Validation of Cleaning Processes

清洁工艺验证

GUIDE TO INSPECTIONS VALIDATION OF CLEANING PROCESSES

清洁工艺验证检查指南

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Content

I. INTRODUCTION 简介

Validation of cleaning procedures has generated considerable discussion since agency documents, including the Inspection Guide for Bulk Pharmaceutical Chemicals and the Biotechnology Inspection Guide, have briefly addressed this issue. These Agency documents clearly establish the expectation that cleaning procedures (processes) be validated.

自从机构文件，包括化学原料药制剂检查指南和生物技术制剂检查指南简明的提及清洁验证规程以来，就对清洁规程验证产生了大量的讨论。这些机构的文件明确建立了清洁规程验证的预期结果。

This guide is designed to establish inspection consistency and uniformity by discussing practices that have been found acceptable (or unacceptable). Simultaneously, one must recognize that for cleaning validation, as with validation of other processes, there may be more than one way to validate a process. In the end, the test of any validation process is whether scientific data shows that the system consistently does as expected and produces a result that consistently meets predetermined specifications.

设计本指南是为了通过讨论已发现的可接受（或不可接受）的实际操作来建立检查的一致性和统一性。同时必须认识到清洁验证和其他过程验证一样，某一过程的验证可能不止一种方式。最后，任何过程验证的检测是科学数据是否反映系统能始终如一按照既定标准运作并持续产生符合既定标准的结果。

This guide is intended to cover equipment cleaning for chemical residues only.

本指南只适用于化学残留物的设备清洁。

II. BACKGROUND 背景

For FDA to require that equipment be clean prior to use is nothing new, the 1963 GMP Regulations (Part 133.4) stated as follows "Equipment *** shall be maintained in a clean and orderly manner ***." A very similar section on equipment cleaning (211.67) was included in the 1978 CGMP regulations. Of course, the main rationale for requiring clean equipment is to prevent contamination or adulteration of drug products. Historically, FDA investigators have looked for gross insanitation due to inadequate cleaning and maintenance of equipment and/or poor dust control systems. Also, historically speaking, FDA was more concerned about the contamination of nonpenicillin drug products with penicillins or the cross-contamination of drug products with potent steroids or hormones. A number of products have been recalled over the past decade due to actual or potential penicillin cross-contamination.

对于 FDA 来说，要求对设备在使用前进行清洁并不是稀奇的事情，1963 年 GMP 法规（133.4 部分）指出“设备***应该按照清洁和有序的方式来进行维护”。在 1978 CGMP 法规中也包含了非常相似的有关设备清洗的章节(211.67)。当然，清洁设备的主要理由是防止药品被污染或掺假。在历史上，FDA 检查官寻找由于对设备不当的清洗和维护和/或不良的灰尘控制系统而带来的总体不卫生情况。而且，从历史上来说，FDA 更

加关注非青霉素药品被青霉素污染、或药品中的活性激素或荷尔蒙交叉污染。由于实际或潜在的青霉素的交叉污染所致，在过去的十年中有很多药品被召回。

One event which increased FDA awareness of the potential for cross contamination due to inadequate procedures was the 1988 recall of a finished drug product, Cholestyramine Resin USP. The bulk pharmaceutical chemical used to produce the product had become contaminated with low levels of intermediates and degradants from the production of agricultural pesticides. The cross-contamination in that case is believed to have been due to the reuse of recovered solvents. The recovered solvents had been contaminated because of a lack of control over the reuse of solvent drums. Drums that had been used to store recovered solvents from a pesticide production process were later used to store recovered solvents used for the resin manufacturing process. The firm did not have adequate controls over these solvent drums, did not do adequate testing of drummed solvents, and did not have validated cleaning procedures for the drums.

1998 年消美国专利药消胆胺树脂制剂的召回，使 FDA 进一步认识到因不当规程而导致交叉污染的可能性。用于生产药品的原料药被生产农用杀虫剂中产生的中间体和降解物污染。本案例中的交叉污染被认为是由于回收溶剂的重新使用。回收溶剂由于缺乏对溶剂桶的重新使用进行控制而被污染。用于储存杀虫剂生产过程中的回收溶剂的溶剂桶，后来又用于储存树脂生产过程的回收溶剂。公司未对这些溶剂桶进行适当的控制，也未对桶中的溶剂进行适当的测试，以及未对桶的清洗过程进行验证。

Some shipments of this pesticide contaminated bulk pharmaceutical were supplied to a second facility at a different location for finishing. This resulted in the contamination of the bags used in that facility's fluid bed dryers with pesticide contamination. This in turn led to cross contamination of lots produced at that site, a site where no pesticides were normally produced.

部分被杀虫剂污染的原料药被运输到在其他地方的另外一家工厂进行最后加工。由于该工厂的流体床干燥器袋子被原料药中的杀虫剂污染，结果导致在该工厂地点生产的很多批次产品相应的被交叉污染，该地点在正常情况下是不生产杀虫剂的。

FDA instituted an import alert in 1992 on a foreign bulk pharmaceutical manufacturer which manufactured potent steroid products as well as non-steroidal products using common equipment. This firm was a multi-use bulk pharmaceutical facility. FDA considered the potential for cross-contamination to be significant and to pose a serious health risk to the public. The firm had only recently started a cleaning validation program at the time of the inspection and it was considered inadequate by FDA. One of the reasons it was considered inadequate was that the firm was only looking for evidence of the absence of the previous compound. The firm had evidence, from TLC tests on the rinse water, of the presence of residues of reaction byproducts and degradants from the previous process.

FDA 在 1992 年对使用普通设备生产活性激素产品和非激素产品的国外原料药生产商提出了进口警告。该公司是多用途原料药制药工厂。FDA 认为交叉污染的可能性非常大，并对公众健康产生严重威胁。公司只是在最近被检查的时候才开始进行清洗验证程序，FDA 认为这是不够的。其中的一个原因是，公司只是收集

了以前化合物不存在的证据。公司从冲洗水的 TLC 测试上有证据表明，来自以前的过程中反应副产品和降解物的残留物的存在。

III. GENERAL REQUIREMENTS 常规要求

FDA expects firms to have written procedures (SOP's) detailing the cleaning processes used for various pieces of equipment. If firms have one cleaning process for cleaning between different batches of the same product and use a different process for cleaning between product changes, we expect the written procedures to address these different scenario. Similarly, if firms have one process for removing water soluble residues and another process for non-water soluble residues, the written procedure should address both scenarios and make it clear when a given procedure is to be followed. Bulk pharmaceutical firms may decide to dedicate certain equipment for certain chemical manufacturing process steps that produce tarry or gummy residues that are difficult to remove from the equipment. Fluid bed dryer bags are another example of equipment that is difficult to clean and is often dedicated to a specific product. Any residues from the cleaning process itself (detergents, solvents, etc.) also have to be removed from the equipment.

FDA 要求公司应具有详细地记录设备各种零件的清洗过程的书面程序（SOP’s）。如果公司在清洁不同批次的相同产品时使用一种清洗过程，而在清洗不同产品时使用一种不同的清洗过程，那么我们要求书面程序能包括这些不同的细节。相似地，如果公司在除掉可溶于水的残留物时使用某一种清洗过程，而对于不可溶于水的残留物时使用另外一种清洗过程，书面程序应当说明这两种过程，并且明确的阐述出何时应该遵守已知的过程。当生产过程会产生难以除去的焦油状或粘状残留物时，原料药公司也许会决定使用特定的设备来进行特定的化学生产步骤。流体床的干燥器袋是很难清洗的设备之一，经常用于特定的产品。清洗过程本身留下的任何残留物也必须清除掉（清洁剂、溶剂等）。

FDA expects firms to have written general procedures on how cleaning processes will be validated.

FDA 要求公司应具有验证清洗过程的常规书面程序。

FDA expects the general validation procedures to address who is responsible for performing and approving the validation study, the acceptance criteria, and when revalidation will be required.

FDA 要求常规验证程序说明负责执行和批准验证研究的负责人员、可接受标准以及再验证时间。

FDA expects firms to prepare specific written validation protocols in advance for the studies to be performed on each manufacturing system or piece of equipment which should address such issues as sampling procedures, and nalytical methods to be used including the sensitivity of those methods.

FDA 要求公司在对每个生产系统或设备部件进行研究之前应准备具体的书面验证方案，验证方案中阐述取样程序、采用的分析方法以及这些方法的灵敏度等问题。

FDA expects firms to conduct the validation studies in accordance with the protocols and to document the results of studies.

FDA 要求公司应按照方案来进行验证研究，并以书面形式记录这些研究结果。

FDA expects a final validation report which is approved by management and which states whether or not the cleaning process is valid. The data should support a conclusion that residues have been reduced to an "acceptable level."

FDA 要求应该有一份经管理部门批准的最终验证报告，并且该报告应指出该清洗过程是否有效。数据应当证明残留物已被减少到“可接受的水平”。

IV. EVALUATION OF CLEANING VALIDATION 清洁验证的评估

The first step is to focus on the objective of the validation process, and we have seen that some companies have failed to develop such objectives. It is not unusual to see manufacturers use extensive sampling and testing programs following the cleaning process without ever really evaluating the effectiveness of the steps used to clean the equipment. Several questions need to be addressed when evaluating the cleaning process. For example, at what point does a piece of equipment or system become clean? Does it have to be scrubbed by hand? What is accomplished by hand scrubbing rather than just a solvent wash? How variable are manual cleaning processes from batch to batch and product to product? The answers to these questions are obviously important to the inspection and evaluation of the cleaning process since one must determine the overall effectiveness of the process. Answers to these questions may also identify steps that can be eliminated for more effective measures and result in resource savings for the company.

第一步应该集中在验证过程的目标上，而且 FDA 发现一些公司未能成功实现这样的目标。生产商在清洗过程中使用大量的样品和检测程序，而从未真正地对设备的清洗步骤进行有效性评估，这样的做法不足为奇。当对清洗规程进行评估时，应当阐明一些问题。例如，认为设备部件或系统是清洁的标准是什么？必须要用手擦洗吗？用手擦洗跟洗涤剂清洗相比应该伴随什么过程？从批次到批次的清洗过程与从产品到产品有什么样的变化？由于我们必须确定整个过程的有效性，所以在检查和评估清洗过程时，回答这些问题的重要性是显而易见的，应为我们必须要确定整个过程的有效性。对这些问题的回答也可能断定哪些步骤可以省略而采用更加有效的方法，来进行评估并为公司节省资源。

Determine the number of cleaning processes for each piece of equipment. Ideally, a piece of equipment or system will have one process for cleaning, however this will depend on the products being produced and whether the cleanup occurs between batches of the same product (as in a large campaign) or between batches of different products. When the cleaning process is used only between batches of the same product (or different lots of the same intermediate in a bulk process) the firm need only meet a criteria of, "visibly clean" for the equipment. Such between batch cleaning processes do not require validation.

确定对每个设备部件的清洗过程的数量。在理想的情况下，每个设备或系统的部件都应该有相应的一种清洗过程。但是，这要取决于被生产的产品，以及清洗是否发生在同一产品的批次之间（如在较大的清洗规模中），还是发生在不同产品的批次之间。当在同一产品的批次之间进行清洗时（或者在原料药工艺中同一中间体的不同批次之间），公司只需要达到“设备目视清洁”的标准就行了。统一品种批间的清洗过程并不需要验证。

1. Equipment Design *设备设计*

Examine the design of equipment, particularly in those large systems that may employ semi-automatic or fully automatic clean-in-place (CIP) systems since they represent significant concern. For example, sanitary type piping without ball valves should be used. When such nonsanitary ball valves are used, as is common in the bulk drug industry, the cleaning process is more difficult.

检查设备的设计。尤其是在那些大的系统中，其可能使用了半自动或全自动的在线清洗系统，这是非常令人担心的。例如，应当使用没有球阀的卫生级管道。当使用非卫生级别的球阀时（在原料药企业中很常见），清洗过程会更加困难些。

When such systems are identified, it is important that operators performing cleaning operations be aware of problems and have special training in cleaning these systems and valves. Determine whether the cleaning operators have knowledge of these systems and the level of training and experience in cleaning these systems. Also check the written and validated cleaning process to determine if these systems have been properly identified and validated.

当这些已明确时，执行清洗操作的人员应该知道问题所在，并且在清洗这些系统和阀门方面经过专项的训练。应该确定清洗工作人员是否具有清洗这些系统以及在清洗系统中的训练程度和经验。另外还要核对书面的经核实的清洗过程来确定这些系统是否被正确的鉴定和验证。

In larger systems, such as those employing long transfer lines or piping, check the flow charts and piping diagrams for the identification of valves and written cleaning procedures. Piping and valves should be tagged and easily identifiable by the operator performing the cleaning function. Sometimes, inadequately identified valves, both on prints and physically, have led to incorrect cleaning practices.

在一些更大的系统中，例如那些使用很长的传送带或管道的系统，应该检查流程图和管道系统图以确认阀门和书面的清洗程序。应当在管道和阀门应加以标识，并且可以被执行清洗过程的工作人员很容易地辨认出。有时，若对阀门的示意图和现场标识不当，会导致不正确的清洗操作。

Always check for the presence of an often critical element in the documentation of the cleaning processes; identifying and controlling the length of time between the end of processing and each cleaning step. This is especially important for topicals, suspensions, and bulk drug operations. In such operations, the drying of residues will directly affect the efficiency of a cleaning process.

应该经常检查清洗过程的文档中通常关键的因素的记录情况；并识别和控制生产过程结束与每个清洗步骤之间的时间长度。这对于外用剂型产品、悬浮剂和原料药操作尤其重要。在这些操作中，残留物的干化将直接影响到清洗过程的效果。

Whether or not CIP systems are used for cleaning of processing equipment, microbiological aspects of equipment cleaning should be considered. This consists largely of preventive measures rather than removal of contamination once it has occurred. There should be some evidence that routine cleaning and storage of equipment does not allow microbial proliferation. For example, equipment should be dried before storage, and under no circumstances should stagnant water be allowed to remain in equipment subsequent to cleaning operations.

无论是否使用 CIP 系统清洗工艺设备，都应该考虑设备清洗的微生概况。这主要是包括指预防措施，而不包括发生微生物污染后的再除掉。应该证据证实，设备的常规清洗和存储时不会有微生物繁殖。例如，设备在存储前应该被干燥，绝对不允许有污水留在清洗后的设备中。

Subsequent to the cleaning process, equipment may be subjected to sterilization or sanitization procedures where such equipment is used for sterile processing, or for nonsterile processing where the products may support microbial growth. While such sterilization or sanitization procedures are beyond the scope of this guide, it is important to note that control of the bioburden through adequate cleaning and storage of equipment is important to ensure that subsequent sterilization or sanitization procedures achieve the necessary assurance of sterility. This is also particularly important from the standpoint of the control of pyrogens in sterile processing since equipment sterilization processes may not be adequate to achieve significant inactivation or removal of pyrogens.

在清洗完成之后，用于无菌过程，或产品有助于微生物繁殖的非无菌过程的设备可能会被灭菌或消毒。虽然灭菌和消毒程序已超出本指南的范围，但值得注意是通过设备的适当清洁和适当存储控制生物负荷对于保证接下来的灭菌或消毒程序达到必要的无菌保证是很重要的。因为设备杀菌过程不能够获得显著的失活或除去热原质，所以这对无菌处理热原控制的立场来看也特别重要。尤其是这也对于无菌工艺的热源控制非常重要，由于设备灭菌过程可能不会充分达到显著的热源灭活和去除。

2. Cleaning Process Written *清洗过程记录*

Procedure and Documentation *规程和记录*

Examine the detail and specificity of the procedure for the (cleaning) process being validated, and the amount of documentation required. We have seen general SOPs, while others use a batch record or log sheet system that requires some type of specific documentation for performing each step. Depending upon the complexity of the system and cleaning process and the ability and training of operators, the amount of documentation necessary for executing various cleaning steps or procedures will vary.

检查被验证的清洗工艺规程的细节和特性，以及必须的文件的数量。FDA 官员已看过通常的 SOPs, 其余的则采用一份批记录或日志单系统，其规定了详细记录每一步操作的一些。执行不同清洁步骤或规程所必须的文件数量因系统和清洁工艺的复杂性以及操作人员的能力和培训而不同。

When more complex cleaning procedures are required, it is important to document the critical cleaning steps (for example certain bulk drug synthesis processes). In this regard, specific documentation on the equipment itself which includes information about who cleaned it and when is valuable. However, for relatively simple cleaning operations, the mere documentation that the overall cleaning process was performed might be sufficient.

当需要更复杂的清洗规程时，记录关键清洗步骤（如某种原料药的合成工艺）是很重要的。这种情况下，设备本身的详细记录文档应包括谁清洗的和清洁有效时限的信息。然而，对于相关简易的清洗操作，只需已执行的完成清洁过程的记录可能就足够了。

Other factors such as history of cleaning, residue levels found after cleaning, and variability of test results may also dictate the amount of documentation required. For example, when variable residue levels are detected following cleaning, particularly for a process that is believed to be acceptable, one must establish the effectiveness of the process and operator performance. Appropriate evaluations must be made and when operator performance is deemed a problem, more extensive documentation (guidance) and training may be required.

其它因素，如清洗历史、清洗后发现的残留物水平、和测试结果的变化趋势，也可能决定所需要文件的数量。例如，如果在后续清洗中发现了不同的残留物水平，特别是对于被认为是可接受的清洗过程，那么就必须确定过程和操作员的执行的有效性。应该做适当的评估，如果认为操作员的执行有问题，就需要更多的文件（指南）和培训。

3. Analytical Methods *分析方法*

Determine the specificity and sensitivity of the analytical method used to detect residuals or contaminants. With advances in analytical technology, residues from the manufacturing and cleaning processes can be detected at very low levels. If levels of contamination or residual are not detected, it does not mean that there is no residual contaminant present after cleaning. It only means that levels of contaminant greater than the sensitivity or detection limit of the analytical method are not present in the sample. The firm should challenge the analytical method in combination with the sampling method(s) used to show that contaminants can be recovered from the equipment surface and at what level, i.e. 50% recovery, 90%, etc. This is necessary before any conclusions can be made based on the sample results. A negative test may also be the result of poor sampling technique (see below).

应该确定用来检测残留物或污染物的分析方法的专属性和灵敏度。用先进的分析技术能检测生产和清洗过程中很低水平的残留物。如果污染或残留物水平不能被检测，并不意味着清洗后不存在残留物污染物。只能说明样品中不存在高于分析方法灵敏度或检测限度的污染物水平。公司应该通过结合从设备表面重新找回残留物及残留物回收率（如 50%或者 90%）的分析方法，对使用的分析方法进行挑战。这在根据取样结果下结论前是很必要的。不当的取样技术可能会导致阴性的测试结果（见下）。

4. Sampling *取样*

There are two general types of sampling that have been found acceptable. The most desirable is the direct method of sampling the surface of the equipment. Another method is the use of rinse solutions.

通常有两种可接受的取样方法。最适当的方法是从设备表面直接取样。另一种方法是使用淋洗溶液。

a. Direct Surface Sampling - Determine the type of sampling material used and its impact on the test data since the sampling material may interfere with the test. For example, the adhesive used in swabs has been found to interfere with the analysis of samples. Therefore, early in the validation program, it is important to assure that the sampling medium and solvent (used for extraction from the medium) are satisfactory and can be readily used.

a. 表面直接取样-确定使用的取样材料类型以及对测试数据产生的影响，因为取样材料可能会干扰测试。例如，发现药签上的粘合剂会干扰样品的分析。因此，在早期的确认程序中，确保取样媒介和溶剂（用于从媒介中萃取）的符合要求并容易使用是很重要的。

Advantages of direct sampling are that areas hardest to clean and which are reasonably accessible can be evaluated, leading to establishing a level of contamination or residue per given surface area. Additionally, residues that are "dried out" or are insoluble can be sampled by physical removal.

直接取样的优点是清洗难点和容易接近的区域可以被评估，从而可确定每个已知表面区域的污染物或残留物的水平。另外，不能溶解的或已干透的残留物可以通过物理取除的方法来取样。

b. Rinse Samples - Two advantages of using rinse samples are that a larger surface area may be sampled, and inaccessible systems or ones that cannot be routinely disassembled can be sampled and evaluated.

b. 淋洗液样品-使用淋洗液样品的两个好处是可以大面积的取样，而且可以对人为不易接近或不能按照方法拆卸的系统进行取样和评估。

A disadvantage of rinse samples is that the residue or contaminant may not be soluble or may be physically occluded in the equipment. An analogy that can be used is the "dirty pot." In the evaluation of cleaning of a dirty pot, particularly with dried out residue, one does not look at the rinse water to see that it is clean; one looks at the pot.

取淋洗液样品的一个缺点是，残留物或污染物可能不溶解或被堵塞在设备中。可以推断“不干净的罐”可以被使用。在评价对不干净的药罐的清洗时，特别是那种有干透残留物的，不应该只看淋洗液样品是否干净，而应该看药罐是否干净。

Check to see that a direct measurement of the residue or contaminant has been made for the rinse water when it is used to validate the cleaning process. For example, it is not acceptable to simply test rinse water for water quality (does it meet the compendia tests) rather than test it for potential contaminates.

在验证清洗过程时，要确保对淋洗液样品的残留物或污染物进行直接测量。例如，只简单检测淋洗液样品的质量（它是否符合测试纲要）而不检测所有潜在的污染物的，这种做法是不被认可的。

c. Routine Production In-Process Control *常规生产过程控制*

Monitoring - Indirect testing, such as conductivity testing, may be of some value for routine monitoring once a cleaning process has been validated. This would be particularly true for the bulk drug substance manufacturer where reactors and centrifuges and piping between such large equipment can be sampled only using rinse solution samples. Any indirect test method must have been shown to correlate with the condition of the equipment. During validation, the firm should document that testing the uncleaned equipment gives a not acceptable result for the indirect test.

监控，即间接检测，如导电率测试，在清洗过程取得验证之后，就可作为常规监控的数值。尤其对那些原料药生产商来说，反应釜、离心机或大设备间的管道系统可以只是取淋洗溶液样品，这样做法是正确的。任何间接测试方法必须表明与设备的状况的相关性。在验证期间，公司必须记录不干净设备的检测（间接测试结果出现不可接受）。

V. ESTABLISHMENT OF LIMITS 确定限度

FDA does not intend to set acceptance specifications or methods for determining whether a cleaning process is validated. It is impractical for FDA to do so due to the wide variation in equipment and products used throughout the bulk and finished dosage form industries. The firm's rationale for the residue limits established should be logical based on the manufacturer's knowledge of the materials involved and be practical, achievable, and verifiable. It is important to define the sensitivity of the analytical methods in order to set reasonable limits. Some limits that have been mentioned by industry representatives in the literature or in presentations include analytical detection levels such as 10 PPM, biological activity levels such as 1/1000 of the normal therapeutic dose, and organoleptic levels such as no visible residue.

FDA 并不想设定决定清洗过程是否有效的可接受标准或方法。因为原料药和成品剂型生产工业中使用的设备和产品的巨大差异，FDA 如果设定标准或方法是不现实的。公司确定的残留物限度的理由应当合理的基于生产商对涉及的原料的知识，而且应当具有可操作性、可实现且可被证实。为了确立合理的限度，明确分析方法的灵敏度是很重要的。行业代表在著作或报告中提到的一些限度包括分析检测级别如 10ppM，生物活性级别如 1/1000 的正常治疗剂量，器官感觉级别如无可见残留物。

Check the manner in which limits are established. Unlike finished pharmaceuticals where the chemical identity of residuals are known (i.e., from actives, inactives, detergents) bulk processes may have partial reactants and unwanted by-products which may never have been chemically identified. In establishing residual limits, it may not be adequate to focus only on the principal reactant since other chemical variations may be more difficult to remove. There are circumstances where TLC screening, in addition to chemical analyses, may be needed. In a bulk process, particularly for very potent chemicals such as some steroids, the issue of by-products needs to be considered if equipment is not dedicated. The objective of the inspection is to ensure that the basis for any limits is scientifically justifiable.

检查限度确立的方法。不像化学残留物（如活性成分，非活性成分和清洁剂）已经被清楚鉴定的成品药物，原料药生产工艺中也许还有一直未进行化学鉴定的部分反应物和多余的副产品。在确定残留物限度时，只集中关注主要的反应物也许是不够的，因为也许有其他的化学衍生产物更难以除去。有的情况下，除了进

行化学分析，薄层色谱分析（TLC）也是必要的。在原料药生产工艺中，特别是某些如激素类的高活性化学制品生产中，如果设备不是专用的，必须要考虑副物的问题。检查的目的就是要保证任何限度的根据都具有科学道理。

VI. OTHER ISSUES 其他问题

a. Placebo Product *无效对照品*

In order to evaluate and validate cleaning processes some manufacturers have processed a placebo batch in the equipment under essentially the same operating parameters used for processing product. A sample of the placebo batch is then tested for residual contamination. However, we have documented several significant issues that need to be addressed when using placebo product to validate cleaning processes.

为了评估和验证清洗过程，有的生产商在设备中按照与加工成品完全相同的操作参数进行无效对照药批次生产。然后检测无效对照药批次的样品的残留物。然而，我们（FDA）有文件可以证明在使用无效药验证清洗过程时需要阐明的几个重要问题。

One cannot assure that the contaminate will be uniformly distributed throughout the system. For example, if the discharge valve or chute of a blender are contaminated, the contaminant would probably not be uniformly dispersed in the placebo; it would most likely be concentrated in the initial discharge portion of the batch. Additionally, if the contaminant or residue is of a larger particle size, it may not be uniformly dispersed in the placebo.

任何人都不能保证污染物在整个系统中是均匀分布的。例如，如果下料阀或混合机的斜槽被污染，污染物就不可能均匀分布在无效批药品中，而是很可能集中在无效批药品在最初出料的部分。另外，如果污染物或残留颗粒物较大，它也不可能均匀分布在无效批药品中。

Some firms have made the assumption that a residual contaminant would be worn off the equipment surface uniformly; this is also an invalid conclusion. Finally, the analytical power may be greatly reduced by dilution of the contaminate. Because of such problems, rinse and/or swab samples should be used in conjunction with the placebo method.

有的公司假定某一残留的污染物均匀的覆盖在设备表面，这样的结论也是不正确的。最终，分析效果会因污染物被稀释而大大削弱。基于这些问题的存在，在使用无效药批次方法时应结合淋洗液样品或擦拭取样方法。

b. Detergent *清洁剂*

If a detergent or soap is used for cleaning, determine and consider the difficulty that may arise when attempting to test for residues. A common problem associated with detergent use is its composition. Many detergent suppliers will not provide specific composition, which makes it difficult for the user to evaluate residues. As with product residues, it is important and it is expected that the manufacturer evaluate the efficiency of the cleaning

process for the removal of residues. However, 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 during the cleaning process. Thus, they should be easily removable. Otherwise, a different detergent should be selected.

如果在清洗中使用了清洁剂或肥皂，应该确定和考虑试图检测残留物时带来的难度。使用清洁剂的普遍问题就是其成分。许多清洁剂供应商不会提供清洁剂的具体成分信息，这使得使用者难以评估残留物。和产品残留物一样，生产商评估除去残留物的清洗过程的有效性也是必要的和重要的。然而，与产品残留物不同的是，在清洗后不希望有清洁剂存在（超灵敏度检测方法-量非常低）。清洁剂并不是生产工艺中的成分，加进去只是为了便于清洗。这样，它们就容易清除。另一方面，还要选择使用不同的清洁剂。

c. Test Until Clean *清洗前检测*

Examine and evaluate the level of testing and the retest results since testing until clean is a concept utilized by some manufacturers. They test, resample, and retest equipment or systems until an "acceptable" residue level is attained. For the system or equipment with a validated cleaning process, this practice of resampling should not be utilized and is acceptable only in rare cases. Constant retesting and resampling can show that the cleaning process is not validated since these retests actually document the presence of unacceptable residue and contaminants from an ineffective cleaning process.

因为有的生产商在清洗前就进行检测，所以应当考察和评估检测和重测的结果。他们要检测，重新取样，重新检测设备或系统，直到达到被认可的残留物水平。因为系统或者设备的清洗过程已经被验证过，所以不能进行重新取样，且重新取样也只适于个别情况。持续的重新取样和重新检测只能说明，清洗过程没无效，因为重新检测事实上证明了无效的清洗后仍然存在不可接受的残留物和污染物。

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