FDANEWS

MANAGEMENT REPORT

Creating a Cleaning Validation Master Plan:

Strategies for an Effective and Compliant Program

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Introduction

Most pharmaceutical manufacturers would assert that they maintain a clean production facility, and to them, cleaning validation may seem like an unnecessary burden. “Cleaning validation is nothing more than manufacturers proving to others that they can produce safe drugs,” according to one industry expert. It is a process to ensure that a manufacturer’s equipment cleaning procedures adequately remove any residue remaining in any of its manufacturing equipment to predetermined levels of acceptability.

Pharmaceutical cleaning validations are defined by the FDA and by the International Conference on Harmonisation (ICH). Equipment cleaning is a part of current good manufacturing practice (cGMP) requirements *(see Appendix A)*. The FDA spelled out the need for a systematic approach to proving the effectiveness of all the cleaning procedures performed by a drug manufacturer in its revised “Guide to Inspections: Validation of Cleaning Processes,” which was released in July 1993 *(see Appendix B)*.

Often, a manufacturer will use the same equipment for processing more than one product. Consequently, it is possible for pharmaceutical products and active pharmaceutical ingredients (APIs) to be contaminated either by other pharmaceutical products, cleaning agents and microorganisms or by other material (for example, airborne particles, dust, lubricants). Contaminants might also include raw materials, intermediates or auxiliaries.

Adequate cleaning procedures are essential to avoid contamination of products. They are even more important with drugs such as penicillin, that require sensitive sampling methods that must be applicable to each specific piece of equipment used in the manufacturing process. Sensitive analytical methods also must be used because of the possibility of contamination between products.

A cleaning validation program involves testing for acceptable residues on surfaces used in manufacturing pharmaceuticals or devices. The validation involves identifying residues, selecting the method (or methods) for residue detection, selecting the sampling method, setting residue acceptance criteria, conducting methods validation and recovery studies, writing a procedure and training operators. This procedure is used to document acceptable residues (three or more times) before putting in place a rational monitoring program to maintain a validated state.

This report addresses the steps that must be taken before cleaning validation on equipment can begin, including developing an overall plan, qualifying equipment and validating analytical methods.

The FDA has found certain types of sampling and analysis procedures to be the most acceptable in cleaning validation. Those procedures include the direct method of sampling the surface of the equipment and the use of rinse solutions. This report also will cover those procedures.

The importance of a cleaning validation master plan (CVMP) cannot be overstated. The essential components of such a plan are key to its success, which is why this report covers in-depth the objective, scope and methodology of the CVMP. A clearly stated plan is also helpful when

product transfer occurs. In recent years, many companies have established multiple locations and sometimes will move the production of a drug from one location to another. That kind of change may mean moving from one state to another or from one continent to another. If a company has a good cleaning validation process in place, then it can pass along the process to another location. Even if the process cannot be used exactly as written at the new site, it provides a good basis from which to begin.

When the FDA comes to call, it is vital for a drug manufacturer to have spelled out its standard operating procedures (SOPs) for cleaning its equipment. And, of course, documentation of those procedures and of all key activities is also essential to meeting the FDA's requirements. That documentation includes information on how drug manufacturers handle special challenges in the manufacturing process.

In one recent warning letter to a manufacturer, the FDA cited MedImmune for a variety of violations, including aseptic practices by personnel and cleaning validation status of equipment. The FDA noted that the company "did not investigate the cleaning validation status for incubators, dispensing and biological safety cabinets or the silicon rubber housing of candling lamps." In addition, manufacturing personnel did not use proper aseptic dispensing techniques to prevent microbial contamination. *(See Appendix C.)*

This report addresses all of these issues and also provides frontline strategies for manufacturers to establish an effective and, more important, compliant program that will meet the FDA's strict guidelines. The test of any cleaning validation process is whether scientific data show that the process consistently does as expected and produces a result that time after time meets predetermined specifications.

This management report includes, in part, materials presented at an FDAnews audioconference by Thomas Altmann, R&D service engineer, Ecolab.

Preparing for Cleaning Validation: Three Important Steps

A complete cleaning validation program is not easy to construct, and a pharmaceutical manufacturer may encounter some pitfalls along the way. As cleaning technology and detection methods expand, the challenges associated with developing and maintaining a scientifically sound cleaning validation program also increase. It makes sense to try to avoid potential problems; therefore, before any cleaning validation of manufacturing equipment can begin, work must be done to prepare for the program.

Industry experts recommend taking three preliminary steps to prepare for cleaning validation. These steps are as follows:

- Prepare a CVMP;
- Qualify equipment for consistent results; and
- Validate analytical methods.

Cleaning Validation Master Plan

A CVMP is a general document that should provide an overview of the complete cleaning validation project. Because it is an overview, it must include all of the various departments within the company. The people working in those various departments should become familiar with the CVMP and understand it.

General requirements must be established as a part of the CVMP, including the creation of predetermined levels of acceptability. To establish acceptable residue limits (ARLs), manufacturers evaluate various product and equipment attributes. Wide variations often exist in ARL values between different product trains and manufacturing facilities. Residue limits should be achievable, verifiable and based on the most toxic residue. Therefore, the most important objective is to prove that the ARL values determined in the cleaning validation program have been established using sound scientific reasoning.

Sampling procedures are also a vital part of the CVMP. A drug manufacturer must develop a procedure for taking samples to make sure its equipment is clean, and it must determine what kind of analytical methods it will use. More about these issues can be found in the section titled “Best Analytical and Sampling Methods.”

The format of the documents used in the CVMP can make or break the success of the plan. If the validation documents have a good, easy-to-follow format, then staff members will be in a much better position to complete any documentation appropriately. Furthermore, if anyone from outside of the company, for example, an FDA inspector or a new colleague, has the occasion to review the documents, then he or she also should be able to understand the plan. Any time a drug manufacturer can accommodate the FDA or other inspectors, the manufacturer ultimately benefits.

Equipment Qualifications

The general idea with equipment qualification is to make sure that equipment is producing the product to meet pre-fixed specifications. How can this verification best be accomplished? The FDA states its expectations in 21 CFR 211.67(a, b, & c) Equipment cleaning and maintenance:

"Equipment, i.e., hoses, temporary vessels, etc. used in the delivery of a medical drug product is considered an integral part of the drug delivery system and as such is regulated under the drug CGMPs. Any equipment used for medical use is required to be cleaned, maintained, and sanitized at appropriate intervals to prevent contamination that would alter the safety, identity, strength, quality, or purity of the drug product beyond the official requirements in the delivery of a medical product."

"Detailed written procedures should be established, and records maintained of the cleaning, sanitizing, and inspection. Another vital CGMP requirement is the assurance that all personnel involved with the equipment on the medical side are adequately trained to perform their designated functions. Problems arise from the contaminants that may be introduced while being used for industrial grade products. Equipment used for industrial products must be qualified prior to being used for medical products, i.e., should be tested for any contaminant that the equipment may have come in contact with, before a medical drug product is introduced."

As noted, a manufacturer must qualify the equipment it is using to validate that it will produce consistent results. Of all of the things a manufacturer must do during the validation phase, this step is key. For example, if a company has equipment that must be heated to a certain temperature and it must sustain that temperature for a given length of time, then the equipment must be designed for that purpose. If the equipment cannot meet those specifications, then the manufacturer also will have problems with validation.

Design Qualification

The FDA requires that the design, operation and performance of pharmaceutical manufacturing equipment also must be qualified. By doing so, a manufacturer is making certain that the equipment meets all of its own specific requirements.

When a pharmaceutical manufacturer buys a new piece of equipment to be used in the manufacture of drugs, it typically meets with the equipment supplier to discuss what that equipment will be used to make and the process by which it will be made. Then, the supplier will make a design qualification, which is the plan for construction of the equipment. As the supplier designs the equipment, he or she must document any dead ends or design problems that could interfere with proper cleaning and cleaning validation. The bottom line is, the supplier must establish that the equipment is properly designed and that the equipment is capable of producing the product in question.

Whenever a piece of manufacturing equipment is installed, all of the installations must be qualified. For example, the manufacturer must be able to track temperatures over the entire production process or check the rinse-out of cleaning agents during the cleaning process. All of the equipment installations must be working properly.

An equipment supplier may tell a drug manufacturer that it can qualify the equipment and pro-

vide documentation about it, but the supplier must have specific information about what process the manufacturer wants to run and what cleaning must be done so that the supplier can do the best possible job in manufacturing the equipment.

Qualifying Existing Equipment

If a manufacturer already has equipment in place that it has been using for some time, but has never created a CVMP or qualified its equipment, then it is possible to work backward and complete those two steps. A manufacturer already should have some documentation about all of the production batches and cleaning that have been done on the equipment. This documentation can be shown to verify that the manufacturer consistently meets requirements, provided that the manufacturer has done its homework concerning cleaning validation.

Case in point: The following case illustrates the importance of performing adequate equipment qualification on each piece of processing equipment and the problems that might result when firms fail to verify equipment supplier representations.

A pharmaceutical firm used two blenders to produce a tablet. Both blenders were from the same equipment manufacturer and had the same model number and design. Although one blender was older than the other, the supplier told the drug manufacturer that the units were "identical." The drug manufacturer took the claim at face value and did not include the older blender as part of its process validation.

The drug company marketed approximately 100 lots of tablets made using the old blender. In testing retained samples, the company found that some lots failed the content uniformity specification.

The firm's investigation traced the out-of-specification lots to one of the two "identical" blenders, namely the old one. The pharmaceutical firm's own investigation found the older blender to have a slightly smaller capacity and different operational characteristics based on revolutions per minute when run at the same settings as the newer blender.

Subsequently, the firm recalled its total production of the product made using the older blender. This extensive recall involved multiple strengths of product totaling approximately half a million bottles from U.S. and foreign consignees. The firm plans to qualify the old blender using production size lots.

Initial Cleaning of New Equipment

Another important consideration when establishing a cleaning validation program is the initial cleaning of any new equipment. If an old machine were to wear out or break down, it would mean that new equipment bought by the manufacturer for any type of improvement or replacement would be received and installed at the site while the equipment validation study is being developed. In such a case, installation is the best time to include the new equipment in the study.

Initial cleaning of any new equipment requires some special considerations. This cleaning should be performed to eliminate any kind of foreign matter or residue introduced through the moving process or processes of maintenance, fabrication or installation.

Avoiding Multiple Uses

Should a pharmaceutical manufacturer produce nonpharmaceuticals in the same equipment used with APIs? The FDA has not specifically addressed this issue in a formal document, but a basic tenet of cGMP is that equipment does not contaminate the drugs or drug purity beyond established specifications (Food, Drug, and Cosmetic Act (FDCA), Section 501(a)(2)(b)).

Some nonpharmaceuticals pose unacceptable risks of cross-contamination and product mix-ups, and should, therefore, not normally be manufactured in the same equipment used with APIs. In some cases, in addition to using separate equipment, it would even be appropriate to use a separate facility for pharmaceutical chemical manufacturing. This precaution is an internationally recognized concept. For example, the World Health Organization's "Guide to Good Manufacturing Practices" discusses the use of separate facilities for the production of certain "nonpharmaceutical products." It adds that "the production of technical poisons, such as pesticides and herbicides," should not take place on the "premises used for the manufacture of pharmaceutical products."

According to a 1996 issue of the FDA's periodic memo *Human Drug CGMP Notes* (Vol. 4, No. 2), "As a general principle, the risks posed by unanticipated mix-ups or cross-contamination should be considered with particular emphasis on chemicals: (1) Known to pose any acute or long-term toxicity concerns; or, (2) of incompletely characterized toxicity. Toxicological assessments normally include information such as acute data (e.g., LD50 determinations) using different routes of administration, mutagenicity, carcinogenicity, teratogenicity, sensitization and irritation. Investigators should be aware that lack of toxicological assessments is not uncommon. These risks are influenced by the nature and intended use of the drug products that will incorporate the API. For example, those risks may be of greater concern when the APIs will be used in dosage forms intended for: (1) large doses, (2) long-term therapy; (3) treating open wounds; (4) injection; or, (5) inhalation."

Even if an API manufacturer considers all of these issues and still determines that the nonpharmaceutical is "harmless" and can be made in the same equipment used with APIs, it is important that the manufacturer still follow cGMPs for APIs.

Validation of Analytical Methods

All analytical methods being used in a cleaning validation project must be validated in accordance with ICH Q2 principles. The ICH has published a guideline that provides information about how to validate an analytical method that gives a manufacturer some statistical data for the method, for example, "limit of quantification" or "limit of detection."

If a pharmaceutical manufacturer has prepared a CVMP, has the equipment qualification on-site and has suitable analytical methods, then the manufacturer can confidently move on to the next step in creating an effective and compliant cleaning validation program. Of course, anyone who is directly involved with the drug manufacturing process must have completed the proper training.

Best Analytical and Sampling Methods

In pharmaceutical cleaning validation, validated analytical methods should be sensitive enough to detect residuals or contaminants such as the residue of the drug being manufactured or the cleaning agent being used. These methods should be written into procedures that are made a part of the CVMP.

The primary questions to address concerning analytical methods relate to what is being analyzed and why it is being analyzed. For example, a manufacturer may want to analyze the API in the residue level limit.

Specific and Nonspecific Analysis

An analytical method may be specific or nonspecific. The choice as to which method to use must be carefully made.

A specific method (selective parameter) detects a unique compound in the presence of potential contaminants. Such methods include high performance liquid chromatography (HPLC), ion chromatography and gas chromatography (GC). In particular situations, for example, if the active ingredient in a drug is highly toxic, then a specific method is typically recommended.

A nonspecific method detects any or all compounds that produce a certain response. These methods include total organic carbon (TOC), pH and conductivity. For example, a nonspecific method, or "sum parameter," will detect all of the substances that can cause conductivity (mineral salts, sodium hydroxide, etc.).

The detection limit for each analytical method should be sufficiently sensitive to detect the established acceptable level of the residue or contaminant. In addition, the method's attainable recovery level also should be established, according to the FDA.

The table below is an overview of selective and sum parameters. These parameters are all analytical methods that are commonly seen in practice for API analysis and for determining cleaning agents.

Table 1. Overview of Selective and Sum Parameters

Selective Parameter	Sum Parameter
HPLC	TOC
GC	Conductivity
Photometric	Surface tension

Sampling Methods

The sampling method to be used depends on what is to be analyzed. The manufacturer may want to analyze an API or detergent residue. Or, it may want to perform microbiological testing. Whatever the manufacturer wants to analyze, the analytical method and sampling methods must always be adjusted to attain the sampling procedure that best fits the subject of interest.

Rinse Sampling

The most commonly used method for sampling is rinse sampling. Rinse samples allow a very large surface area to be sampled. Rinse sampling also makes it easier to sample and evaluate inaccessible systems or those that cannot be routinely disassembled. For example, if a sieve is part of the manufacturing equipment, it may be difficult to take a swab in this area. However, the sieve can be immersed in a suitable rinse agent.

Drug manufacturers may believe that they can sample the final rinse, but this approach usually does not work because the final rinse may still be bringing out substances. Therefore, the rinse sample should be taken as one more step after the final rinse is complete.

The solvent used for a rinse sampling should be able to absorb all the residues of the drug of interest. When all of the ingredients in a drug are completely water soluble, water can be used as an analytical rinse. However, in some instances — especially with APIs — it is possible that the ingredients are much more soluble in methanol or another organic solvent. If that situation is the case, then it is preferable to make a rinse with that nonwater solvent. Whatever solvent is used, it must not damage the manufacturing equipment. And, of course, it must be nontoxic to employees and the environment.

Dilution Effects

Special attention must be paid to dilution effects. There are times when a very high amount of solvent (water, organic solvent, etc.) must be used, and the detection limit is affected in a negative way. For example, if a manufacturer wants to do a rinse sampling of a 100-liter granulator with 100 liters of solvent inside, then very low levels of residue will appear on the surface because of the high amount of solvent. If there is any problem detecting the residue, an enrichment step can be taken.

An enrichment can be made with a solid phase extraction (SPE). Of the various techniques used for sample preparation, SPE now plays a prominent role. The extracted material can then be diluted out of the solid phase and brought into an HPLC, which is used to separate the components of a mixture by a variety of chemical interactions.

Keep in mind, if an enrichment step is taken, it must be validated and documented as a suitable analytical method. All steps must be described in detail.

Swab or Direct Surface Sampling

Swab sampling is preferred by the FDA. In fact, the FDA requires it and states in its guidance on validated cleaning processes that a rinse sample does not ensure the removal of the residue, especially if a drug manufacturer has a “hardly soluble substance.”

Not all swab materials are created equal. Therefore, it is important to carefully consider all aspects of the swab-sampling process when selecting swab material. For example, a manufacturer may have to analyze the residue on a stainless steel surface. The swab material must be able to remove all the leftover residue on the equipment and absorb the substances into the swab material. Whatever is found on the swab pad must then be analyzed.

A suitable medium must be selected to extract the residue from the swab. The swab material must not only take the residue off of a stainless steel surface but also must release it for analysis after a suitable solvent is added for the extraction.

The absorption and desorption process can be tricky, according to industry experts. A manufacturer must review the recovery rates for each different type of swab material. Not all swab materials have the same traits. Some have good adhesion properties and can absorb residue, but these same materials may not have good desorption properties.

The selection of good swab materials also has a bearing on the analytical side of the validation process. The adhesive used in some swabs has been found to interfere with the analysis of samples. Therefore, to avoid the appearance of "ghost peaks" or spikes in a chromatogram (analytic technology to discover the chemical composition of a product), it is important to ensure early in the process that the sampling medium and solvent used for extraction from the medium are appropriate and will not cause interference with the analysis.

Another aspect to consider when selecting swab materials is the location of the supplier. If a drug manufacturer has manufacturing sites in different states or countries, as many do, it makes sense to choose a supplier that also has locations worldwide. Close location is not only a matter of convenience but also a matter of making sure that results are comparable from one analysis to another.

Other Types of Sampling

Swab and rinse sampling are not the only types of sampling methods a manufacturer can use. For example, placebo product sampling is sometimes used, although it is not necessarily acceptable to the FDA. In this method, manufacturers will process a placebo batch in the equipment under essentially the same operating parameters used for processing a product. A sample of the placebo batch is then tested for residual contamination.

Some problems have been documented with respect to using placebo products to validate cleaning processes. For example, if the discharge valve or chute of a blender is contaminated, then the contaminant would probably not be uniformly disbursed in the placebo but would most likely be concentrated in the initial discharged portion of the batch. And, if the contaminant or residue was of a larger particle size, it may not be uniformly dispersed.

Steam sampling is another method used by some facilities. In this type of sampling, the equipment is put into a steam bath, and the water coming out of the system is analyzed. This type of sampling could provide a good indication of all water soluble and hot-water soluble substances, but it also requires time to heat up the equipment and prepare the defined steam quality, among other things, which could present more problems than the rinse and swab type of sampling.

Other Factors Affecting Sampling Method

When determining the type of sampling method to use, a manufacturer also must consider its production equipment. For example, does the company have a system with a good open area where a swab sampling can easily be done? Or, does the company have a closed system with some critical areas inside that must be cleaned?

If a cabin washer is used to clean the equipment, the company must be sure to look for dead or black spots after the cabin washer has been used. A rinse sampling and a swab sampling of the equipment should be taken.

Sampling is also dependent on the solubility of the residue left in the equipment. As previously noted, the FDA requires swab sampling to be done because it is a better method for analyzing insoluble substances. The equipment can be rinsed with a solvent and also swabbed, thereby removing the substance from the equipment and making it available for analysis.

Microbiological Testing

Microbiological testing for bacteria is another essential part of a cleaning validation program. The most important aspect of microbiological testing is finding the proper location on the equipment to conduct the tests. The sampling location for bacteria must not be done in the same area where the API and detergent samples are taken. Instead, testing for microorganisms such as germs and bacteria must be done where the bacteria are most likely to grow. In many instances, that will be anywhere there is water in the equipment.

Experts suggest conducting microbiological testing at any point where it is possible for germs to enter a piece of equipment. Entry points may occur by means of a human operator, when he or she must handle or dismantle something, or when air enters the equipment.

Cleaning Validation Master Plan Overview

"FDA Guide to Inspections Validation of Cleaning Processes" states, "The first step in a CVMP is to focus on the objective of the validation process, and we have seen that some companies have failed to develop such objectives." The CVMP has been referred to as the backbone of a good cleaning program. A good CVMP should contain all relevant information and procedures concerning cleaning validation. The five most important components of a CVMP are as follows:

- Objective;
- Scope;
- Responsibilities;
- Risk assessments; and
- Methodology.

Objective

As noted above, the FDA suggests that the objective be the focal point of a good CVMP. Industry experts recommend that when a manufacturer begins a cleaning validation project, it should be sure to include a carefully considered objective that covers what is to be accomplished with the cleaning validation project as well as sets specific and attainable goals for all of the various departments involved in the plan.

Scope

The scope of the cleaning validation project concerns the different areas that it covers. The scope may include the manufacturing of the product, the packaging area or any of the areas within the process.

Responsibilities

This portion is perhaps the most important part of the CVMP. It spells out in detail who must fulfill each role in the plan. Someone must be responsible for each step, including preparation, verification, document approval, sampling, analyses, proving analyses, sourcing of the materials and other tasks. The responsibilities must be made clear in the CVMP.

It is worth noting that recent FDA inspection trends reveal a focus on personal responsibility in violations of good manufacturing practice (GMP). Recent enforcement actions reflect how the FDA is placing great importance on the individuals responsible for a company's acts. Criminal prosecutions usually name not only the corporation but individuals as well. *(Editor's note: See the section "FDA Inspection Trends" in this report.)*

Risk Assessment

Risk-based assessment tools are used by a variety of industries to help promote an understanding of processes, to control process variability and to improve product quality. By using a risk-based approach when determining the cleaning validation requirements for existing and

prospective processes, a manufacturer can demonstrate compliance with FDA regulations and provide an efficient, effective and sustainable cleaning validation program. The approach also serves as an effective tool for the continued monitoring and control of the manufacturing processes.

The risk assessment should include the following:

- Acceptance criteria;
- Procedure to follow if equipment goes out of specification;
- Cleaning agents to be used;
- Cleaning SOP to be used;
- Sampling methods to be used;
- Worst case scenarios; and
- In-process controls to be run after cleaning.

Methodology

The CVMP should include a methodology that covers several specific issues, including the following:

- Execution of the cleaning validation program;
- Maintenance of the program; and
- Revalidation statement.

A CVMP can also be very helpful if a manufacturer wants to make a product transfer to another location. It would be difficult, however, to imagine a situation in which the CVMP from one site would transfer perfectly to another site. Therefore, the CVMP must be adapted to the conditions on each particular site.

Like most written policies, portions of the CVMP are likely to change over time. Therefore, it makes sense to plan to review the document at regular intervals to make sure it is still relevant.

Key Points for a Cleaning Validation Project

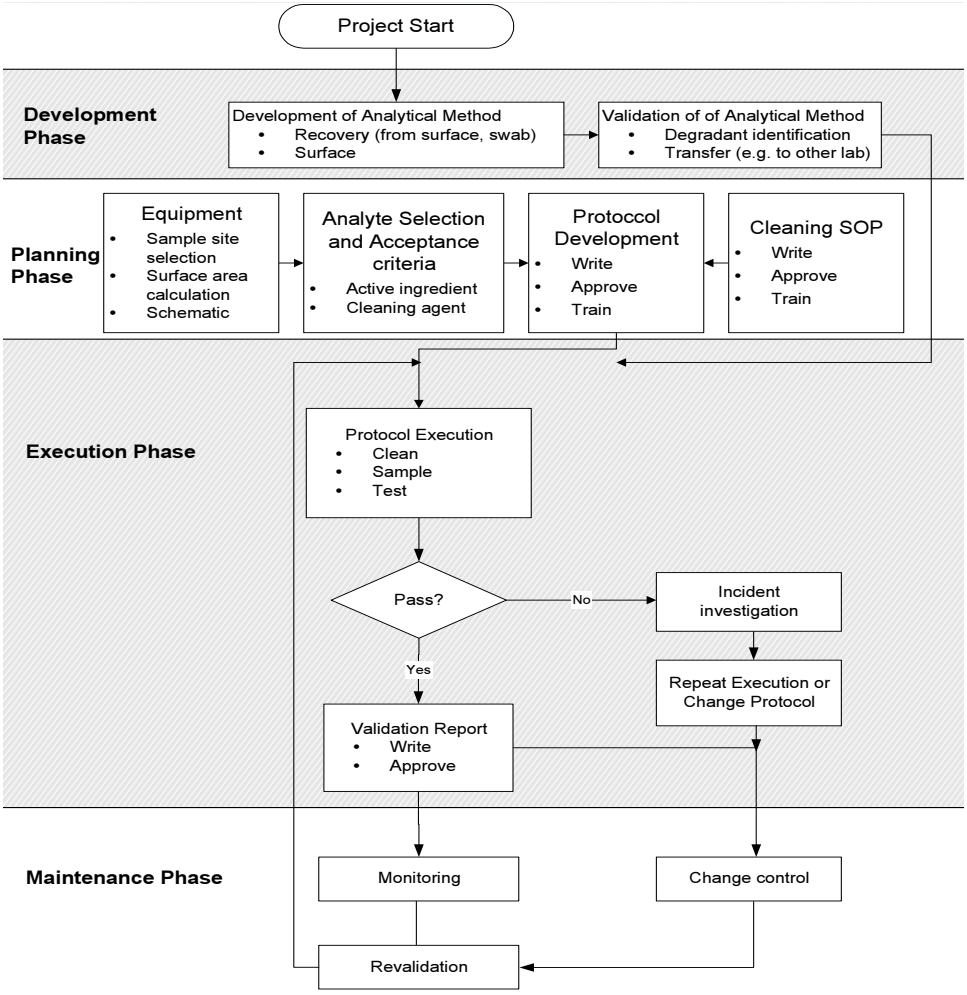
The following flowchart (Figure 1) illustrates the various phases of a cleaning validation project. The different phases of the project are listed on the left side of the chart.

The first phases of the project are primarily done from a desk. The development phase of the project includes upfront work in the lab to develop analytical methodology and validation of that methodology. Next is a planning phase, which includes looking at the manufacturing equipment, but it has not yet reached the hands-on equipment phase.

In the execution phase, the real hands-on work begins. The cleaning, testing and analysis of the equipment takes place.

After all of the executions have been done, all the tests have been passed, the samples have been taken, and the equipment is clean, a validation report must be written and approved. Finally, the maintenance phase is implemented, along with a monitoring and revalidation section.

Figure 1. Phases of a Cleaning Validation Project



Documentation and Standard Operating Procedures for Cleaning

In a thorough cleaning validation program, it is necessary to document all the procedures that are connected with cleaning agents and testing equipment. The selection of a cleaning agent depends on a variety of issues, including the following:

- Type of residue to be cleaned;
- Mode of application (clean in place, or (CIP); clean out of place); manual process. If a manual process is in place, the cleaning agent must be suitable for it so that workers are not harmed by the cleaning agent;
- Material compatibility;
- Ecological and toxicological profile; and
- Appropriate analytical methods. A supplier may be able to provide information as to what kind of methods can be used to analyze this cleaning agent in the parts-per-million range.

Detergents

Although detergents are sometimes used as cleaning agents, the FDA is not necessarily in favor of them. "FDA Guide to Inspections, Validation of Cleaning Processes" states the FDA's opinion of detergents (V1.b.): "A common problem associated with detergent use is the composition. Many detergent suppliers will not provide specific composition [to their customers]." If a manufacturer buys a detergent for equipment cleaning, the company must determine what the detergent is made of so it knows what kind of chemicals are being introduced into its manufacturing system.

"FDA Guide to Inspections, Validation of Cleaning Processes" goes on to say, "It is expected that no (or for ultra sensitive analytical test methods — very low) detergent levels remain after cleaning. … They should be easily removable. Otherwise, a different detergent should be selected."

The Pharmaceutical Inspection Convention (PIC) also has requirements with respect to the use of detergents for cleaning. It states the following in PI 006-2: July 2004:

- Define acceptable limits for detergent;
- Determine the composition of detergents before using;
- Ask for notification of any critical changes in the formulation of the detergent; and
- Consider detergent breakdown when validating cleaning.

Detergent Documentation

Standard documentation should be provided by a supplier when cleaning agents are purchased. The standard documents should include a product data sheet, material safety data sheet, ecological evaluation and toxicological evaluation.

To conduct a cleaning validation program, however, drug manufacturers should obtain specific documentation from suppliers about any cleaning agents it intends to use to clean equipment. The following outlines the desired documentation:

- Formulation must be unchanged;
- Certain critical substances must be avoided, including:
    - Toxicological (including an LD50 value);
    - Ecological; and
    - Rinse properties of raw materials (for example, quaternary ammonium compounds that are very difficult to remove).
- Colorants and perfumes must be avoided (these are cosmetic, not necessary for proper cleaning);
- Available analytical methods;
- Breakdown of substances must be considered (ask supplier); and
- GMP production (not required, but many companies ask for it, depending on their internal policies).

Using the Appropriate Cleaning Agent

For best results, industry experts advise drug manufacturers to always use the appropriate chemistry for cleaning. That is, they should consider the conditions in which a cleaning agent works best. For example, a manual cleaner is primarily useful for manual cleaning, and a CIP cleaner is meant for cleaning in place. Most of the time, a supplier can provide a manufacturer with the information about which cleaner works best in which specific situations.

Documentation of Equipment Testing

The FDA requires drug manufacturers to provide certain documentation with respect to the testing of production equipment. The following should be included in this documentation:

- Numeration for recognition (providing a system of symbols or numbers to items in a group);
- Software approval, which includes the backup system, installation, security, ease of installation, transparent data storage (system configuration);
- Logbook;
- Maintenance records;
- Reference materials used; and
- Training records for special analysts.

A logbook, as mentioned, can be a helpful resource in documenting the testing of equipment and in providing information with respect to the work that has been done in a cleaning valida-

tion program. The logbook may include the samples that have been analyzed, calibrations, documentation of equipment maintenance, steps toward reconditioning, documentation of reference material and training records for specific staff members.

A log may be included in a company's software program. If not, a manual logbook is also valuable. It is worth noting that the FDA does, in fact, take note of the logbooks used by drug manufacturers — and will regularly inspect them. In an excerpt from an FDA warning letter dated April 28, 2006, to Pliva Croatia, the FDA cites the company for poor record keeping as follows:

> "Laboratory records did not always include a description and identification of the sample received for testing, the date the sample was taken, the date the sample was received for testing and the data derived from the testing.
>
> There was no record that the laboratory received personnel monitoring samples of one person for the [redacted] fills of [redacted] and [redacted] There was no record of analysis, yet the results were reviewed as acceptable. We are concerned about the failure to effectively review records at your facility.
>
> In addition, analysts in the [redacted] Microbiology Laboratory do not enter the date on which the results are read into the logbook. Your proposed corrective action appears acceptable, but again there were several logbook recordkeeping deficiencies noted on the previous FDA 483 dated 8/30/2002."

Special Challenges in Cleaning Validation

Pharmaceutical manufacturers should be aware of special challenges that may arise in a cleaning validation project. Certain types of equipment, utensils and procedures may create such challenges, according to industry experts. Three examples of potential problem areas in a cleaning validation program include the small parts washer, the coater and the manual cleaning of equipment.

Small Parts Washer

When a drug manufacturer uses a small parts washer, it can be easy to simply place the parts into the washer, push a button and then walk away. If the washer is not inspected and carefully cleaned, however, deposits can form in the equipment. Routine cleaning is not sufficient to address these deposits because the rotating and spray devices in the equipment cannot reach every part of the small parts washer.

The solution is to look at the washer as more than just a black box into which various parts are placed. Keep in mind that there is something going on inside of the box that requires maintenance. A daily maintenance wash will help to get rid of any deposits that have formed.

Coater

In the coating process, very low mechanical actions and very low temperature are necessary. A coater may be nothing more than a rotating drum and, in a worst case scenario, a company may use only hot water to clean it.

With a coater, as is the case with any piece of machinery used to produce drugs, the proper chemical must be chosen for cleaning it. The proper cleaning time is also important. Some experts suggest using the rinse and swab method of cleaning, but they suggest adding manual cleaning on this piece of equipment as well.

Manual Cleaning

Inherent in manual cleaning are a number of possibilities for problems to occur. It is necessary to fix all the parameters and requirements for the dismantling of the equipment, including any special tools that must be used to take the equipment apart.

The proper cleaning materials must be selected. For example, the process may require rinsing from a particular side of the equipment because of the way the equipment is installed. If so, this fact must be documented.

The water quality and water temperature also may be important in manual cleaning. If a product contains pigments, it may be necessary to use softened water for cleaning before tap water is used. Very often, the detergent and disinfectants are a critical issue because not all detergents can be used in a manual application.

Finally, manual cleaning procedures require periodic verification that they are still valid. Included in that effort is the establishment of maintenance and cleaning schedules, assigning responsibility for cleaning and maintaining equipment, and an ongoing training program for those who conduct the cleaning procedures.

It may be easy to say that one will clean every day, but industry experts indicate that it does not always happen that way. In fact, some pharmaceutical manufacturers designate a semiannual "cleaning day" just to verify that they have manual cleaning procedures under control.

FDA Inspection Trends

When agency inspectors perform a routine inspection, they can be expected to look at certain systems. For example, they always look at Quality Assurance (QA, also known as Quality Control). They may also look at facilities and equipment, materials, production, packaging and labeling, and cleaning validation. They are checking to see that change control is documented, evaluated and approved and that the need for revalidation has been assessed.

A good FDA inspector may ask for a list of all a manufacturer's recent change control requests to see how long the changes have been in process. The agency will see red flags (and so should the manufacturer) if they see such things as a large number of pending change requests, changes performed without QA knowledge and approval, the existence of a "bootleg" system to avoid formal procedures or lack of a monitoring system to routinely check trends.

Device Requirements

For devices, the FDA routinely inspects one or two systems, focusing on four key aspects: design controls, management controls, production and process controls, and corrective and preventive actions (CAPAs). For example, with design controls, the FDA inspectors will look to see whether documentation and control of design changes begins when initial design inputs are approved and continues for the life of the project. They will also look to see whether postproduction design changes loop back into design controls and whether all changes were controlled using validation or verification.

Biologics

Because biologic products are more susceptible to contamination, the FDA will check to see whether a manufacturer is controlling for the prevention of contamination in the manufacturing process. That inspection will likely include a review of the manufacturer's cleaning validation program. A review of recent warning letters from the FDA reveals that the agency is citing companies for not maintaining proper cleaning procedures. Also, the FDA is confirming that any changes that were made have been validated using an approved protocol and that the validation is adequately documented.

Focus on Personal Responsibility

It is well worth noting that FDA inspectors also have been focusing on determining which individuals are responsible for GMP violations found during inspections. Recent enforcement actions reflect how the FDA places great importance on individual responsibility for a company's acts, according to industry insiders. For example, warning letters are typically addressed to a company's president and CEO, and criminal prosecutions usually name individuals as well as the corporation.

Because of this focus, agency investigators are trained to look for and develop evidence on which person to charge in a regulatory action resulting from an inspection. (The FDCA is a strict liability statute, which means that the FDA does not have to show a person intended to violate the law to charge the company or individual with a violation.)

Inspectors look at which employees have the duty and power to detect, prevent and correct the violation as well as at who had the responsibility to do so. To document each employee's responsibilities, duties and power, inspectors may ask questions about an employee's direct reports, supervisors and limits on his or her authority to act without higher approval.

The FDA's "Investigators Operations Manual" instructs investigators to consider questions such as the following:

- Who knew of violative conditions;
- Who should have known of the conditions;
- Who ordered steps to correct the conditions; and
- Who approved or denied steps to correct the conditions.

Observation of how employees work together in the firm during the inspection helps investigators determine who is responsible, according to experts. Investigators will look for employees who issue orders, employees who react to orders, employees who show understanding of the equipment and manufacturing issues, and employees who supervise others.

Inspectors also look at what other employees say about who is in charge, whose approval is necessary and who overrules whom. Inspectors need to find out the differences between what the organization chart says and what real-life authority and functions in the office are like, insiders said. They can use statements as leads and will look for documented evidence to support them.

Employees should avoid misrepresenting the extent of their authority, blaming others and giving the FDA inspectors documents that are beyond the scope of their inspection authority. Employees also should make sure that sensitive documents are out of plain sight.

To determine responsibility, investigators also may talk to people outside the company, including contractors, consultants and pest control services.

FDA inspectors typically look at the following:

- Drug product: Quality Control unit procedures and whether production and process control SOPs are lacking;
- Devices: Design change procedures, corrective and preventive action plan procedures, quality audits, management controls;
- Biologics: unit oversight, quality agreements with contract manufacturers, underreporting of changes in annual reports, incomplete supplements being received;
- Good clinical practices: Failure to ensure that investigations are done according to an investigational plan, failure to submit accurate reports to the institutional review board; and
- Good laboratory practices: Outdated SOPs that do not reflect current practice, the existence of "maverick" SOPs.

Manufacturers will be one step ahead in the game if they have a good idea of what to expect when the FDA inspectors pay a visit. A good CVMP is important. Also important is an effective change-control system that not only helps to solve problems but serves to monitor performance and site shifts that might indicate a future problem as well.

(Editor's note: For more information about FDA inspection procedures, manufacturers may want to review the agency's compliance program guidance manuals. View or download these documents on the FDA web site at www.fda.gov/ora/cpgm.)

FAQs

This Q&A is taken, in part, from an FDAnews audioconference by Thomas Altmann, R&D service engineer, Ecolab.

Q: *What is the most difficult aspect of implementing a good cleaning validation program?*

A: The key factor is bringing all of the different departments and all the people in those departments together, creating a structure for working together so everyone knows his or her job and there is enough capacity to run the program.

Q: *It is the first time cleaning a fermenter. What are the areas that a pharmaceutical manufacturer should watch for?*

A: In the fermentation process, very often some silicon is incorporated into the process for defoaming properties. In that case, there could be a layer of silicon oil left behind that must be carefully cleaned to avoid bringing some of that substance into the next fermentation batch.

What is very often seen in fermentation is that after the fermentation is ready and the product is made, an enrichment is made. The fermenter must be inactivated before cleaning can take place. Often, there will be strongly burned-on residues that are difficult to clean.

In this instance, CIP methods should be used to clean process equipment and storage vessels before sterilization in place is performed. CIP methods might include fill-and-soak-agitate systems, solvent refluxing, high-impact spray cleaning, spray cleaning by sheeting action or turbulent flow systems.

Q: *How can a drug manufacturer know whether there has been a degradation of a product?*

A: The most practical way to determine whether a degradation has occurred is to take a product and incorporate it or incubate it with the chemical cleaning agent in the concentration that the manufacturer expects to have during the cleaning process. For example, if a manufacturer knows that it can generally find 0.2 ppm of an active pharmaceutical ingredient, then an appropriate person should incubate it for the cleaning time, say, 20 minutes at 60 degrees Celsius. After 20 minutes, he or she should check to see whether there is still 0.2 ppm of the ingredient. If it is gone, then appropriate personnel should consider what is happening and what are the possible reactions — for example, what can take place in strong alkaline or in strong acid or with active oxygen or whatever agent is used for cleaning. In other words, the process should involve taking the cleaning agent and the active ingredient and putting them together to see whether they produce a reaction.

Q: *How often should a drug manufacturer monitor its cleaning process? And, what should be included in the monitoring process?*

A: Normally, some in-process controls should first be established. These should be easy-to-measure things such as conductivity and temperature control. Try the cleaning process three times (using three batches) to be sure that the process achieves consistent results over all three batches. Why three times? According to one industry insider, an FDA agent was once asked,

"Why do three batches?" The answer was because if it comes out right once, it is an accident; twice, a coincidence; and three times, a validation.

Next, go on to the monitoring process. For example, monitor pH by conductivity, by online TOC, etc. This monitoring should be done at each cleaning. The procedures should be established in the standard operating cleaning procedure, including the kind of parameters that are relevant for this particular cleaning process.

All the data that arise from this monitoring process should be included in a logbook, and after a period of time, perhaps once a year or every two years, those data should be reviewed. This approach is the way to be certain that the process is still valid.

Q: *What is a good approach to determining and specifying an acceptable rinse limit? And, in calculating this rinse limit in practice, when is it appropriate to take surface area or volume into account?*

A: There is a standard calculation of rinse limits that is done by using the minimum therapeutic dose of an API. For cleaning agents or detergents, there is no therapeutic dose because it is just a cleaner. But, because it is being used frequently, it also should be documented that there is an LD50 value that can be used. This value should be taken into account, and then nearly the same calculation as for the therapeutic dose should be done.

Concerning the surface area or volume, it is a matter of what kind of sample one would like to make. If a swab sample must be taken, then one must consider either the surface area to be swabbed in relation to the complete inner surface or the product contact surface of the equipment. Then it can be said that the surface area is really relevant for limit calculations.

If the volume approach is taken, however, and one makes an analytical rinse, then one must consider the volume used for the rinse. And, one must make sure that this volume can completely cover the entire inner surface with which the product comes into contact.

For example, say a manufacturer uses a 100-liter container and does a rinse with just 20 liters of water by a spray ball. The advantage is that this process uses a lower limit of water, which is good for the limit of detection. If it is certain that the entire inner surface of this container is covered, then that surface area is what should be taken into account for a swab sample.

Q: *Say a company has equipment that uses separate parts in the manufacturing process. For example, perhaps there is a chamber and a pipe that would be taken apart for cleaning purposes. Therefore, should there be one analytical result for the chamber and another analytical result for the pipe? If there is a specific limit, can the company essentially use additive results for each of those sections?*

Suppose there were a limit of 10 ppm overall. The chamber happened to indicate 12 ppm, but the pipe indicated only 1 ppm. Are those results still under the limit, or would one section fail because it was over the limit?

A: Typically, each part should be under the limit, meaning that, in this situation, if the measurement is at 12 ppm, then this point of sampling is not completely clean.

Of course, the additive approach can be taken, but an FDA or PIC inspector might suggest that the situation could be improved by using a spray ball or by enhancing the cleaning temperature to bring the part under the limit.

Say that a manufacturer has a blender or mixer as well as a coater, all of which are used in the production of a drug. The manufacturer should look at each piece of equipment individually and be certain that the limits make sense for the entire system.

Q: *What can be done about "unknown peaks" and can they be used to calculate total residue?*

A: Unknown peaks or "ghost peaks" can occur as a result of rapid changes in solvent composition. It makes sense to find out where they are originating by conducting qualitative tests to determine whether there has been any contamination. Often, companies use the HPLC method with fluorescence detection. Then they start to make HPLC coupled with mass spectroscopy to find out the molecular weight and to verify what kind of molecule it could be, because they know what chemicals are used in the equipment.

When a company discovers what is causing the peaks, it can conduct a risk assessment, determining whether it is really a risk to have the unknown peaks. Is it an acceptable risk, or is it a critical issue? Do the peaks have to be incorporated into the cleaning validation?

Q: *If one is truly interested only in the API when validating the actual swab method, does one use the full product to test for interferences? Or, is it generally just a question of looking at the API? Should the company spike the plate with API or spike the plate with the product?*

A: Many people conducting a risk assessment might say, for example, "I know I am producing a pill that contains lactose. Lactose is easily water soluble, but my API is very hard water soluble." They conduct a risk assessment and say, "Yes, I can now assume that only API is left over on the equipment and I can make recovery studies on it."

Others might wait and use their finished product, which would include all possible interferences.

Q: *How does one establish the limit for carryover of API if there isn't much information available? For example, perhaps a producer has an investigational drug and doesn't yet know the lowest therapeutic dose. Is there some kind of industry standard limit such as 10 ppm or 5 ppm of API carryover?*

A: The FDA accepts 10 ppm of any substances coming into the next batch, but if there is little information about the drug, then it can be a problem. What some producers do is consider their most potent drug and make the calculations on the surface residues based on this most potent ingredient. If they are making an investigational drug, they will just take half of it, to be safe. That is, take the general limit of 10 ppm of that API carrier, but not the total product.

Q: *What should the micro limits be for equipment producing nonsterile, solid, all-dose forms?*

A: There is no industry standard for this type of equipment, but many microbiological experts suggest that producers must look to the process and find out what would be harmful to the

product. Consider what kind of germs might be seen, and set the limit as low as possible. A company also might have a list of "critical bugs" that it would not like to encounter.

The issue of microbes in a nonsterile area is quite critical. But it is best considered on a case-by-case basis, according to experts.

Q: *I have a cleaning process validated for dedicated equipment, and I want to move to using that equipment for multiple products. What approach should be taken? Is a revalidation of the cleaning process necessary?*

A: First of all, look at the new products to be produced. Are they more critical than the old products or has the more critical product already been validated on the dedicated equipment? Also, consider the worst-case ingredient.

Then, make ensure verification that the cleaning of the new product is the same as the old product. If true, then the existing cleaning validation process can be used for the new products, too. It is important to verify that all the other products one intends to use in the equipment are also cleaned in the same way, with the same process.

Conclusion

A cleaning validation process is used in the manufacturing of drugs to prove that the cleaning system performs as expected and provides scientific data that consistently meet predetermined specifications for the residuals. The cleaning validation process must be written into detailed protocols and SOPs that are specific for the different pieces of equipment and instrumentation used by a facility for each type of drug product being produced. Additional protocols and SOPs based on the type of product manufactured or process used (such as a batch or bulk process or shared versus dedicated equipment) are required if cleaning is performed.

Before any cleaning program can begin, however, certain specific steps should be taken in preparation. These steps include equipment qualification, validation of analytical methods to be used and, most important, preparation of a CVMP.

The CVMP is a general document that provides an overview about the complete cleaning validation project. It has been referred to as the backbone of a good cleaning program. The CVMP should contain all relevant information and procedures concerning cleaning validation, including five important components. One of the components is the objective, which has been endorsed by the FDA. In fact, the FDA suggests that the objective be the focal point of a good CVMP. Industry experts recommend that when a manufacturer begins a cleaning validation project, it should be sure to include a carefully considered objective.

A good CVMP should include a risk assessment methodology. Risk-based assessment tools are used by a variety of industries to help promote an understanding of processes, to control process variability and to improve product quality. By using a risk-based approach when determining its cleaning validation requirements, a manufacturer can demonstrate compliance with FDA regulations and provide an efficient and effective cleaning validation program. The approach also serves as an effective tool for the continued monitoring and control of the manufacturing processes.

In pharmaceutical cleaning validation, validated analytical methods and sampling methods sensitive enough to detect residuals or contaminants should be in place. The method could be a specific method used to analyze a particular API, or it could be used to analyze a parameter such as the TOC content of rinse water.

The detection limit for each analytical method should be sufficiently sensitive to detect the established acceptable level of the residue or contaminant. And, the method's attainable recovery level should also be established, according to the FDA.

The sampling method to be used depends on what a manufacturer wants to analyze. A manufacturer may want to analyze an API or detergent residue. Or, it may want to perform microbiological testing. Swab sampling is preferred by the FDA. In fact, the FDA requires it and states in its guidance on validated cleaning processes that a rinse sample does not ensure the removal of the residue, especially if a drug manufacturer has a "hardly soluble substance." Whatever the manufacturer wants to analyze, the analytical method and sampling methods must always be adjusted to attain the sampling procedure that best fits the subject of interest.

As part of a cleaning validation program, drug manufacturers should also create documentation and SOPs for cleaning agents and testing equipment. In a cleaning validation program, it is necessary to document all the procedures that are connected with cleaning agents and testing equipment. The selection of a cleaning agent is dependent on a variety of issues, including the type of residue to clean, the mode of application, ecological profile and the analytical methods to be used.

As for documenting the testing of equipment, the use of a logbook can be a helpful resource, providing information with respect to the work that has been done in a cleaning validation program. The logbook may include the samples that have been analyzed, calibrations, documentation of equipment maintenance, steps toward reconditioning, documentation of reference material, and training records for specific staff members.

Despite the best laid plans there are times when disasters occur. In fact, there are certain types of equipment and certain utensils that frequently create special challenges, and facilities must be careful not to fall prey to the problems they can bring.

For example, when a facility uses a small parts washer, it can be easy to simply place the parts into the washer, push a button and then walk away. If the washer is not inspected and carefully cleaned, however, deposits can form in the equipment contaminating the parts that are being washed. This buildup can happen because the manufacturer doesn't perform proper maintenance on the washer. A routine cleaning is not sufficient to properly clean the washer. What is needed is a maintenance wash each day to get rid of any deposits that may have formed.

The solution to these challenges is to be alert to possible problems. Some industry experts even suggest a regular "cleaning day" that can be used to look for any unusual problems and to verify that a cleaning program is still valid.

All of the foregoing and more make up a solid cleaning validation program. Documentation of the cleaning validation system will attest that the process is in control and cleans as expected. The report also should detail when and why revalidation needs to take place because no program can be assumed to be reliable forever.

FDANEWS

APPENDICES

Creating a Cleaning Validation Master Plan:

Strategies for an Effective and Compliant Program

Creating a Cleaning Validation Master Plan: Strategies for an Effective and Compliant Program

Appendices

(Click on the title below to view a document.)

Appendix A. Guidance for Industry — Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients (API)

Appendix B. Guide to Inspections: Validation of Cleaning Processes

Appendix C. FDA Warning Letter to MedImmune, dated May 24, 2007

Guidance for Industry

Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
August 2001
ICH

Guidance for Industry

Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients

Additional copies are available from:

Office of Training and Communications
Division of Communications Management
Drug Information Branch, HFD-210
5600 Fishers Lane
Rockville, MD 20857
(Tel) 301-827-4573
(Internet) http://www.fda.gov/cder/guidance/index.htm

or

Office of Communication, Training and
Manufacturers Assistance, HFM-40
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike, Rockville, MD 20852-1448
Internet: http://www.fda.gov/cber/guidelines.htm.
Fax: 1-888-CBERFAX or 301-827-3844
Mail: the Voice Information System at 800-835-4709 or 301-827-1800

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
August 2001
ICH

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Guidance for Industry[1]
Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients

I. INTRODUCTION (1)

A. Objective (1.1)

This document is intended to provide guidance regarding good manufacturing practice (GMP) for the manufacturing of active pharmaceutical ingredients (APIs) under an appropriate system for managing quality. It is also intended to help ensure that APIs meet the quality and purity characteristics that they purport, or are represented, to possess.

In this guidance, the term *manufacturing* is defined to include all operations of receipt of materials, production, packaging, repackaging, labeling, relabeling, quality control, release, storage and distribution of APIs and the related controls. In this guidance, the term *should* identifies recommendations that, when followed, will ensure compliance with CGMPs. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes. For the purposes of this guidance, the terms *current good manufacturing practices* and *good manufacturing practices* are equivalent.

[1] This guidance was developed within the Expert Working Group (Q7A) of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and has been subject to consultation by the regulatory parties, in accordance with the ICH process. This document has been endorsed by the ICH Steering Committee at *Step 4* of the ICH process, November 2000. At *Step 4* of the process, the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan, and the United States.

Arabic numbers in subheadings reflect the organizational breakdown in the document endorsed by the ICH Steering Committee at Step 4 of the ICH process, November 2000.

The guidance as a whole does not cover safety aspects for the personnel engaged in manufacturing, nor aspects related to protecting the environment. These controls are inherent responsibilities of the manufacturer and are governed by national laws.

This guidance is not intended to define registration and/or filing requirements or modify pharmacopoeial requirements. This guidance does not affect the ability of the responsible regulatory agency to establish specific registration/filing requirements regarding APIs within the context of marketing/manufacturing authorizations or drug applications. All commitments in registration/filing documents should be met.

B. Regulatory Applicability (1.2)

Within the world community, materials may vary as to their legal classification as an API. When a material is classified as an API in the region or country in which it is manufactured or used in a drug product, it should be manufactured according to this guidance.

C. Scope (1.3)

This guidance applies to the manufacture of APIs for use in human drug (medicinal) products. It applies to the manufacture of sterile APIs only up to the point immediately prior to the APIs being rendered sterile. The sterilization and aseptic processing of sterile APIs are not covered by this guidance, but should be performed in accordance with GMP guidances for drug (medicinal) products as defined by local authorities.

This guidance covers APIs that are manufactured by chemical synthesis, extraction, cell culture/fermentation, recovery from natural sources, or any combination of these processes. Specific guidance for APIs manufactured by cell culture/fermentation is described in Section XVIII (18).

This guidance excludes all vaccines, whole cells, whole blood and plasma, blood and plasma derivatives (plasma fractionation), and gene therapy APIs. However, it does include APIs that are produced using blood or plasma as raw materials. Note that cell substrates (mammalian, plant, insect or microbial cells, tissue or animal sources including transgenic animals) and early process steps may be subject to GMP but are not covered by this guidance. In addition, the guidance does not apply to medical gases, bulk-packaged drug (medicinal) products (e.g., tablets or capsules in bulk containers), or radiopharmaceuticals.

Section XIX (19) contains guidance that only applies to the manufacture of APIs used in the production of drug (medicinal) products specifically for clinical trials (investigational medicinal products).

An *API starting material* is a raw material, an intermediate, or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. An API starting material can be an article of commerce, a material

purchased from one or more suppliers under contract or commercial agreement, or produced in-house. API starting materials normally have defined chemical properties and structure.

The company should designate and document the rationale for the point at which production of the API begins. For synthetic processes, this is known as the point at which API starting materials are entered into the process. For other processes (e.g., fermentation, extraction, purification), this rationale should be established on a case-by-case basis. Table 1 gives guidance on the point at which the API starting material is normally introduced into the process.

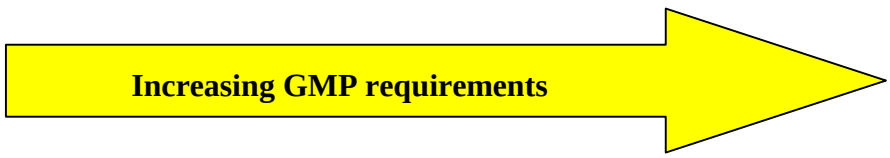
From this point on, appropriate GMP as defined in this guidance should be applied to these intermediate and/or API manufacturing steps. This would include the validation of critical process steps determined to impact the quality of the API. However, it should be noted that the fact that a company chooses to validate a process step does not necessarily define that step as critical.

The guidance in this document would normally be applied to the steps shown in gray in Table 1. However, all steps shown may not need to be completed. The stringency of GMP in API manufacturing should increase as the process proceeds from early API steps to final steps, purification, and packaging. Physical processing of APIs, such as granulation, coating or physical manipulation of particle size (e.g., milling, micronizing) should be conducted according to this guidance.

This GMP guidance does not apply to steps prior to the introduction of the defined API starting material.

Table 1: Application of this Guidance to API Manufacturing

Type of Manufacturing	**Application of this guidance to steps (shown in gray) used in this type of manufacturing**				
Chemical Manufacturing	Production of the API starting material	Introduction of the API starting material into process	Production of Intermediate(s)	Isolation and purification	Physical processing, and packaging
API derived from animal sources	Collection of organ, fluid, or tissue	Cutting, mixing, and/or initial processing	Introduction of the API starting material into process	Isolation and purification	Physical processing, and packaging
API extracted from plant sources	Collection of plant	Cutting and initial extraction(s)	Introduction of the API starting material into process	Isolation and purification	Physical processing, and packaging
Herbal extracts used as API	Collection of plants	Cutting and initial extraction		Further extraction	Physical processing, and packaging
API consisting of comminuted or powdered herbs	Collection of plants and/or cultivation and harvesting	Cutting/ comminuting			Physical processing, and packaging
Biotechnology: fermentation/ cell culture	Establish-ment of master cell bank and working cell bank	Maintenance of working cell bank	Cell culture and/or fermentation	Isolation and purification	Physical processing, and packaging
"Classical" Fermentation to produce an API	Establish-ment of cell bank	Maintenance of the cell bank	Introduction of the cells into fermentation	Isolation and purification	Physical processing, and packaging



II. QUALITY MANAGEMENT (2)

A. Principles (2.1)

Quality should be the responsibility of all persons involved in manufacturing.

Each manufacturer should establish, document, and implement an effective system for managing quality that involves the active participation of management and appropriate manufacturing personnel.

The system for managing quality should encompass the organizational structure, procedures, processes and resources, as well as activities to ensure confidence that the API will meet its intended specifications for quality and purity. All quality-related activities should be defined and documented.

There should be a quality unit(s) that is independent of production and that fulfills both quality assurance *(QA)* and quality control *(QC)* responsibilities. The quality unit can be in the form of separate QA and QC units or a single individual or group, depending upon the size and structure of the organization.

The persons authorized to release intermediates and APIs should be specified.

All quality-related activities should be recorded at the time they are performed.

Any deviation from established procedures should be documented and explained. Critical deviations should be investigated, and the investigation and its conclusions should be documented.

No materials should be released or used before the satisfactory completion of evaluation by the quality unit(s) unless there are appropriate systems in place to allow for such use (e.g., release under quarantine as described in Section X (10) or the use of raw materials or intermediates pending completion of evaluation).

Procedures should exist for notifying responsible management in a timely manner of regulatory inspections, serious GMP deficiencies, product defects and related actions (e.g., quality-related complaints, recalls, and regulatory actions).

B. Responsibilities of the Quality Unit(s) (2.2)

The quality unit(s) should be involved in all quality-related matters.

The quality unit(s) should review and approve all appropriate quality-related documents.

The main responsibilities of the independent quality unit(s) should not be delegated. These responsibilities should be described in writing and should include, but not necessarily be limited to:

1. Releasing or rejecting all APIs. Releasing or rejecting intermediates for use outside the control of the manufacturing company

2. Establishing a system to release or reject raw materials, intermediates, packaging, and labeling materials

3. Reviewing completed batch production and laboratory control records of critical process steps before release of the API for distribution

4. Making sure that critical deviations are investigated and resolved

5. Approving all specifications and master production instructions

6. Approving all procedures affecting the quality of intermediates or APIs

7. Making sure that internal audits (self-inspections) are performed

8. Approving intermediate and API contract manufacturers

9. Approving changes that potentially affect intermediate or API quality

10. Reviewing and approving validation protocols and reports

11. Making sure that quality-related complaints are investigated and resolved

12. Making sure that effective systems are used for maintaining and calibrating critical equipment

13. Making sure that materials are appropriately tested and the results are reported

14. Making sure that there is stability data to support retest or expiry dates and storage conditions on APIs and/or intermediates, where appropriate

15. Performing product quality reviews (as defined in Section 2.5)

C. Responsibility for Production Activities (2.3)

The responsibility for production activities should be described in writing and should include, but not necessarily be limited to:

1. Preparing, reviewing, approving, and distributing the instructions for the production of intermediates or APIs according to written procedures

2. Producing APIs and, when appropriate, intermediates according to pre-approved instructions

3. Reviewing all production batch records and ensuring that these are completed and signed

4. Making sure that all production deviations are reported and evaluated and that critical deviations are investigated and the conclusions are recorded

5. Making sure that production facilities are clean and, when appropriate, disinfected

6. Making sure that the necessary calibrations are performed and records kept

7. Making sure that the premises and equipment are maintained and records kept

8. Making sure that validation protocols and reports are reviewed and approved

9. Evaluating proposed changes in product, process or equipment

10. Making sure that new and, when appropriate, modified facilities and equipment are qualified

D. Internal Audits (Self Inspection) (2.4)

To verify compliance with the principles of GMP for APIs, regular internal audits should be performed in accordance with an approved schedule.

Audit findings and corrective actions should be documented and brought to the attention of responsible management of the firm. Agreed corrective actions should be completed in a timely and effective manner.

E. Product Quality Review (2.5)

Regular quality-reviews of APIs should be conducted with the objective of verifying the consistency of the process. Such reviews should normally be conducted and documented annually and should include at least:

- A review of critical in-process control and critical API test results
- A review of all batches that failed to meet established specification(s)
- A review of all critical deviations or nonconformances and related investigations
- A review of any changes carried out to the processes or analytical methods;
- A review of results of the stability monitoring program

- A review of all quality-related returns, complaints and recalls
- A review of adequacy of corrective actions

The results of this review should be evaluated and an assessment made of whether corrective action or any revalidation should be undertaken. Reasons for such corrective action should be documented. Agreed corrective actions should be completed in a timely and effective manner.

III. PERSONNEL (3)

A. Personnel Qualifications (3.1)

There should be an adequate number of personnel qualified by appropriate education, training, and/or experience to perform and supervise the manufacture of intermediates and APIs.

The responsibilities of all personnel engaged in the manufacture of intermediates and APIs should be specified in writing.

Training should be regularly conducted by qualified individuals and should cover, at a minimum, the particular operations that the employee performs and GMP as it relates to the employee's functions. Records of training should be maintained. Training should be periodically assessed.

B. Personnel Hygiene (3.2)

Personnel should practice good sanitation and health habits.

Personnel should wear clean clothing suitable for the manufacturing activity with which they are involved and this clothing should be changed, when appropriate. Additional protective apparel, such as head, face, hand, and arm coverings, should be worn, when necessary, to protect intermediates and APIs from contamination.

Personnel should avoid direct contact with intermediates or APIs.

Smoking, eating, drinking, chewing and the storage of food should be restricted to certain designated areas separate from the manufacturing areas.

Personnel suffering from an infectious disease or having open lesions on the exposed surface of the body should not engage in activities that could result in compromising the quality of APIs. Any person shown at any time (either by medical examination or supervisory observation) to have an apparent illness or open lesions should be excluded from activities where the health condition could adversely affect the quality of the APIs until the condition is corrected or qualified medical personnel determine that the person's inclusion would not jeopardize the safety or quality of the APIs.

C. Consultants (3.3)

Consultants advising on the manufacture and control of intermediates or APIs should have sufficient education, training, and experience, or any combination thereof, to advise on the subject for which they are retained.

Records should be maintained stating the name, address, qualifications, and type of service provided by these consultants.

IV. BUILDINGS AND FACILITIES (4)

A. Design and Construction (4.1)

Buildings and facilities used in the manufacture of intermediates and APIs should be located, designed, and constructed to facilitate cleaning, maintenance, and operations as appropriate to the type and stage of manufacture. Facilities should also be designed to minimize potential contamination. Where microbiological specifications have been established for the intermediate or API, facilities should also be designed to limit exposure to objectionable microbiological contaminants, as appropriate.

Buildings and facilities should have adequate space for the orderly placement of equipment and materials to prevent mix-ups and contamination.

Where the equipment itself (e.g., closed or contained systems) provides adequate protection of the material, such equipment can be located outdoors.

The flow of materials and personnel through the building or facilities should be designed to prevent mix-ups or contamination.

There should be defined areas or other control systems for the following activities:

- Receipt, identification, sampling, and quarantine of incoming materials, pending release or rejection
- Quarantine before release or rejection of intermediates and APIs
- Sampling of intermediates and APIs
- Holding rejected materials before further disposition (e.g., return, reprocessing or destruction)
- Storage of released materials
- Production operations
- Packaging and labeling operations
- Laboratory operations

Adequate and clean washing and toilet facilities should be provided for personnel. These facilities should be equipped with hot and cold water, as appropriate, soap or detergent, air

dryers, or single service towels. The washing and toilet facilities should be separate from, but easily accessible to, manufacturing areas. Adequate facilities for showering and/or changing clothes should be provided, when appropriate.

Laboratory areas/operations should normally be separated from production areas. Some laboratory areas, in particular those used for in-process controls, can be located in production areas, provided the operations of the production process do not adversely affect the accuracy of the laboratory measurements, and the laboratory and its operations do not adversely affect the production process, intermediate, or API.

B. Utilities (4.2)

All utilities that could affect product quality (e.g., steam, gas, compressed air, heating, ventilation, and air conditioning) should be qualified and appropriately monitored and action should be taken when limits are exceeded. Drawings for these utility systems should be available.

Adequate ventilation, air filtration and exhaust systems should be provided, where appropriate. These systems should be designed and constructed to minimize risks of contamination and cross-contamination and should include equipment for control of air pressure, microorganisms (if appropriate), dust, humidity, and temperature, as appropriate to the stage of manufacture. Particular attention should be given to areas where APIs are exposed to the environment.

If air is recirculated to production areas, appropriate measures should be taken to control risks of contamination and cross-contamination.

Permanently installed pipework should be appropriately identified. This can be accomplished by identifying individual lines, documentation, computer control systems, or alternative means. Pipework should be located to avoid risks of contamination of the intermediate or API.

Drains should be of adequate size and should be provided with an air break or a suitable device to prevent back-siphonage, when appropriate.

C. Water (4.3)

Water used in the manufacture of APIs should be demonstrated to be suitable for its intended use.

Unless otherwise justified, process water should, at a minimum, meet World Health Organization (WHO) guidelines for drinking (potable) water quality.

If drinking (potable) water is insufficient to ensure API quality and tighter chemical and/or microbiological water quality specifications are called for, appropriate specifications for physical/chemical attributes, total microbial counts, objectionable organisms, and/or endotoxins should be established.

Where water used in the process is treated by the manufacturer to achieve a defined quality, the treatment process should be validated and monitored with appropriate action limits.

Where the manufacturer of a nonsterile API either intends or claims that it is suitable for use in further processing to produce a sterile drug (medicinal) product, water used in the final isolation and purification steps should be monitored and controlled for total microbial counts, objectionable organisms, and endotoxins.

D. Containment (4.4)

Dedicated production areas, which can include facilities, air handling equipment and/or process equipment, should be employed in the production of highly sensitizing materials, such as penicillins or cephalosporins.

The use of dedicated production areas should also be considered when material of an infectious nature or high pharmacological activity or toxicity is involved (e.g., certain steroids or cytotoxic anti-cancer agents) unless validated inactivation and/or cleaning procedures are established and maintained.

Appropriate measures should be established and implemented to prevent cross-contamination from personnel and materials moving from one dedicated area to another.

Any production activities (including weighing, milling, or packaging) of highly toxic nonpharmaceutical materials, such as herbicides and pesticides, should not be conducted using the buildings and/or equipment being used for the production of APIs. Handling and storage of these highly toxic nonpharmaceutical materials should be separate from APIs.

E. Lighting (4.5)

Adequate lighting should be provided in all areas to facilitate cleaning, maintenance, and proper operations.

F. Sewage and Refuse (4.6)

Sewage, refuse, and other waste (e.g., solids, liquids, or gaseous by-products from manufacturing) in and from buildings and the immediate surrounding area should be disposed of in a safe, timely, and sanitary manner. Containers and/or pipes for waste material should be clearly identified.

G. Sanitation and Maintenance (4.7)

Buildings used in the manufacture of intermediates and APIs should be properly maintained and repaired and kept in a clean condition.

Written procedures should be established assigning responsibility for sanitation and describing the cleaning schedules, methods, equipment, and materials to be used in cleaning buildings and facilities.

When necessary, written procedures should also be established for the use of suitable rodenticides, insecticides, fungicides, fumigating agents, and cleaning and sanitizing agents to prevent the contamination of equipment, raw materials, packaging/labeling materials, intermediates, and APIs.

V. PROCESS EQUIPMENT (5)

A. Design and Construction (5.1)

Equipment used in the manufacture of intermediates and APIs should be of appropriate design and adequate size, and suitably located for its intended use, cleaning, sanitation (where appropriate), and maintenance.

Equipment should be constructed so that surfaces that contact raw materials, intermediates, or APIs do not alter the quality of the intermediates and APIs beyond the official or other established specifications.

Production equipment should only be used within its qualified operating range.

Major equipment (e.g., reactors, storage containers) and permanently installed processing lines used during the production of an intermediate or API should be appropriately identified.

Any substances associated with the operation of equipment, such as lubricants, heating fluids or coolants, should not contact intermediates or APIs so as to alter the quality of APIs or intermediates beyond the official or other established specifications. Any deviations from this practice should be evaluated to ensure that there are no detrimental effects on the material's fitness for use. Wherever possible, food grade lubricants and oils should be used.

Closed or contained equipment should be used whenever appropriate. Where open equipment is used, or equipment is opened, appropriate precautions should be taken to minimize the risk of contamination.

A set of current drawings should be maintained for equipment and critical installations (e.g., instrumentation and utility systems).

B. Equipment Maintenance and Cleaning (5.2)

Schedules and procedures (including assignment of responsibility) should be established for the preventative maintenance of equipment.

Written procedures should be established for cleaning equipment and its subsequent release for use in the manufacture of intermediates and APIs. Cleaning procedures should contain sufficient details to enable operators to clean each type of equipment in a reproducible and effective manner. These procedures should include:

- Assignment of responsibility for cleaning of equipment
- Cleaning schedules, including, where appropriate, sanitizing schedules
- A complete description of the methods and materials, including dilution of cleaning agents used to clean equipment
- When appropriate, instructions for disassembling and reassembling each article of equipment to ensure proper cleaning
- Instructions for the removal or obliteration of previous batch identification
- Instructions for the protection of clean equipment from contamination prior to use
- Inspection of equipment for cleanliness immediately before use, if practical
- Establishing the maximum time that may elapse between the completion of processing and equipment cleaning, when appropriate

Equipment and utensils should be cleaned, stored, and, where appropriate, sanitized or sterilized to prevent contamination or carry-over of a material that would alter the quality of the intermediate or API beyond the official or other established specifications.

Where equipment is assigned to continuous production or campaign production of successive batches of the same intermediate or API, equipment should be cleaned at appropriate intervals to prevent build-up and carry-over of contaminants (e.g., degradants or objectionable levels of microorganisms).

Nondedicated equipment should be cleaned between production of different materials to prevent cross-contamination.

Acceptance criteria for residues and the choice of cleaning procedures and cleaning agents should be defined and justified.

Equipment should be identified as to its contents and its cleanliness status by appropriate means.

C. Calibration (5.3)

Control, weighing, measuring, monitoring, and testing equipment critical for ensuring the quality of intermediates or APIs should be calibrated according to written procedures and an established schedule.

Equipment calibrations should be performed using standards traceable to certified standards, if they exist.

Records of these calibrations should be maintained.

The current calibration status of critical equipment should be known and verifiable.

Instruments that do not meet calibration criteria should not be used.

Deviations from approved standards of calibration on critical instruments should be investigated to determine if these could have had an effect on the quality of the intermediate(s) or API(s) manufactured using this equipment since the last successful calibration.

D. Computerized Systems (5.4)

GMP-related computerized systems should be validated. The depth and scope of validation depends on the diversity, complexity, and criticality of the computerized application.

Appropriate installation and operational qualifications should demonstrate the suitability of computer hardware and software to perform assigned tasks.

Commercially available software that has been qualified does not require the same level of testing. If an existing system was not validated at time of installation, a retrospective validation could be conducted if appropriate documentation is available.

Computerized systems should have sufficient controls to prevent unauthorized access or changes to data. There should be controls to prevent omissions in data (e.g., system turned off and data not captured). There should be a record of any data change made, the previous entry, who made the change, and when the change was made.

Written procedures should be available for the operation and maintenance of computerized systems.

Where critical data are being entered manually, there should be an additional check on the accuracy of the entry. This can be done by a second operator or by the system itself.

Incidents related to computerized systems that could affect the quality of intermediates or APIs or the reliability of records or test results should be recorded and investigated.

Changes to computerized systems should be made according to a change procedure and should be formally authorized, documented, and tested. Records should be kept of all changes, including modifications and enhancements made to the hardware, software, and any other critical component of the system. These records should demonstrate that the system is maintained in a validated state.

If system breakdowns or failures would result in the permanent loss of records, a back-up system should be provided. A means of ensuring data protection should be established for all computerized systems.

Data can be recorded by a second means in addition to the computer system.

VI. DOCUMENTATION AND RECORDS (6)

A. Documentation System and Specifications (6.1)

All documents related to the manufacture of intermediates or APIs should be prepared, reviewed, approved, and distributed according to written procedures. Such documents can be in paper or electronic form.

The issuance, revision, superseding, and withdrawal of all documents should be controlled by maintaining revision histories.

A procedure should be established for retaining all appropriate documents (e.g., development history reports, scale-up reports, technical transfer reports, process validation reports, training records, production records, control records, and distribution records). The retention periods for these documents should be specified.

All production, control, and distribution records should be retained for at least 1 year after the expiry date of the batch. For APIs with retest dates, records should be retained for at least 3 years after the batch is completely distributed.

When entries are made in records, these should be made indelibly in spaces provided for such entries, directly after performing the activities, and should identify the person making the entry. Corrections to entries should be dated and signed and leave the original entry still legible.

During the retention period, originals or copies of records should be readily available at the establishment where the activities described in such records occurred. Records that can be promptly retrieved from another location by electronic or other means are acceptable.

Specifications, instructions, procedures, and records can be retained either as originals or as true copies such as photocopies, microfilm, microfiche, or other accurate reproductions of the original records. Where reduction techniques such as microfilming or electronic records are used, suitable retrieval equipment and a means to produce a hard copy should be readily available.

Specifications should be established and documented for raw materials, intermediates where necessary, APIs, and labeling and packaging materials. In addition, specifications may be appropriate for certain other materials, such as process aids, gaskets, or other materials used during the production of intermediates or APIs that could critically affect quality. Acceptance criteria should be established and documented for in-process controls.

If electronic signatures are used on documents, they should be authenticated and secure.

B. Equipment Cleaning and Use Record (6.2)

Records of major equipment use, cleaning, sanitation, and/or sterilization and maintenance should show the date, time (if appropriate), product, and batch number of each batch processed in the equipment and the person who performed the cleaning and maintenance.

If equipment is dedicated to manufacturing one intermediate or API, individual equipment records are not necessary if batches of the intermediate or API follow in traceable sequence. In cases where dedicated equipment is employed, the records of cleaning, maintenance, and use can be part of the batch record or maintained separately.

C. Records of Raw Materials, Intermediates, API Labeling and Packaging Materials (6.3)

Records should be maintained including:

- The name of the manufacturer, identity, and quantity of each shipment of each batch of raw materials, intermediates, or labeling and packaging materials for API's; the name of the supplier; the supplier's control number(s), if known, or other identification number; the number allocated on receipt; and the date of receipt
- The results of any test or examination performed and the conclusions derived from this
- Records tracing the use of materials
- Documentation of the examination and review of API labeling and packaging materials for conformity with established specifications
- The final decision regarding rejected raw materials, intermediates, or API labeling and packaging materials

Master (approved) labels should be maintained for comparison to issued labels.

D. Master Production Instructions (Master Production and Control Records) (6.4)

To ensure uniformity from batch to batch, master production instructions for each intermediate and API should be prepared, dated, and signed by one person and independently checked, dated, and signed by a person in the quality unit(s).

Master production instructions should include:

- The name of the intermediate or API being manufactured and an identifying document reference code, if applicable
- A complete list of raw materials and intermediates designated by names or codes sufficiently specific to identify any special quality characteristics
- An accurate statement of the quantity or ratio of each raw material or intermediate to be used, including the unit of measure. Where the quantity is not fixed, the calculation for

each batch size or rate of production should be included. Variations to quantities should be included where they are justified

- The production location and major production equipment to be used
- Detailed production instructions, including the:

  - sequences to be followed

  - ranges of process parameters to be used

  - sampling instructions and in-process controls with their acceptance criteria, where appropriate

  - time limits for completion of individual processing steps and/or the total process, where appropriate

  - expected yield ranges at appropriate phases of processing or time

- Where appropriate, special notations and precautions to be followed, or cross-references to these
- The instructions for storage of the intermediate or API to ensure its suitability for use, including the labelling and packaging materials and special storage conditions with time limits, where appropriate.

E. Batch Production Records (Batch Production and Control Records) (6.5)

Batch production records should be prepared for each intermediate and API and should include complete information relating to the production and control of each batch. The batch production record should be checked before issuance to ensure that it is the correct version and a legible accurate reproduction of the appropriate master production instruction. If the batch production record is produced from a separate part of the master document, that document should include a reference to the current master production instruction being used.

These records should be numbered with a unique batch or identification number, dated and signed when issued. In continuous production, the product code together with the date and time can serve as the unique identifier until the final number is allocated.

Documentation of completion of each significant step in the batch production records (batch production and control records) should include:

- Dates and, when appropriate, times
- Identity of major equipment (e.g., reactors, driers, mills, etc.) used
- Specific identification of each batch, including weights, measures, and batch numbers of raw materials, intermediates, or any reprocessed materials used during manufacturing
- Actual results recorded for critical process parameters
- Any sampling performed

- Signatures of the persons performing and directly supervising or checking each critical step in the operation
- In-process and laboratory test results
- Actual yield at appropriate phases or times
- Description of packaging and label for intermediate or API
- Representative label of API or intermediate if made commercially available
- Any deviation noted, its evaluation, investigation conducted (if appropriate) or reference to that investigation if stored separately
- Results of release testing

Written procedures should be established and followed for investigating critical deviations or the failure of a batch of intermediate or API to meet specifications. The investigation should extend to other batches that may have been associated with the specific failure or deviation.

F. Laboratory Control Records (6.6)

Laboratory control records should include complete data derived from all tests conducted to ensure compliance with established specifications and standards, including examinations and assays, as follows:

- A description of samples received for testing, including the material name or source, batch number or other distinctive code, date sample was taken, and, where appropriate, the quantity and date the sample was received for testing
- A statement of or reference to each test method used
- A statement of the weight or measure of sample used for each test as described by the method; data on or cross-reference to the preparation and testing of reference standards, reagents and standard solutions
- A complete record of all raw data generated during each test, in addition to graphs, charts and spectra from laboratory instrumentation, properly identified to show the specific material and batch tested
- A record of all calculations performed in connection with the test, including, for example, units of measure, conversion factors, and equivalency factors
- A statement of the test results and how they compare with established acceptance criteria
- The signature of the person who performed each test and the date(s) the tests were performed
- The date and signature of a second person showing that the original records have been reviewed for accuracy, completeness, and compliance with established standards

Complete records should also be maintained for:

- Any modifications to an established analytical method
- Periodic calibration of laboratory instruments, apparatus, gauges, and recording devices

- All stability testing performed on APIs
- Out-of-specification (OOS) investigations

G. Batch Production Record Review (6.7)

Written procedures should be established and followed for the review and approval of batch production and laboratory control records, including packaging and labeling, to determine compliance of the intermediate or API with established specifications before a batch is released or distributed.

Batch production and laboratory control records of critical process steps should be reviewed and approved by the quality unit(s) before an API batch is released or distributed. Production and laboratory control records of noncritical process steps can be reviewed by qualified production personnel or other units following procedures approved by the quality unit(s).

All deviation, investigation, and OOS reports should be reviewed as part of the batch record review before the batch is released.

The quality unit(s) can delegate to the production unit the responsibility and authority for release of intermediates, except for those shipped outside the control of the manufacturing company.

VII. MATERIALS MANAGEMENT (7)

A. General Controls (7.1)

There should be written procedures describing the receipt, identification, quarantine, storage, handling, sampling, testing, and approval or rejection of materials.

Manufacturers of intermediates and/or APIs should have a system for evaluating the suppliers of critical materials.

Materials should be purchased against an agreed specification, from a supplier, or suppliers, approved by the quality unit(s).

If the supplier of a critical material is not the manufacturer of that material, the name and address of that manufacturer should be known by the intermediate and/or API manufacturer.

Changing the source of supply of critical raw materials should be treated according to Section 13, Change Control.

B. Receipt and Quarantine (7.2)

Upon receipt and before acceptance, each container or grouping of containers of materials should be examined visually for correct labeling (including correlation between the name used by the

supplier and the in-house name, if these are different), container damage, broken seals and evidence of tampering or contamination. Materials should be held under quarantine until they have been sampled, examined, or tested, as appropriate, and released for use.

Before incoming materials are mixed with existing stocks (e.g., solvents or stocks in silos), they should be identified as correct, tested, if appropriate, and released. Procedures should be available to prevent discharging incoming materials wrongly into the existing stock.

If bulk deliveries are made in nondedicated tankers, there should be assurance of no cross-contamination from the tanker. Means of providing this assurance could include one or more of the following:

- certificate of cleaning
- testing for trace impurities
- audit of the supplier

Large storage containers and their attendant manifolds, filling, and discharge lines should be appropriately identified.

Each container or grouping of containers (batches) of materials should be assigned and identified with a distinctive code, batch, or receipt number. This number should be used in recording the disposition of each batch. A system should be in place to identify the status of each batch.

C. Sampling and Testing of Incoming Production Materials (7.3)

At least one test to verify the identity of each batch of material should be conducted, with the exception of the materials described below. A *supplier's certificate of analysis* can be used in place of performing other tests, provided that the manufacturer has a system in place to evaluate suppliers.

Supplier approval should include an evaluation that provides adequate evidence (e.g., past quality history) that the manufacturer can consistently provide material meeting specifications. Complete analyses should be conducted on at least three batches before reducing in-house testing. However, as a minimum, a complete analysis should be performed at appropriate intervals and compared with the certificates of analysis. Reliability of certificates of analysis should be checked at regular intervals.

Processing aids, hazardous or highly toxic raw materials, other special materials, or materials transferred to another unit within the company’s control do not need to be tested if the manufacturer’s certificate of analysis is obtained, showing that these raw materials conform to established specifications. Visual examination of containers, labels, and recording of batch numbers should help in establishing the identity of these materials. The lack of on-site testing for these materials should be justified and documented.

Samples should be representative of the batch of material from which they are taken. Sampling methods should specify the number of containers to be sampled, which part of the container to sample, and the amount of material to be taken from each container. The number of containers to sample and the sample size should be based on a sampling plan that takes into consideration the criticality of the material, material variability, past quality history of the supplier, and the quantity needed for analysis.

Sampling should be conducted at defined locations and by procedures designed to prevent contamination of the material sampled and contamination of other materials.

Containers from which samples are withdrawn should be opened carefully and subsequently reclosed. They should be marked to indicate that a sample has been taken.

D. Storage (7.4)

Materials should be handled and stored in a manner to prevent degradation, contamination, and cross-contamination.

Materials stored in fiber drums, bags, or boxes should be stored off the floor and, when appropriate, suitably spaced to permit cleaning and inspection.

Materials should be stored under conditions and for a period that have no adverse effect on their quality, and should normally be controlled so that the oldest stock is used first.

Certain materials in suitable containers can be stored outdoors, provided identifying labels remain legible and containers are appropriately cleaned before opening and use.

Rejected materials should be identified and controlled under a quarantine system designed to prevent their unauthorized use in manufacturing.

E. Re-evaluation (7.5)

Materials should be re-evaluated, as appropriate, to determine their suitability for use (e.g., after prolonged storage or exposure to heat or humidity).

VIII. PRODUCTION AND IN-PROCESS CONTROLS (8)

A. Production Operations (8.1)

Raw materials for intermediate and API manufacturing should be weighed or measured under appropriate conditions that do not affect their suitability for use. Weighing and measuring devices should be of suitable accuracy for the intended use.

If a material is subdivided for later use in production operations, the container receiving the material should be suitable and should be so identified that the following information is available:

- Material name and/or item code
- Receiving or control number
- Weight or measure of material in the new container
- Re-evaluation or retest date if appropriate

Critical weighing, measuring, or subdividing operations should be witnessed or subjected to an equivalent control. Prior to use, production personnel should verify that the materials are those specified in the batch record for the intended intermediate or API.

Other critical activities should be witnessed or subjected to an equivalent control.

Actual yields should be compared with expected yields at designated steps in the production process. Expected yields with appropriate ranges should be established based on previous laboratory, pilot scale, or manufacturing data. Deviations in yield associated with critical process steps should be investigated to determine their impact or potential impact on the resulting quality of affected batches.

Any deviation should be documented and explained. Any critical deviation should be investigated.

The processing status of major units of equipment should be indicated either on the individual units of equipment or by appropriate documentation, computer control systems, or alternative means.

Materials to be reprocessed or reworked should be appropriately controlled to prevent unauthorized use.

B. Time Limits (8.2)

If time limits are specified in the master production instruction (see 6.40), these time limits should be met to ensure the quality of intermediates and APIs. Deviations should be documented and evaluated. Time limits may be inappropriate when processing to a target value (e.g., pH adjustment, hydrogenation, drying to predetermined specification) because completion of reactions or processing steps are determined by in-process sampling and testing.

Intermediates held for further processing should be stored under appropriate conditions to ensure their suitability for use.

C. In-process Sampling and Controls (8.3)

Written procedures should be established to monitor the progress and control the performance of processing steps that cause variability in the quality characteristics of intermediates and APIs. In-process controls and their acceptance criteria should be defined based on the information gained during the developmental stage or from historical data.

The acceptance criteria and type and extent of testing can depend on the nature of the intermediate or API being manufactured, the reaction or process step being conducted, and the degree to which the process introduces variability in the product's quality. Less stringent in-process controls may be appropriate in early processing steps, whereas tighter controls may be appropriate for later processing steps (e.g., isolation and purification steps).

Critical in-process controls (and critical process monitoring), including control points and methods, should be stated in writing and approved by the quality unit(s).

In-process controls can be performed by qualified production department personnel and the process adjusted without prior quality unit(s) approval if the adjustments are made within pre-established limits approved by the quality unit(s). All tests and results should be fully documented as part of the batch record.

Written procedures should describe the sampling methods for in-process materials, intermediates, and APIs. Sampling plans and procedures should be based on scientifically sound sampling practices.

In-process sampling should be conducted using procedures designed to prevent contamination of the sampled material and other intermediates or APIs. Procedures should be established to ensure the integrity of samples after collection.

Out-of-specification (OOS) investigations are not normally needed for in-process tests that are performed for the purpose of monitoring and/or adjusting the process.

D. Blending Batches of Intermediates or APIs (8.4)

For the purpose of this document, blending is defined as the process of combining materials within the same specification to produce a homogeneous intermediate or API. In-process mixing of fractions from single batches (e.g., collecting several centrifuge loads from a single crystallization batch) or combining fractions from several batches for further processing is considered to be part of the production process and is not considered to be blending.

Out-of-specification batches should not be blended with other batches for the purpose of meeting specifications. Each batch incorporated into the blend should have been manufactured using an established process and should have been individually tested and found to meet appropriate specifications prior to blending.

Acceptable blending operations include, but are not limited to:

- Blending of small batches to increase batch size
- Blending of tailings (i.e., relatively small quantities of isolated material) from batches of the same intermediate or API to form a single batch

Blending processes should be adequately controlled and documented, and the blended batch should be tested for conformance to established specifications, where appropriate.

The batch record of the blending process should allow traceability back to the individual batches that make up the blend.

Where physical attributes of the API are critical (e.g., APIs intended for use in solid oral dosage forms or suspensions), blending operations should be validated to show homogeneity of the combined batch. Validation should include testing of critical attributes (e.g., particle size distribution, bulk density, and tap density) that may be affected by the blending process.

If the blending could adversely affect stability, stability testing of the final blended batches should be performed.

The expiry or retest date of the blended batch should be based on the manufacturing date of the oldest tailings or batch in the blend.

E. Contamination Control (8.5)

Residual materials can be carried over into successive batches of the same intermediate or API if there is adequate control. Examples include residue adhering to the wall of a micronizer, residual layer of damp crystals remaining in a centrifuge bowl after discharge, and incomplete discharge of fluids or crystals from a processing vessel upon transfer of the material to the next step in the process. Such carryover should not result in the carryover of degradants or microbial contamination that may adversely alter the established API impurity profile.

Production operations should be conducted in a manner that prevents contamination of intermediates or APIs by other materials.

Precautions to avoid contamination should be taken when APIs are handled after purification.

IX. PACKAGING AND IDENTIFICATION LABELING OF APIs AND INTERMEDIATES (9)

A. General (9.1)

There should be written procedures describing the receipt, identification, quarantine, sampling, examination, and/or testing, release, and handling of packaging and labeling materials.

Packaging and labeling materials should conform to established specifications. Those that do not comply with such specifications should be rejected to prevent their use in operations for which they are unsuitable.

Records should be maintained for each shipment of labels and packaging materials showing receipt, examination, or testing, and whether accepted or rejected.

B. Packaging Materials (9.2)

Containers should provide adequate protection against deterioration or contamination of the intermediate or API that may occur during transportation and recommended storage.

Containers should be clean and, where indicated by the nature of the intermediate or API, sanitized to ensure that they are suitable for their intended use. These containers should not be reactive, additive, or absorptive so as to alter the quality of the intermediate or API beyond the specified limits.

If containers are reused, they should be cleaned in accordance with documented procedures, and all previous labels should be removed or defaced.

C. Label Issuance and Control (9.3)

Access to the label storage areas should be limited to authorized personnel.

Procedures should be established to reconcile the quantities of labels issued, used, and returned and to evaluate discrepancies found between the number of containers labeled and the number of labels issued. Such discrepancies should be investigated, and the investigation should be approved by the quality unit(s).

All excess labels bearing batch numbers or other batch-related printing should be destroyed. Returned labels should be maintained and stored in a manner that prevents mix-ups and provides proper identification.

Obsolete and out-dated labels should be destroyed.

Printing devices used to print labels for packaging operations should be controlled to ensure that all imprinting conforms to the print specified in the batch production record.

Printed labels issued for a batch should be carefully examined for proper identity and conformity to specifications in the master production record. The results of this examination should be documented.

A printed label representative of those used should be included in the batch production record.

D. Packaging and Labeling Operations (9.4)

There should be documented procedures designed to ensure that correct packaging materials and labels are used.

Labeling operations should be designed to prevent mix-ups. There should be physical or spatial separation from operations involving other intermediates or APIs.

Labels used on containers of intermediates or APIs should indicate the name or identifying code, batch number, and storage conditions when such information is critical to ensure the quality of intermediate or API.

If the intermediate or API is intended to be transferred outside the control of the manufacturer's material management system, the name and address of the manufacturer, quantity of contents, special transport conditions, and any special legal requirements should also be included on the label. For intermediates or APIs with an expiry date, the expiry date should be indicated on the label and certificate of analysis. For intermediates or APIs with a retest date, the retest date should be indicated on the label and/or certificate of analysis.

Packaging and labeling facilities should be inspected immediately before use to ensure that all materials not needed for the next packaging operation have been removed. This examination should be documented in the batch production records, the facility log, or other documentation system.

Packaged and labeled intermediates or APIs should be examined to ensure that containers and packages in the batch have the correct label. This examination should be part of the packaging operation. Results of these examinations should be recorded in the batch production or control records.

Intermediate or API containers that are transported outside of the manufacturer's control should be sealed in a manner such that, if the seal is breached or missing, the recipient will be alerted to the possibility that the contents may have been altered.

X. STORAGE AND DISTRIBUTION (10)

A. Warehousing Procedures (10.1)

Facilities should be available for the storage of all materials under appropriate conditions (e.g., controlled temperature and humidity when necessary). Records should be maintained of these conditions if they are critical for the maintenance of material characteristics.

Unless there is an alternative system to prevent the unintentional or unauthorized use of quarantined, rejected, returned, or recalled materials, separate storage areas should be assigned for their temporary storage until the decision as to their future use has been made.

B. Distribution Procedures (10.2)

APIs and intermediates should only be released for distribution to third parties after they have been released by the quality unit(s). APIs and intermediates can be transferred under quarantine to another unit under the company's control when authorized by the quality unit(s) and if appropriate controls and documentation are in place.

APIs and intermediates should be transported in a manner that does not adversely affect their quality.

Special transport or storage conditions for an API or intermediate should be stated on the label.

The manufacturer should ensure that the contract acceptor (contractor) for transportation of the API or intermediate knows and follows the appropriate transport and storage conditions.

A system should be in place by which the distribution of each batch of intermediate and/or API can be readily determined to permit its recall.

XI. LABORATORY CONTROLS (11)

A. General Controls (11.1)

The independent quality unit(s) should have at its disposal adequate laboratory facilities.

There should be documented procedures describing sampling, testing, approval, or rejection of materials and recording and storage of laboratory data. Laboratory records should be maintained in accordance with Section 6.6.

All specifications, sampling plans, and test procedures should be scientifically sound and appropriate to ensure that raw materials, intermediates, APIs, and labels and packaging materials conform to established standards of quality and/or purity. Specifications and test procedures should be consistent with those included in the registration/filing. There can be specifications in addition to those in the registration/filing. Specifications, sampling plans, and test procedures, including changes to them, should be drafted by the appropriate organizational unit and reviewed and approved by the quality unit(s).

Appropriate specifications should be established for APIs in accordance with accepted standards and consistent with the manufacturing process. The specifications should include control of impurities (e.g., organic impurities, inorganic impurities, and residual solvents). If the API has a specification for microbiological purity, appropriate action limits for total microbial counts and objectionable organisms should be established and met. If the API has a specification for endotoxins, appropriate action limits should be established and met.

Laboratory controls should be followed and documented at the time of performance. Any departures from the above-described procedures should be documented and explained.

Any out-of-specification result obtained should be investigated and documented according to a procedure. This procedure should include analysis of the data, assessment of whether a significant problem exists, allocation of the tasks for corrective actions, and conclusions. Any resampling and/or retesting after OOS results should be performed according to a documented procedure.

Reagents and standard solutions should be prepared and labeled following written procedures. *Use by* dates should be applied, as appropriate, for analytical reagents or standard solutions.

Primary reference standards should be obtained, as appropriate, for the manufacture of APIs. The source of each primary reference standard should be documented. Records should be maintained of each primary reference standard's storage and use in accordance with the supplier's recommendations. Primary reference standards obtained from an officially recognized source are normally used without testing if stored under conditions consistent with the supplier's recommendations.

Where a primary reference standard is not available from an officially recognized source, an *in-house primary standard* should be established. Appropriate testing should be performed to establish fully the identity and purity of the primary reference standard. Appropriate documentation of this testing should be maintained.

Secondary reference standards should be appropriately prepared, identified, tested, approved, and stored. The suitability of each batch of secondary reference standard should be determined prior to first use by comparing against a primary reference standard. Each batch of secondary reference standard should be periodically requalified in accordance with a written protocol.

B. Testing of Intermediates and APIs (11.2)

For each batch of intermediate and API, appropriate laboratory tests should be conducted to determine conformance to specifications.

An impurity profile describing the identified and unidentified impurities present in a typical batch produced by a specific controlled production process should normally be established for each API. The impurity profile should include the identity or some qualitative analytical designation (e.g., retention time), the range of each impurity observed, and classification of each identified impurity (e.g., inorganic, organic, solvent). The impurity profile is normally dependent upon the production process and origin of the API. Impurity profiles are normally not necessary for APIs from herbal or animal tissue origin. Biotechnology considerations are covered in ICH guidance Q6B.

The impurity profile should be compared at appropriate intervals against the impurity profile in the regulatory submission or compared against historical data to detect changes to the API

resulting from modifications in raw materials, equipment operating parameters, or the production process.

Appropriate microbiological tests should be conducted on each batch of intermediate and API where microbial quality is specified.

C. Validation of Analytical Procedures - See Section 12. (11.3)

D. Certificates of Analysis (11.4)

Authentic certificates of analysis should be issued for each batch of intermediate or API on request.

Information on the name of the intermediate or API including, where appropriate, its grade, the batch number, and the date of release should be provided on the certificate of analysis. For intermediates or APIs with an expiry date, the expiry date should be provided on the label and certificate of analysis. For intermediates or APIs with a retest date, the retest date should be indicated on the label and/or certificate of analysis.

The certificate should list each test performed in accordance with compendial or customer requirements, including the acceptance limits, and the numerical results obtained (if test results are numerical).

Certificates should be dated and signed by authorized personnel of the quality unit(s) and should show the name, address, and telephone number of the original manufacturer. Where the analysis has been carried out by a repacker or reprocessor, the certificate of analysis should show the name, address, and telephone number of the repacker/reprocessor and reference the name of the original manufacturer.

If new certificates are issued by or on behalf of repackers/reprocessors, agents or brokers, these certificates should show the name, address and telephone number of the laboratory that performed the analysis. They should also contain a reference to the name and address of the original manufacturer and to the original batch certificate, a copy of which should be attached.

E. Stability Monitoring of APIs (11.5)

A documented, on-going testing program should be established to monitor the stability characteristics of APIs, and the results should be used to confirm appropriate storage conditions and retest or expiry dates.

The test procedures used in stability testing should be validated and be stability indicating.

Stability samples should be stored in containers that simulate the market container. For example, if the API is marketed in bags within fiber drums, stability samples can be packaged in bags of

the same material and in small-scale drums of similar or identical material composition to the market drums.

Normally, the first three commercial production batches should be placed on the stability monitoring program to confirm the retest or expiry date. However, where data from previous studies show that the API is expected to remain stable for at least 2 years, fewer than three batches can be used.

Thereafter, at least one batch per year of API manufactured (unless none is produced that year) should be added to the stability monitoring program and tested at least annually to confirm the stability.

For APIs with short shelf-lives, testing should be done more frequently. For example, for those biotechnological/biologic and other APIs with shelf-lives of one year or less, stability samples should be obtained and should be tested monthly for the first 3 months, and at 3-month intervals after that. When data exist that confirm that the stability of the API is not compromised, elimination of specific test intervals (e.g., 9-month testing) can be considered.

Where appropriate, the stability storage conditions should be consistent with the ICH guidances on stability.

F. Expiry and Retest Dating (11.6)

When an intermediate is intended to be transferred outside the control of the manufacturer's material management system and an expiry or retest date is assigned, supporting stability information should be available (e.g., published data, test results).

An API expiry or retest date should be based on an evaluation of data derived from stability studies. Common practice is to use a retest date, not an expiration date.

Preliminary API expiry or retest dates can be based on pilot scale batches if (1) the pilot batches employ a method of manufacture and procedure that simulates the final process to be used on a commercial manufacturing scale and (2) the quality of the API represents the material to be made on a commercial scale.

A representative sample should be taken for the purpose of performing a retest.

G. Reserve/Retention Samples (11.7)

The packaging and holding of reserve samples is for the purpose of potential future evaluation of the quality of batches of API and not for future stability testing purposes.

Appropriately identified reserve samples of each API batch should be retained for 1 year after the expiry date of the batch assigned by the manufacturer, or for 3 years after distribution of the

batch, whichever is longer. For APIs with retest dates, similar reserve samples should be retained for 3 years after the batch is completely distributed by the manufacturer.

The reserve sample should be stored in the same packaging system in which the API is stored or in one that is equivalent to or more protective than the marketed packaging system. Sufficient quantities should be retained to conduct at least two full compendial analyses or, when there is no pharmacopoeial monograph, two full specification analyses.

XII. VALIDATION (12)

A. Validation Policy (12.1)

The company's overall policy, intentions, and approach to validation, including the validation of production processes, cleaning procedures, analytical methods, in-process control test procedures, computerized systems, and persons responsible for design, review, approval, and documentation of each validation phase, should be documented.

The critical parameters/attributes should normally be identified during the development stage or from historical data, and the necessary ranges for the reproducible operation should be defined. This should include:

- Defining the API in terms of its critical product attributes
- Identifying process parameters that could affect the critical quality attributes of the API
- Determining the range for each critical process parameter expected to be used during routine manufacturing and process control

Validation should extend to those operations determined to be critical to the quality and purity of the API.

B. Validation Documentation (12.2)

A written validation protocol should be established that specifies how validation of a particular process will be conducted. The protocol should be reviewed and approved by the quality unit(s) and other designated units.

The validation protocol should specify critical process steps and acceptance criteria as well as the type of validation to be conducted (e.g., retrospective, prospective, concurrent) and the number of process runs.

A validation report that cross-references the validation protocol should be prepared, summarizing the results obtained, commenting on any deviations observed, and drawing the appropriate conclusions, including recommending changes to correct deficiencies.

Any variations from the validation protocol should be documented with appropriate justification.

C. Qualification (12.3)

Before initiating process validation activities, appropriate qualification of critical equipment and ancillary systems should be completed. Qualification is usually carried out by conducting the following activities, individually or combined:

- Design Qualification (DQ): documented verification that the proposed design of the facilities, equipment, or systems is suitable for the intended purpose

- Installation Qualification (IQ): documented verification that the equipment or systems, as installed or modified, comply with the approved design, the manufacturer's recommendations and/or user requirements

- Operational Qualification (OQ): documented verification that the equipment or systems, as installed or modified, perform as intended throughout the anticipated operating ranges

- Performance Qualification (PQ): documented verification that the equipment and ancillary systems, as connected together, can perform effectively and reproducibly based on the approved process method and specifications

D. Approaches to Process Validation (12.4)

Process Validation (PV) is the documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce an intermediate or API meeting its predetermined specifications and quality attributes.

There are three approaches to validation. Prospective validation is the preferred approach, but there are situations where the other approaches can be used. These approaches and their applicability are discussed here.

Prospective validation should normally be performed for all API processes as defined in 12.1. Prospective validation of an API process should be completed before the commercial distribution of the final drug product manufactured from that API.

Concurrent validation can be conducted when data from replicate production runs are unavailable because only a limited number of API batches have been produced, API batches are produced infrequently, or API batches are produced by a validated process that has been modified. Prior to the completion of concurrent validation, batches can be released and used in final drug product for commercial distribution based on thorough monitoring and testing of the API batches.

An exception can be made for retrospective validation of well-established processes that have been used without significant changes to API quality due to changes in raw materials, equipment, systems, facilities, or the production process. This validation approach may be used where:

1. Critical quality attributes and critical process parameters have been identified

2. Appropriate in-process acceptance criteria and controls have been established

3. There have not been significant process/product failures attributable to causes other than operator error or equipment failures unrelated to equipment suitability

4. Impurity profiles have been established for the existing API

Batches selected for retrospective validation should be representative of all batches produced during the review period, including any batches that failed to meet specifications, and should be sufficient in number to demonstrate process consistency. Retained samples can be tested to obtain data to retrospectively validate the process.

E. Process Validation Program (12.5)

The number of process runs for validation should depend on the complexity of the process or the magnitude of the process change being considered. For prospective and concurrent validation, three consecutive successful production batches should be used as a guide, but there may be situations where additional process runs are warranted to prove consistency of the process (e.g., complex API processes or API processes with prolonged completion times). For retrospective validation, generally data from 10 to 30 consecutive batches should be examined to assess process consistency, but fewer batches can be examined if justified.

Critical process parameters should be controlled and monitored during process validation studies. Process parameters unrelated to quality, such as variables controlled to minimize energy consumption or equipment use, need not be included in the process validation.

Process validation should confirm that the impurity profile for each API is within the limits specified. The impurity profile should be comparable to, or better than, historical data and, where applicable, the profile determined during process development or for batches used for pivotal clinical and toxicological studies.

F. Periodic Review of Validated Systems (12.6)

Systems and processes should be periodically evaluated to verify that they are still operating in a valid manner. Where no significant changes have been made to the system or process, and a quality review confirms that the system or process is consistently producing material meeting its specifications, there is normally no need for revalidation.

G. Cleaning Validation (12.7)

Cleaning procedures should normally be validated. In general, cleaning validation should be directed to situations or process steps where contamination or carryover of materials poses the greatest risk to API quality. For example, in early production it may be unnecessary to validate equipment cleaning procedures where residues are removed by subsequent purification steps.

Validation of cleaning procedures should reflect actual equipment usage patterns. If various APIs or intermediates are manufactured in the same equipment and the equipment is cleaned by the same process, a representative intermediate or API can be selected for cleaning validation. This selection should be based on the solubility and difficulty of cleaning and the calculation of residue limits based on potency, toxicity, and stability.

The cleaning validation protocol should describe the equipment to be cleaned, procedures, materials, acceptable cleaning levels, parameters to be monitored and controlled, and analytical methods. The protocol should also indicate the type of samples to be obtained and how they are collected and labeled.

Sampling should include swabbing, rinsing, or alternative methods (e.g., direct extraction), as appropriate, to detect both insoluble and soluble residues. The sampling methods used should be capable of quantitatively measuring levels of residues remaining on the equipment surfaces after cleaning. Swab sampling may be impractical when product contact surfaces are not easily accessible due to equipment design and/or process limitations (e.g., inner surfaces of hoses, transfer pipes, reactor tanks with small ports or handling toxic materials, and small intricate equipment such as micronizers and microfluidizers).

Validated analytical methods having sensitivity to detect residues or contaminants should be used. The detection limit for each analytical method should be sufficiently sensitive to detect the established acceptable level of the residue or contaminant. The method's attainable recovery level should be established. Residue limits should be practical, achievable, verifiable, and based on the most deleterious residue. Limits can be established based on the minimum known pharmacological, toxicological, or physiological activity of the API or its most deleterious component.

Equipment cleaning/sanitation studies should address microbiological and endotoxin contamination for those processes where there is a need to reduce total microbiological count or endotoxins in the API, or other processes where such contamination could be of concern (e.g., non-sterile APIs used to manufacture sterile products).

Cleaning procedures should be monitored at appropriate intervals after validation to ensure that these procedures are effective when used during routine production. Equipment cleanliness can be monitored by analytical testing and visual examination, where feasible. Visual inspection can allow detection of gross contamination concentrated in small areas that could otherwise go undetected by sampling and/or analysis.

H. Validation of Analytical Methods (12.8)

Analytical methods should be validated unless the method employed is included in the relevant pharmacopoeia or other recognized standard reference. The suitability of all testing methods used should nonetheless be verified under actual conditions of use and documented.

Methods should be validated to include consideration of characteristics included within the ICH guidances on validation of analytical methods. The degree of analytical validation performed should reflect the purpose of the analysis and the stage of the API production process.

Appropriate qualification of analytical equipment should be considered before initiating validation of analytical methods.

Complete records should be maintained of any modification of a validated analytical method. Such records should include the reason for the modification and appropriate data to verify that the modification produces results that are as accurate and reliable as the established method.

XIII. CHANGE CONTROL (13)

A formal change control system should be established to evaluate all changes that could affect the production and control of the intermediate or API.

Written procedures should provide for the identification, documentation, appropriate review, and approval of changes in raw materials, specifications, analytical methods, facilities, support systems, equipment (including computer hardware), processing steps, labeling and packaging materials, and computer software.

Any proposals for GMP relevant changes should be drafted, reviewed, and approved by the appropriate organizational units and reviewed and approved by the quality unit(s).

The potential impact of the proposed change on the quality of the intermediate or API should be evaluated. A classification procedure may help in determining the level of testing, validation, and documentation needed to justify changes to a validated process. Changes can be classified (e.g., as minor or major) depending on the nature and extent of the changes, and the effects these changes may impart on the process. Scientific judgment should determine what additional testing and validation studies are appropriate to justify a change in a validated process.

When implementing approved changes, measures should be taken to ensure that all documents affected by the changes are revised.

After the change has been implemented, there should be an evaluation of the first batches produced or tested under the change.

The potential for critical changes to affect established retest or expiry dates should be evaluated. If necessary, samples of the intermediate or API produced by the modified process can be placed on an accelerated stability program and/or can be added to the stability monitoring program.

Current dosage form manufacturers should be notified of changes from established production and process control procedures that can affect the quality of the API.

XIV. REJECTION AND RE-USE OF MATERIALS (14)

A. Rejection (14.1)

Intermediates and APIs failing to meet established specifications should be identified as such and quarantined. These intermediates or APIs can be reprocessed or reworked as described below. The final disposition of rejected materials should be recorded.

B. Reprocessing (14.2)

Introducing an intermediate or API, including one that does not conform to standards or specifications, back into the process and reprocessing by repeating a crystallization step or other appropriate chemical or physical manipulation steps (e.g., distillation, filtration, chromatography, milling) that are part of the established manufacturing process is generally considered acceptable. However, if such reprocessing is used for a majority of batches, such reprocessing should be included as part of the standard manufacturing process.

Continuation of a process step after an in-process control test has shown that the step is incomplete is considered to be part of the normal process. This is not considered to be reprocessing.

Introducing unreacted material back into a process and repeating a chemical reaction is considered to be reprocessing unless it is part of the established process. Such reprocessing should be preceded by careful evaluation to ensure that the quality of the intermediate or API is not adversely affected due to the potential formation of by-products and over-reacted materials.

C. Reworking (14.3)

Before a decision is taken to rework batches that do not conform to established standards or specifications, an investigation into the reason for nonconformance should be performed.

Batches that have been reworked should be subjected to appropriate evaluation, testing, stability testing if warranted, and documentation to show that the reworked product is of equivalent quality to that produced by the original process. Concurrent validation is often the appropriate validation approach for rework procedures. This allows a protocol to define the rework procedure, how it will be carried out, and the expected results. If there is only one batch to be reworked, a report can be written and the batch released once it is found to be acceptable.

Procedures should provide for comparing the impurity profile of each reworked batch against batches manufactured by the established process. Where routine analytical methods are inadequate to characterize the reworked batch, additional methods should be used.

D. Recovery of Materials and Solvents (14.4)

Recovery (e.g., from mother liquor or filtrates) of reactants, intermediates, or the API is considered acceptable, provided that approved procedures exist for the recovery and the recovered materials meet specifications suitable for their intended use.

Solvents can be recovered and reused in the same processes or in different processes, provided that the recovery procedures are controlled and monitored to ensure that solvents meet appropriate standards before reuse or commingling with other approved materials.

Fresh and recovered solvents and reagents can be combined if adequate testing has shown their suitability for all manufacturing processes in which they may be used.

The use of recovered solvents, mother liquors, and other recovered materials should be adequately documented.

E. Returns (14.5)

Returned intermediates or APIs should be identified as such and quarantined.

If the conditions under which returned intermediates or APIs have been stored or shipped before or during their return or the condition of their containers casts doubt on their quality, the returned intermediates or APIs should be reprocessed, reworked, or destroyed, as appropriate.

Records of returned intermediates or APIs should be maintained. For each return, documentation should include:

- Name and address of the consignee
- Intermediate or API, batch number, and quantity returned
- Reason for return
- Use or disposal of the returned intermediate or API

XV. COMPLAINTS AND RECALLS (15)

All quality-related complaints, whether received orally or in writing, should be recorded and investigated according to a written procedure.

Complaint records should include:

- Name and address of complainant
- Name (and, where appropriate, title) and phone number of person submitting the complaint
- Complaint nature (including name and batch number of the API)
- Date complaint is received
- Action initially taken (including dates and identity of person taking the action);
- Any follow-up action taken
- Response provided to the originator of complaint (including date response sent)
- Final decision on intermediate or API batch or lot

Records of complaints should be retained to evaluate trends, product-related frequencies, and severity with a view to taking additional, and if appropriate, immediate corrective action.

There should be a written procedure that defines the circumstances under which a recall of an intermediate or API should be considered.

The recall procedure should designate who should be involved in evaluating the information, how a recall should be initiated, who should be informed about the recall, and how the recalled material should be treated.

In the event of a serious or potentially life-threatening situation, local, national, and/or international authorities should be informed and their advice sought.

XVI. CONTRACT MANUFACTURERS (INCLUDING LABORATORIES) (16)

All contract manufacturers (including laboratories) should comply with the GMP defined in this guidance. Special consideration should be given to the prevention of cross-contamination and to maintaining traceability.

Companies should evaluate any contractors (including laboratories) to ensure GMP compliance of the specific operations occurring at the contractor sites.

There should be a written and approved contract or formal agreement between a company and its contractors that defines in detail the GMP responsibilities, including the quality measures, of each party.

A contract should permit a company to audit its contractor's facilities for compliance with GMP.

Where subcontracting is allowed, a contractor should not pass to a third party any of the work entrusted to it under the contract without the company's prior evaluation and approval of the arrangements.

Manufacturing and laboratory records should be kept at the site where the activity occurs and be readily available.

Changes in the process, equipment, test methods, specifications, or other contractual requirements should not be made unless the contract giver is informed and approves the changes.

XVII. AGENTS, BROKERS, TRADERS, DISTRIBUTORS, REPACKERS, AND RELABELLERS (17)

A. Applicability (17.1)

This section applies to any party other than the original manufacturer who may trade and/or take possession, repack, relabel, manipulate, distribute, or store an API or intermediate.

All agents, brokers, traders, distributors, repackers, and relabelers should comply with GMP as defined in this guidance.

B. Traceability of Distributed APIs and Intermediates (17.2)

Agents, brokers, traders, distributors, repackers, or relabelers should maintain complete traceability of APIs and intermediates that they distribute. Documents that should be retained and available include:

- Identity of original manufacturer
- Address of original manufacturer
- Purchase orders
- Bills of lading (transportation documentation)
- Receipt documents
- Name or designation of API or intermediate
- Manufacturer's batch number
- Transportation and distribution records
- All authentic Certificates of Analysis, including those of the original manufacturer
- Retest or expiry date

C. Quality Management (17.3)

Agents, brokers, traders, distributors, repackers, or relabelers should establish, document and implement an effective system of managing quality, as specified in Section 2.

D. Repackaging, Relabeling, and Holding of APIs and Intermediates (17.4)

Repackaging, relabeling, and holding APIs and intermediates should be performed under appropriate GMP controls, as stipulated in this guidance, to avoid mix-ups and loss of API or intermediate identity or purity.

Repackaging should be conducted under appropriate environmental conditions to avoid contamination and cross-contamination.

E. Stability (17.5)

Stability studies to justify assigned expiration or retest dates should be conducted if the API or intermediate is repackaged in a different type of container than that used by the API or intermediate manufacturer.

F. Transfer of Information (17.6)

Agents, brokers, distributors, repackers, or relabelers should transfer all quality or regulatory information received from an API or intermediate manufacturer to the customer, and from the customer to the API or intermediate manufacturer.

The agent, broker, trader, distributor, repacker, or relabeler who supplies the API or intermediate to the customer should provide the name of the original API or intermediate manufacturer and the batch number(s) supplied.

The agent should also provide the identity of the original API or intermediate manufacturer to regulatory authorities upon request. The original manufacturer can respond to the regulatory authority directly or through its authorized agents, depending on the legal relationship between the authorized agents and the original API or intermediate manufacturer. (In this context *authorized* refers to authorized by the manufacturer.)

The specific guidance for certificate of analysis included in Section 11.4 should be met.

G. Handling of Complaints and Recalls (17.7)

Agents, brokers, traders, distributors, repackers, or relabelers should maintain records of complaints and recalls, as specified in Section 15, for all complaints and recalls that come to their attention.

If the situation warrants, the agents, brokers, traders, distributors, repackers, or relabelers should review the complaint with the original API or intermediate manufacturer to determine whether any further action, either with other customers who may have received this API or intermediate or with the regulatory authority, or both, should be initiated. The investigation into the cause for the complaint or recall should be conducted and documented by the appropriate party.

Where a complaint is referred to the original API or intermediate manufacturer, the record maintained by the agents, brokers, traders, distributors, repackers, or relabelers should include any response received from the original API or intermediate manufacturer (including date and information provided).

H. Handling of Returns (17.8)

Returns should be handled as specified in Section 14.5. The agents, brokers, traders, distributors, repackers, or relabelers should maintain documentation of returned APIs and intermediates.

XVIII. SPECIFIC GUIDANCE FOR APIs MANUFACTURED BY CELL CULTURE/FERMENTATION (18)

A. General (18.1)

Section 18 is intended to address specific controls for APIs or intermediates manufactured by cell culture or fermentation using natural or recombinant organisms and that have not been covered adequately in the previous sections. It is not intended to be a stand-alone section. In general, the GMP principles in the other sections of this document apply. Note that the principles of fermentation for *classical* processes for production of small molecules and for processes using recombinant and nonrecombinant organisms for production of proteins and/or polypeptides are the same, although the degree of control will differ. Where practical, this section will address these differences. In general, the degree of control for biotechnological processes used to produce proteins and polypeptides is greater than that for classical fermentation processes.

The term *biotechnological process* (biotech) refers to the use of cells or organisms that have been generated or modified by recombinant DNA, hybridoma, or other technology to produce APIs. The APIs produced by biotechnological processes normally consist of high molecular weight substances, such as proteins and polypeptides, for which specific guidance is given in this Section. Certain APIs of low molecular weight, such as antibiotics, amino acids, vitamins, and carbohydrates, can also be produced by recombinant DNA technology. The level of control for these types of APIs is similar to that employed for classical fermentation.

The term *classical fermentation* refers to processes that use microorganisms existing in nature and/or modified by conventional methods (e.g., irradiation or chemical mutagenesis) to produce APIs. APIs produced by *classical fermentation* are normally low molecular weight products such as antibiotics, amino acids, vitamins, and carbohydrates.

Production of APIs or intermediates from cell culture or fermentation involves biological processes such as cultivation of cells or extraction and purification of material from living organisms. Note that there may be additional process steps, such as physicochemical modification, that are part of the manufacturing process. The raw materials used (media, buffer components) may provide the potential for growth of microbiological contaminants. Depending on the source, method of preparation, and the intended use of the API or intermediate, control of bioburden, viral contamination, and/or endotoxins during manufacturing and monitoring of the process at appropriate stages may be necessary.

Appropriate controls should be established at all stages of manufacturing to ensure intermediate and/or API quality. While this guidance starts at the cell culture/fermentation step, prior steps

(e.g., cell banking) should be performed under appropriate process controls. This guidance covers cell culture/fermentation from the point at which a vial of the cell bank is retrieved for use in manufacturing.

Appropriate equipment and environmental controls should be used to minimize the risk of contamination. The acceptance criteria for determining environmental quality and the frequency of monitoring should depend on the step in production and the production conditions (open, closed, or contained systems).

In general, process controls should take into account:

- Maintenance of the working cell bank (where appropriate)
- Proper inoculation and expansion of the culture
- Control of the critical operating parameters during fermentation/cell culture
- Monitoring of the process for cell growth, viability (for most cell culture processes) and productivity, where appropriate
- Harvest and purification procedures that remove cells, cellular debris and media components while protecting the intermediate or API from contamination (particularly of a microbiological nature) and from loss of quality
- Monitoring of bioburden and, where needed, endotoxin levels at appropriate stages of production
- Viral safety concerns as described in ICH guidance Q5A *Quality of Biotechnological Products: Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin*

Where appropriate, the removal of media components, host cell proteins, other process-related impurities, product-related impurities and contaminants should be demonstrated.

B. Cell Bank Maintenance and Record Keeping (18.2)

Access to cell banks should be limited to authorized personnel.

Cell banks should be maintained under storage conditions designed to maintain viability and prevent contamination.

Records of the use of the vials from the cell banks and storage conditions should be maintained.

Where appropriate, cell banks should be periodically monitored to determine suitability for use.

See ICH guidance Q5D *Quality of Biotechnological Products: Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products* for a more complete discussion of cell banking.

C. Cell Culture/Fermentation (18.3)

Where cell substrates, media, buffers, and gases are to be added under aseptic conditions, closed or contained systems should be used where possible. If the inoculation of the initial vessel or subsequent transfers or additions (media, buffers) are performed in open vessels, there should be controls and procedures in place to minimize the risk of contamination.

Where the quality of the API can be affected by microbial contamination, manipulations using open vessels should be performed in a biosafety cabinet or similarly controlled environment.

Personnel should be appropriately gowned and take special precautions handling the cultures.

Critical operating parameters (for example temperature, pH, agitation rates, addition of gases, pressure) should be monitored to ensure consistency with the established process. Cell growth, viability (for most cell culture processes), and, where appropriate, productivity should also be monitored. Critical parameters will vary from one process to another, and for classical fermentation, certain parameters (cell viability, for example) may not need to be monitored.

Cell culture equipment should be cleaned and sterilized after use. As appropriate, fermentation equipment should be cleaned, sanitized, or sterilized.

Culture media should be sterilized before use, when necessary, to protect the quality of the API.

Appropriate procedures should be in place to detect contamination and determine the course of action to be taken. Procedures should be available to determine the impact of the contamination on the product and to decontaminate the equipment and return it to a condition to be used in subsequent batches. Foreign organisms observed during fermentation processes should be identified, as appropriate, and the effect of their presence on product quality should be assessed, if necessary. The results of such assessments should be taken into consideration in the disposition of the material produced.

Records of contamination events should be maintained.

Shared (multi-product) equipment may warrant additional testing after cleaning between product campaigns, as appropriate, to minimize the risk of cross-contamination.

D. Harvesting, Isolation and Purification (18.4)

Harvesting steps, either to remove cells or cellular components or to collect cellular components after disruption should be performed in equipment and areas designed to minimize the risk of contamination.

Harvest and purification procedures that remove or inactivate the producing organism, cellular debris and media components (while minimizing degradation, contamination, and loss of quality) should be adequate to ensure that the intermediate or API is recovered with consistent quality.

All equipment should be properly cleaned and, as appropriate, sanitized after use. Multiple successive batching without cleaning can be used if intermediate or API quality is not compromised.

If open systems are used, purification should be performed under environmental conditions appropriate for the preservation of product quality.

Additional controls, such as the use of dedicated chromatography resins or additional testing, may be appropriate if equipment is to be used for multiple products.

E. Viral Removal/Inactivation steps (18.5)

See ICH guidance Q5A *Quality of Biotechnological Products: Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin* for more specific information.

Viral removal and viral inactivation steps are critical processing steps for some processes and should be performed within their validated parameters.

Appropriate precautions should be taken to prevent potential viral contamination from previral to postviral removal/inactivation steps. Therefore, open processing should be performed in areas that are separate from other processing activities and have separate air handling units.

The same equipment is not normally used for different purification steps. However, if the same equipment is to be used, the equipment should be appropriately cleaned and sanitized before reuse. Appropriate precautions should be taken to prevent potential virus carry-over (e.g., through equipment or environment) from previous steps.

XIX. APIs FOR USE IN CLINICAL TRIALS (19)

A. General (19.1)

Not all the controls in the previous sections of this guidance are appropriate for the manufacture of a new API for investigational use during its development. Section XIX (19) provides specific guidance unique to these circumstances.

The controls used in the manufacture of APIs for use in clinical trials should be consistent with the stage of development of the drug product incorporating the API. Process and test procedures should be flexible to provide for changes as knowledge of the process increases and clinical testing of a drug product progresses from pre-clinical stages through clinical stages. Once drug development reaches the stage where the API is produced for use in drug products intended for clinical trials, manufacturers should ensure that APIs are manufactured in suitable facilities using appropriate production and control procedures to ensure the quality of the API.

B. Quality (19.2)

Appropriate GMP concepts should be applied in the production of APIs for use in clinical trials with a suitable mechanism for approval of each batch.

A quality unit(s) independent from production should be established for the approval or rejection of each batch of API for use in clinical trials.

Some of the testing functions commonly performed by the quality unit(s) can be performed within other organizational units.

Quality measures should include a system for testing of raw materials, packaging materials, intermediates, and APIs.

Process and quality problems should be evaluated.

Labeling for APIs intended for use in clinical trials should be appropriately controlled and should identify the material as being for investigational use.

C. Equipment and Facilities (19.3)

During all phases of clinical development, including the use of small-scale facilities or laboratories to manufacture batches of APIs for use in clinical trials, procedures should be in place to ensure that equipment is calibrated, clean, and suitable for its intended use.

Procedures for the use of facilities should ensure that materials are handled in a manner that minimizes the risk of contamination and cross-contamination.

D. Control of Raw Materials (19.4)

Raw materials used in production of APIs for use in clinical trials should be evaluated by testing, or received with a supplier’s analysis and subjected to identity testing. When a material is considered hazardous, a supplier's analysis should suffice.

In some instances, the suitability of a raw material can be determined before use based on acceptability in small-scale reactions (i.e., use testing) rather than on analytical testing alone.

E. Production (19.5)

The production of APIs for use in clinical trials should be documented in laboratory notebooks, batch records, or by other appropriate means. These documents should include information on the use of production materials, equipment, processing, and scientific observations.

Expected yields can be more variable and less defined than the expected yields used in commercial processes. Investigations into yield variations are not expected.

F. Validation (19.6)

Process validation for the production of APIs for use in clinical trials is normally inappropriate, where a single API batch is produced or where process changes during API development make batch replication difficult or inexact. The combination of controls, calibration, and, where appropriate, equipment qualification ensures API quality during this development phase.

Process validation should be conducted in accordance with Section 12 when batches are produced for commercial use, even when such batches are produced on a pilot or small scale.

G. Changes (19.7)

Changes are expected during development, as knowledge is gained and the production is scaled up. Every change in the production, specifications, or test procedures should be adequately recorded.

H. Laboratory Controls (19.8)

While analytical methods performed to evaluate a batch of API for clinical trials may not yet be validated, they should be scientifically sound.

A system for retaining reserve samples of all batches should be in place. This system should ensure that a sufficient quantity of each reserve sample is retained for an appropriate length of time after approval, termination, or discontinuation of an application.

Expiry and retest dating as defined in Section 11.6 applies to existing APIs used in clinical trials. For new APIs, Section 11.6 does not normally apply in early stages of clinical trials.

I. Documentation (19.9)

A system should be in place to ensure that information gained during the development and the manufacture of APIs for use in clinical trials is documented and available.

The development and implementation of the analytical methods used to support the release of a batch of API for use in clinical trials should be appropriately documented.

A system for retaining production and control records and documents should be used. This system should ensure that records and documents are retained for an appropriate length of time after the approval, termination, or discontinuation of an application.

GLOSSARY (20)

Acceptance Criteria: Numerical limits, ranges, or other suitable measures for acceptance of test results.

Active Pharmaceutical Ingredient (API) ***(or Drug Substance):*** Any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product and that, when used in the production of a drug, becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body.

API Starting Material: A raw material, intermediate, or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. An API starting material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or produced in-house. API starting materials are normally of defined chemical properties and structure.

Batch (or Lot): A specific quantity of material produced in a process or series of processes so that it is expected to be homogeneous within specified limits. In the case of continuous production, a batch may correspond to a defined fraction of the production. The batch size can be defined either by a fixed quantity or by the amount produced in a fixed time interval.

Batch Number (or Lot Number): A unique combination of numbers, letters, and/or symbols that identifies a batch (or lot) and from which the production and distribution history can be determined.

Bioburden: The level and type (e.g., objectionable or not) of microorganisms that can be present in raw materials, API starting materials, intermediates or APIs. Bioburden should not be considered contamination unless the levels have been exceeded or defined objectionable organisms have been detected.

Calibration: The demonstration that a particular instrument or device produces results within specified limits by comparison with results produced by a reference or traceable standard over an appropriate range of measurements.

Computer System: A group of hardware components and associated software designed and assembled to perform a specific function or group of functions.

Computerized System: A process or operation integrated with a computer system.

Contamination: The undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or onto a raw material, intermediate, or API during production, sampling, packaging, or repackaging, storage or transport.

Contract Manufacturer: A manufacturer who performs some aspect of manufacturing on behalf of the original manufacturer.

Critical: Describes a process step, process condition, test requirement, or other relevant parameter or item that must be controlled within predetermined criteria to ensure that the API meets its specification.

Cross-Contamination: Contamination of a material or product with another material or product.

Deviation: Departure from an approved instruction or established standard.

Drug (Medicinal) Product: The dosage form in the final immediate packaging intended for marketing. (Reference Q1A)

Drug Substance: See Active Pharmaceutical Ingredient.

Expiry Date (or Expiration Date): The date placed on the container/labels of an API designating the time during which the API is expected to remain within established shelf life specifications if stored under defined conditions and after which it should not be used.

Impurity: Any component present in the intermediate or API that is not the desired entity.

Impurity Profile: A description of the identified and unidentified impurities present in an API.

In-Process Control (or Process Control): Checks performed during production to monitor and, if appropriate, to adjust the process and/or to ensure that the intermediate or API conforms to its specifications.

Intermediate: A material produced during steps of the processing of an API that undergoes further molecular change or purification before it becomes an API. Intermediates may or may not be isolated. (Note: this guidance only addresses those intermediates produced after the point that a company has defined as the point at which the production of the API begins.)

Lot: See Batch

Lot Number: See *Batch Number*

Manufacture: All operations of receipt of materials, production, packaging, repackaging, labeling, relabeling, quality control, release, storage, and distribution of APIs and related controls.

Material: A general term used to denote raw materials (starting materials, reagents, solvents), process aids, intermediates, APIs, and packaging and labeling materials.

Mother Liquor: The residual liquid that remains after the crystallization or isolation processes. A mother liquor may contain unreacted materials, intermediates, levels of the API, and/or impurities. It can be used for further processing.

Packaging Material: Any material intended to protect an intermediate or API during storage and transport.

Procedure: A documented description of the operations to be performed, the precautions to be taken, and measures to be applied directly or indirectly related to the manufacture of an intermediate or API.

Process Aids: Materials, excluding solvents, used as an aid in the manufacture of an intermediate or API that do not themselves participate in a chemical or biological reaction (e.g., filter aid, activated carbon).

Process Control: See ***In-Process Control.***

Production: All operations involved in the preparation of an API from receipt of materials through processing and packaging of the API.

Qualification: Action of proving and documenting that equipment or ancillary systems are properly installed, work correctly, and actually lead to the expected results. Qualification is part of validation, but the individual qualification steps alone do not constitute process validation.

Quality Assurance (QA): The sum total of the organized arrangements made with the object of ensuring that all APIs are of the quality required for their intended use and that quality systems are maintained.

Quality Control (QC): Checking or testing that specifications are met.

Quality Unit(s): An organizational unit independent of production that fulfills both quality assurance and quality control responsibilities. This can be in the form of separate QA and QC units or a single individual or group, depending upon the size and structure of the organization.

Quarantine: The status of materials isolated physically or by other effective means pending a decision on their subsequent approval or rejection.

Raw Material: A general term used to denote starting materials, reagents, and solvents intended for use in the production of intermediates or APIs.

Reference Standard, Primary: A substance that has been shown by an extensive set of analytical tests to be authentic material that should be of high purity. This standard can be: (1) obtained from an officially recognized source, (2) prepared by independent synthesis, (3) obtained from existing production material of high purity, or (4) prepared by further purification of existing production material.

Reference Standard, Secondary: A substance of established quality and purity, as shown by comparison to a primary reference standard, used as a reference standard for routine laboratory analysis.

Reprocessing: Introducing an intermediate or API, including one that does not conform to standards or specifications, back into the process and repeating a crystallization step or other appropriate chemical or physical manipulation steps (e.g., distillation, filtration, chromatography, milling) that are part of the established manufacturing process. Continuation of a process step after an in-process control test has shown that the step is incomplete, is considered to be part of the normal process, and is not reprocessing.

Retest Date: The date when a material should be re-examined to ensure that it is still suitable for use.

Reworking: Subjecting an intermediate or API that does not conform to standards or specifications to one or more processing steps that are different from the established manufacturing process to obtain acceptable quality intermediate or API (e.g., recrystallizing with a different solvent).

Signature (signed): See definition for signed.

Signed (signature): The record of the individual who performed a particular action or review. This record can be initials, full handwritten signature, personal seal, or authenticated and secure electronic signature.

Solvent: An inorganic or organic liquid used as a vehicle for the preparation of solutions or suspensions in the manufacture of an intermediate or API.

Specification: A list of tests, references to analytical procedures, and appropriate acceptance criteria that are numerical limits, ranges, or other criteria for the test described. It establishes the set of criteria to which a material should conform to be considered acceptable for its intended use. *Conformance to specification* means that the material, when tested according to the listed analytical procedures, will meet the listed acceptance criteria.

Validation: A documented program that provides a high degree of assurance that a specific process, method, or system will consistently produce a result meeting predetermined acceptance criteria.

Validation Protocol: A written plan stating how validation will be conducted and defining acceptance criteria. For example, the protocol for a manufacturing process identifies processing equipment, critical process parameters and/or operating ranges, product characteristics, sampling, test data to be collected, number of validation runs, and acceptable test results.

Yield, Expected: The quantity of material or the percentage of theoretical yield anticipated at any appropriate phase of production based on previous laboratory, pilot scale, or manufacturing data.

Yield, Theoretical: The quantity that would be produced at any appropriate phase of production based upon the quantity of material to be used, in the absence of any loss or error in actual production.

GUIDE TO INSPECTIONS VALIDATION OF CLEANING PROCESSES

Note: This document is reference material for investigators and other FDA personnel. The document does not bind FDA, and does no confer any rights, privileges, benefits, or immunities for or on any person(s).

I. INTRODUCTION

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.

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.

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

II. BACKGROUND

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.

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.

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.

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.

III. GENERAL REQUIREMENTS

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

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 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 analytical methods to be used including the sensitivity of those methods.

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

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."

IV. EVALUATION OF CLEANING VALIDATION

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.

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.

1. Equipment Design

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.

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.

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.

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.

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.

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.

2. Cleaning Process Written Procedure and Documentation

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.

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.

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.

3. Analytical Methods

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).

4. Sampling

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.

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.

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.

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.

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.

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.

c. Routine Production In-Process Control

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.

V. ESTABLISHMENT OF LIMITS

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.

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.

VI. OTHER ISSUES

a. Placebo Product

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.

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.

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.

b. Detergent

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.

c. Test Until Clean

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.

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May 24, 2007

CBER-07-010

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Mr. David M. Mott
President and Chief Executive Officer
MedImmune, Inc.
One MedImmune Way
Gaithersburg, MD 20878

Dear Mr. Mott:

The Food and Drug Administration (FDA) conducted an inspection of MedImmune U.K. Ltd, a subsidiary of MedImmune, Inc. (hereinafter "MedImmune" or "your firm"), Plot 6 Renaissance Way, Boulevard Industry Park, Speke, Liverpool L24 9JW, United Kingdom, between March 21 and March 29, 2007. During the inspection, FDA investigators documented significant deviations

from current good manufacturing practice (CGMP) in the manufacture of FluMist bulk monovalent lots used to manufacture In fluenza Virus Vaccine Live, Intranasal. These deviations from CGMP include deviations from the applicable requirements of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), as well as requirements of your biologics license application approved under Section 351(a) of the Public Health Service Act (PHS Act) and Title 21, Code of Federal Regulations (21 CFR), Part 601.

At the close of the inspection, FDA issued a Form FDA 483, Inspectional Observations, which described a number of significant deviations in the manufacture of your bulk monovalent lots that are used to formulate In fluenza Virus Vaccine Live, Intranasal, FluMist. Specific areas of concern include, but are not limited to:

INVESTIGATION OF BIOBURDEN EXCURSIONS

1. As a condition of the December 22, 2005, approval of a supplement (pursuant to 21 CFR 601.12(b)) to your Biologics License Application (BLA) for In fluenza Virus Vaccine Live, Intranasal (STN 125020/12), you committed to FDA to agreed-upon interim bioburden alert and action limits, to investigate any excursions from those limits under defined conditions, and to re-evaluate the interim limits based on data from the 2006/2007 campaign. During the 2006/2007 campaign, five out of **[redacted]** FluMist bulk monovalent lots manufactured between February 2006 and April 2006 exceeded the **[redacted]** virus harvest interim bioburden action limit of **[redacted]** cfu/ml and/or the **[redacted]** virus harvest interim bioburden action limit of **[redacted]** cfu/ml. Three of the five FluMist bulk monovalent lots that exceeded the interim bioburden action limits were used in the formulation of final product (lots 600147, 600153, and 600157). We acknowledge that

the subsequently filtered monovalent lots and the final vaccine product resulting from those lots met all specifications. However, based on FDA's experience, there is a high probability that the observed CGMP deviations, if not corrected, would substantially increase the risk of product failures. Of particular concern are your inadequate investigations into such excursions, and your lack of implementation of appropriate corrective and preventive actions, coupled with deficiencies in: aseptic practices by personnel, cleaning validation of equipment and effectiveness of the cleaning and disinfection processes used in your manufacturing facility and by your personnel. Adequate investigations and correcting deficiencies in the process before they result in product failures are underlying principles of CGMP.

The investigations that your firm performed for the interim bioburden action limit excursions did not adequately satisfy your December 2005 commitment to the agency which was incorporated into you BLA through the approval of your supplemental application (STN 125020/12). In addition, your investigations were not performed in accordance with CGMP because they were inadequate, and because corrective and/or preventive actions were neither identified nor implemented to prevent recurrence. Specifically:

a) Your firm generally concluded that all isolates from the interim bioburden action limit excursions were associated with eggs. However, some microorganisms identified included those commonly associated with the environment and/or water (e.g., *Brevibacterium ssp, Pseudomonas stutzeri, Staphylococcus aureus*), in addition to those commonly associated with eggs (e.g., *Enterococcusfaecalis, Escherichia coli*). We also note that the

microorganisms you have identified as being associated with eggs have also been identified during environmental monitoring of your manufacturing facility and your personnel (see item c below). No corrective actions have been proposed or implemented to control microbial contamination of the eggs or to minimize the introduction of microbial contamination from the manufacturing facility or personnel, all of which are important in ensuring the quality of your product.

b) For any of the action limit excursions you identified as being associated with eggs, your firm did not perform a review of the flock from which the eggs were obtained and/or make a determination as to whether the flock should be used for future production of vaccine. You committed to perform such a review for each action limit excursion in your December 8, 2005 correspondence to the agency, which was incorporated into your BLA through the approved supplemental application. Such a review should also include an evaluation of your egg suppliers' sanitation and handling practices to determine whether any corrective actions could be implemented to minimize microbial contamination of eggs.

c) Your firm's conclusions after investigations conducted into the interim bioburden action limit excursions, which your firm repeated in its response to the agency, arecontradicted in many cases by documentation collected during our inspection. For example:

During the manufacture of A/Wisconsin lot 600157, two of the **[redacted]** sub-lots exceeded the **[redacted]** virus harvest interim bioburden action limit of **[redacted]** cfu/ml: 1.25 x 10*4* and 9.4 x 103 cfu/ml, respectively. Deviation Report 3463, initiated for those interim bioburden action limit excursions for A/Wisconsin lot

600157, concluded that that "the root cause investigation conducted has not determined any anomlies [anomalies] or deviations associated with either the QC testing or manufacture of batch 600157 that could have resulted or contributed to the bioburden excursion observed . . . ." The report also stated: "Environmental control was maintained throughout. It is likely that the contamination originated from the eggs and were [was] present before use within manufacturing." The product impact assessment concluded that there are not "product implications" and includes the following reasons: "Environmental control was maintained throughout the critical and non-critical manufacturing stages," and "No deviations or anomalies were identified from the manufacturing review which could have resulted in the bioburden excursion."

We also note that the deviation reports associated with the interim bioburden action limit excursions generally contain the very same conclusions.

Contrary to those conclusions - that nothing in the environment or personnel could have contributed to the high bioburden in the monovalent sub-lots - your firm's records reveal environmental and personnel monitoring excursions directly associated with the manufacture of this lot during harvest and downstream processing operations. The isolates identified from the environment and personnel included the same microorganisms identified in the interim bioburden action limit excursions (e.g. *Staphylococcus aureus, Escherichia coli, Brevibacterium spp., and Enterococcus faecalis*.) Consequently, your firm should have investigated the possibility that the bioburden in the lots came, at least in part, from your facility's environment and/or personnel. In addition, according to your own firm's Quality Assurance review, you used some

[redacted] and the [redacted] pipette controllers to manufacture this lot before your firm finished pre-cleaning that equipment. Clearly, several potential sources could have contributed to the lot's high bioburden, and your firm should have investigated those potential sources thoroughly.

d) Your firm's investigations also did not include review of the cleaning validation status for the [redacted] the [redacted] incubators, the dispensing and Biological Safety Cabinets, or the silicon rubber housing of the candling lamps (see Item 6) or the effectiveness of your cleaning and disinfection processes used in your manufacturing facility and by your personnel (see Item 4).

We acknowledge that you did re-evaluate the interim limits based on data from the 2006/2007 campaign and that you set bioburden limits for the 2007/2008 campaign, inaccordance to your commitment. Based on the data, the [redacted] virus harvest alertand action limits were increased to [redacted] cfu/ml and [redacted] cfu/n 1, respectively, and the [redacted] virus harvest alert and action limits were decreased to [redacted] cfu/m1 and [redacted] cfu/ml, respectively.

At the time of the inspection, two of the [redacted] bulk monovalent lots that had been produced for the 2007/2008 campaign exceeded the adjusted bioburden action and/or alert limits that you established based on your own data from last season. You must investigate those excursions thoroughly, as you committed to the agency to do, and as your BLA now requires. Your investigations into these excursions were ongoing at the time of the inspection.

PRODUCTION AND PROCESS CONTROLS

2. You failed to ensure that operators performing setup, sterile filtration and/or aseptic dispensing use proper aseptic techniques to prevent microbial contamination of monovalent lots. Specifically:

a) Operators were observed wearing safety glasses allowing for skin to be exposed and, therefore, increasing the opportunity for contamination.

b) On March 28, 2007, an operator was observed removing his/her safety glasses, then removing and cleaning his/her prescription type glasses, thus allowing for skin to be exposed.

c) Also, an operator was observed sampling his/her fingers onto an agar touch plate and without sanitizing or changing his/her gloves, mixing the sterile filtered monovalent.

3. Master and batch production records lack specificity. This issue was discussed with senior management at your firm during the March 6 to March 9, 2006, inspection and correction was promised, but has not been achieved. For example:

a) Master Production Record for B/Malaysia/2506/04 Batch Number: 600169 entitled "The Decontamination and Disassembly of the Ultracentrifuge within the Downstream Processing Room" does not document the maximum soiled hold time limit you established for the [redacted] Ultracentrifuge rotor. Such documentation is important to ensure that subsequent cleanings are performed within validated timeframes. It is important to clean within the validated timeframes

to ensure complete removal of product related material and microorganisms.

b) Master Production Record for B/Malaysia/2506/04 Batch Number: 600169 entitled "Filter Preparation, Sterile Filtration and Dispensing of Monovalent Bulk" does not include an established time limit for the aseptic dispensing step.

BUILDINGS AND FACILITIES

4. You have failed to establish the effectiveness of the cleaning and disinfectionprocesses used in your manufacturing facility and by your personnel. For example:

a) From April 14- May 3, 2006, there were numerous environmental monitoring excursions for mold in Downstream Processing Room **[redacted]** Deviation report 3089 discusses the isolation of mold from the curtains around the laminar flow units after cleaning; from an operator's hand during filter connection activities in the Biological Safety Cabinet; from the ceiling Heating, Ventilation and Air Conditioning (HVAC) vent; and from the filter integrity tester, in addition to other locations. During this time, monovalent lots 600156 and 600157 were processed in room **[redacted]**. One of the conclusions of your firm's root cause analysis was as follows, "A number of environmental monitoring excursions investigations have come to the conclusion that the cleaning performed in UK-1 [Medimmune's manufacturing site] may not always be effective." However, there is no

indication that you reviewed the effectiveness of the cleaning or disinfecting agents used.

b) In addition, other microorganisms were found in the egg incubator, on a harvesting room operator's hand, on the harvest room table, and on a downstream processing room operator's hands. These microorganisms, including *Staphyloccoccus aureus, Escherichia coli, and Enterococcus faecalis* are the same isolates found in sub-lots of monovalent 600157. There is no indication that you reviewed the effectiveness of the cleaning or disinfecting agent used.

c) The November 2003 disinfectant effectiveness validation study of **[redacted]** used to disinfect your facility, did not meet your established **[redacted]** log reduction acceptance criterion for **[redacted]** set forth in your validation study protocol. **[redacted]** is the study microorganism used to evaluate the effectiveness of cleaning agents on fungi and mold.

d) There is no assurance that the disinfectant **[redacted]** is effective against mold, since it did not meet your established recovery rate acceptance criterion in the December 2001 "Disinfectant Validation and Efficacy Study **[redacted]** of by the Surface Test Method" study.

e) There has been no evaluation of whether the **[redacted]** solution, used to decontaminate outer egg

shells during the virus harvest step, is ettective in the manner used by your firm.

5. Your firm failed to establish separate or de fined areas or other control systems for your operations to prevent contamination or mix-ups. For example:

a) There is no procedure in place regarding controlled access to the Medlmmune offsite warehouse used for receipt and storage of raw materials known as [redacted]

b) Rejected materials were observed stored with released and un-released raw materials.

CLEANING AND MAINTENANCE OF EQUIPMENT

6. Cleaning validation for the [redacted] the [redacted] incubators, the dispensing and Biological Safety cabinets, and the silicon rubber housing of the candling lamps has not been performed.

The deficiencies described in this letter are indicative of your quality control unit not fulfilling its responsibility to assure the identity, strength, quality, and purity of your components/in-process materials. Please describe in detail how Medtmmune will attain CGMP compliance with regard to monovalent bulk failure/deviation investigations. Please include in that description how Medlmmune will use all of the relevant information to conduct a root cause analysis, to ensure that adequate steps are taken to evaluate whether deviations impact product, and to implement effective corrective and preventive actions.

We acknowledge receipt of your written response dated April 27, 2007, which addresses the inspectional observations on the Form FDA 483 issued at the close of the inspection. Corrective actions addressed in your letter may be referenced in your response to this letter; however, we believe that your response did not provide sufficient detail to fully assess the adequacy of the corrective actions. Our comments and requests for further information regarding corrective action are detailed below. The items correspond to the observations listed on the Form FDA 483:

Production system, items 1-2

We agree with your response that excursions above alert or action limits do not necessarily mean that product should be rejected and we also agree with your statement that comprehensive investigations should be performed when alert and/or action limits are exceeded. We also acknowledge your previous discussions with CBER regarding the establishment of interim bioburden action/alert limits.

However, as described in this letter, MedImmune has not performed adequate and complete investigations into the deviations, as required by section 501(a)(2)(B) of the FD&C Act and by your biologics license application that FDA approved under section 351 of the PHS Act, as supplemented pursuant to 21 C.F.R. §601.12(b). Although your firm did perform investigations for the interim bioburden action limit excursions, the investigations were not performed in accordance with CGMP in that they were inadequate, and that corrective and/or preventive actions were not identified or implemented to prevent recurrence. In addition, the investigations did not satisfy your December 2005 commitment to the agency, which was incorporated into your BLA, to investigate the root cause and determine approp riate corrective actions when interim bioburden action/alert limits were exceeded.

Please provide all investigation reports for the bulk monovalent lots produced for the 2007/2008 campaign which exceeded the bioburden action and/or alert limits

Production system, item 4a-b

Your response states that relevant [redacted] Standards were used in the study protocols to set the criteria for disinfectant [redacted] effectiveness and that although the results did not meet the stated [redacted] Standard acceptance criterion, the study demonstrated that the disinfectant was reasonably effective in fungal inactivation. Your response also states that a disinfectant [redacted] effectiveness study was performed and that preestablished recovery rate acceptance criterion was not consistently met during the execution of the protocol. Based on the environmental monito ring results mentioned above, we recommend that you perform disinfectants effectiveness studies in which all your acceptance criteria are met.

We also note that beginning in 2007 the European Union banned the use of [redacted] and [redacted] disinfectants. Please provide us your plans for the replacement of these disinfectants and their validation.

Facility and Equipment systems, items 8b and 9b-c

Your response indicates that microbiological control of non-product contact surfaces, including equipment and ISO classified rooms is validated for cleaning effectiveness utilizing the standard IQ, OQ, and environmental monitoring PQ approach. However, based on the documentation collected during our inspection, there is no assurance that your cleaning is effective, since microorganisms associated with eggs have also been identified during environmental monitoring of your manufacturing facility and your personnel.

Neither this letter nor the list of inspectional observations (Form FDA 483) is meant to be an all-inclusive list of deficiencies that may exist at your facility. It is your responsibility as management to assure that your establishment is in compliance with the provisions of the FD&C Act, PHS Act, and applicable federal regulations. Federal agencies are advised of the issuance of all Warning Letters about drugs so that they may take this information into account when conside ring the award of contracts.

You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in FDA initiating regulatory action without further notice. Such action may include license suspension and/or revocation.

To facilitate your remediation effort we request a meeting with you and other senior management at MedImmune to further discuss the issues cited in this letter and your proposed responses to address them. Given the potential contributions of safe, pure and potent influenza virus vaccine to the public health, we encourage regularly scheduled and frequent interactions between your technical staff and FDA in an effort to help MedImmune move forward with corrective actions as rapidly as possible.

Please notify us in writing, within 15 working days of receipt of this letter, of any additional steps you have taken or will take to correct the noted violations and to prevent their recurrence. Include any documentation necessary to show that correction has been achieved. If corrective actions cannot be completed within 15 working days, state the reason for the delay and the time within which the corrections will be completed.

Your reply should be sent to me at the U.S. Food and Drug Administration, Center for Biologics Evaluation and Research, HFM-600, 1401 Rockville Pike, Suite 200 N, Rockville, Maryland 20852-1448. If you have any questions regarding this letter, please contact Mr. Robert A. Sausville, Director, Division of Case Management, at (301) 827-6201.

Sincerely,

/S/

Mary A. Malarkey

Director

Office of Compliance and Biologics Quality

Center for Biologics Evaluation and Research

Cc: Mike Austin

Senior Director, Site Operations

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