circumstances for using equipment pending release should be defined within the company.

11.0 References

Bracketing and Worst Case Rating

1 USP 24, The United States Pharmacopoeia, United States Pharmacopeial Convention, Inc., 12601 Twinbrook Parkway, Rockville, MD 20852.

Determination of the Amount of Residue

1. FDA Guide to Inspections Validation of Cleaning Processes, http://www.fda.gov/ICECI/Inspections/InspectionGuides/ucm074922.htm

3. ICH Q2 (R1), Validation of Analytical Procedures: Text and Methodology, November 2005.
4. Parenteral Drug Association (PDA) Guidance for Industry.Technical Report No. 29 (Revised 2012) Points to Consider for Cleaning Validation, Destin A. LeBlanc, Gretchen Allison, Jennifer L. Carlson, Koshy George, Igor Gorsky, Irwin S. Hirsh, Jamie Osborne, Greg Randall, Pierre-Michel Riss, George Verghese, Jenn Walsh, Vivienne Yankah.

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12.0 Glossary

A i Area for the tested piece of equipment # i.

ADE Acceptable Daily Exposure (µg/day)

CO True (measured) total quantity of substance (possible carryover) on the cleaned surface in contact with the product, calculated from results of swab tests.

CONC Concentration (kg/kg or ppm) of "previous" substance in the next batch. Based on MACO calculated from therapeutic doses and/or tox data.

LD50 Lethal Dose 50 in g/kg animal. The identification of the animal (mouse rat etc.) and the way of entry (IV, oral etc.) is important.

LOD Limit of detection.

LOQ Limit of quantification.

m i Quantity (in weight/area) for each swab per area of swabbed surface (normally 1 dm 2).

MACO Maximum Allowable Carryover: acceptable transferred amount from the investigated product ("previous").

MACO ppm Maximum Allowable Carryover: acceptable transferred amount from the investigated product ("previous"). Calculated from general ppm limit.

MAXCONC General limit for maximum allowed concentration (kg/kg or ppm) of "previous" substance in the next batch.

MBS Minimum batch size for the next product(s) (where MACO can end up).

NOEL No Observed Effect Level.

NOAEL No Observed Adverse Effect Level

Rinsing cycle Sometimes rinsing cycles/runs may follow the washing cycles. The rinsing cycles may be part of the routine cleaning procedure (e.g. to rinse out the washing solvent) or may be used for sampling purposes (e.g. rinsing with water after washing with detergents). Rinsing cycles that are not part of the routine cleaning procedure may be used for enhanced sampling during the cleaning validation exercise.

SF Safety factor.

S rel Relative standard deviation, coefficient of variation.

TDD next Standard therapeutic dose of the daily dose for the next product.

TDD previous Standard therapeutic dose of the investigated product (in the same

dosage form as TDD next).
Washing Usually the API equipment will be washed through with several cycle portions of solvent one after the other by the same repeated process. One cleaning process repetition with one of these portions is termed washing cycle (run).
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汇总分析:

Determination of the Amount of Residue (chapter 8) 残留量的检测（第 8 章）

At the beginning of chapter 8 a practical guidance is provided concerning the validation of analytical methods in the course of a cleaning validation; regulatory requirements (for example FDA) and guidelines are indicated (such as ICH Q2 R1). The second part addresses sampling methods (swab/rinse). A combination of the two methods is described as being generally the most desirable. Interestingly, the subchapter swab sampling mentions the analysis of the first production batch of the following product for impurities as "may" option. In its cleaning validation guidance FDA is critical as concerns this procedure. For swab sampling as well as for rinse or solvent sampling equations are given.

在第 8 章开头就给出了关于清洁验证中分析方法的验证实用指南，指出了法规要求（例如 FDA）和指南（例如 ICH Q2R1）。第二部分写的是取样方法（擦拭取样/淋洗取样），以及两方法并用的方式。通常两法并用是实际所需要的。有意思的是，关于擦拭取样的章节中提到对下一产品第一个生产批次的杂质分析“可能”是一种选择。在 FDA 的清洁验证指南中，FDA 对此相当关注。在文给出了擦拭取样、淋洗取样及溶剂取样的计算公式。

There is also mentioned a third method which is rather unknown - the so-called "stamps" or "coins". These elements are placed on appropriate sampling points in the equipment and remain there during the manufacture of the previous product and during cleaning. After cleaning, the contamination on the coins is analysed and the overall contamination is calculated.

文中还提到第 3 种较少为人知的方法，称为“邮票”或“贴片”法。该方法是将一个“贴片”贴在设备取样点，进行上一产品的生产和清洁，在清洁后，对“贴片”上的清洁物进行分析，计算整体污染水平。

Cleaning Validation Protocol (chapter 9) 清洁验证方案（第 9 章）

In chapter 9 you can find a cleaning validation protocol which is six pages long and divided into 9 chapters:

在第 9 章中，你会看到一份 6 页的清洁验证方案，分为 9 个部分：

- Background 背景
- Purpose 目的
- Scope 范围
- Responsibility 职责
- Sampling procedure 取样程序
- Testing procedure 检测方法
- Acceptance criteria 可接受标准
- Deviations 偏差
- Revalidation 再验证

In **Chapter 10 "Validation Questions"** frequently asked questions are answered in the style of a Q&A paper. In this document "A" is short for "advice". The questions are answered with references to the single chapters/subchapters in the document.

在第 10 章“验证问题”中，以问答方式对常见问题进行了回答。在本文件中，“A”是建议“ADVICE”的缩写。问题回答中参考了文件中相关章节。