Manufacturing and validation 19

19.1 Introduction

In all pharmaceutical microbiology control laboratories, the frequency of "failure" in product related testing is exceedingly low. This is so with finished product testing, intermediate testing, and, in sterile manufacture, for environmental monitoring. With water testing, periodic out-of-limits will occur, as there will be with some starting materials; and with environmental monitoring of lower grade cleanrooms and within nonsterile facilities, there will be occasional excursions, especially from surface contact plates. However, overall microbial data deviations represent a small proportion of the collected total number of samples.

This state of control exists because manufacture is performed in equipment and facilities which have been hygienically designed, and which are operated and maintained according to hygienic principles. This is the consequence of successful application of the principles of good manufacturing practice (GMP) and quality assurance.

The basic principle of both good manufacturing practice and quality assurance is that only by having properly designed and operated processes can it be possible to obtain satisfactory product from unit to unit within a batch, and from one batch to other batches manufactured using different equipment and/or on different occasions. Achieving this requires that manufacturing facilities, equipment, and processes should be validated prior to being released for routine use; and subsequently in routine use they should always be operated to procedures accurately reflecting the conditions shown to be effective in validation.

This chapter focuses on two broad topics: manufacturing procedures and validation. It is important that the pharmaceutical microbiologist understands how manufacturing procedures and validation under-pin all aspects of quality and are, therefore, not wholly divorced from a requirement for microbiological input. In risk assessment terms, this reduces the severity of a hazard and the probability of that hazard occurring, with microbiological testing functioning as the detection tool (risk assessment terms are defined in Chapter 18).

19.2 Manufacturing procedures

GMP provides an important structure from which manufacturing procedures are shaped. Some key GMP elements are [1]:

- specifications describe in detail the requirements with which the products or materials used or obtained during manufacture have to conform;
- manufacturing formulae, processing and packaging instructions state all the starting and packaging materials used and, additionally, lay down all processing and packaging operations;

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- procedures give directions for performing certain operations, for example, cleaning, clothing, environmental control, sampling, testing, and equipment operation;
- records provide a history of each batch of product including its distribution, and also of all other relevant circumstances pertinent to the quality of the final product.

These documented aspects will now be examined in more detail.

19.2.1 Specifications

Specifications may be organized and laid out differently from company to company, but essentially they all must contain the same elements. These are [2]:

(a) The identity of what is being specified. This should be unambiguous, but also intelligible. A name is usually accompanied by a code number or a part number. The identity of starting materials may be according to a pharmacopoeia or they may be simple or complex chemical molecules. Specifications for most chemicals should be accompanied by a reference to a method by which their identity should be confirmed. The identity of a finished product should refer to the concentration of the active ingredient(s) and other information pertaining to its registered formula; specifications for finished products are in this respect usually more detailed than specifications for starting materials;

(b) Limits on impurities or defects. These may be chemical or physical. Microbiological contamination is strictly speaking an impurity;

(c) Other characteristics determined to be of importance. It may be that the particle size of a starting material is of importance as to how it runs on a piece of equipment, or how it binds to form a tablet, or how it forms an emulsion in a cream or ointment, or even how the finished drug product performs therapeutically as in inhalation products. It may be that the pH of a finished injection product affects its therapeutic effects.

Specifically for pharmaceutical microbiology, limits on impurities or defects are of the greatest importance. These can be specified in a variety of ways. In the context of starting materials, these limits should be specified to protect the quality specifications of the finished product into which the materials are being incorporated. Attention is importance here since the cost of rejecting a batch of starting materials is considerably less than the cost of rejecting a batch of finished product.

For instance, with the case of an oral liquid in aqueous solution comprising some colorants, flavorings and preservatives together making up less than 1%, plus an active at 2%, and having a finished product specification of not more than 10^3 microorganisms per milliliter. The major starting material is purified water. The microbiological limit of not more than 10^2 microorganisms per milliliter placed on purified water is quite adequate to protect the finished product's microbiological specification even if all of the other starting materials were to be specified at the normal level for starting materials of not more than 10^3 microorganisms per gram or milliliter.

In contrast, considering a syrup, again with an active at 2%, but containing 80% sucrose. If the sucrose were to have a specification of not more than 10^3 microorganisms per gram there would be very little protection afforded to the finished product's microbiological specification. In this case, the specification for the sucrose would have to be sensibly tightened.

Defects in packaging materials may be specified with associated acceptable quality levels (AQLs). These are expressions of the worst quality level that is still considered

satisfactory. Different AQLs may be applied to different defects according to their criticality. For instance, the inside diameter of the neck of a glass vial is likely to be a critical quality characteristic because of its potential effect on the maintenance of sterility, but glass flaws may be defined only as cosmetic quality characteristics and thus have "weaker" AQLs. The AQL is a statistical concept which when used in association with published tables defines the number of items that should be sampled and tested and how many defective items may be tolerable within a particular sample size.

It is customary that each batch of finished pharmaceutical products is sampled and tested against its specification for purposes of deciding it is suitable for release. For microbiological specifications, this is not always the case:

(a) where parametric release has been allowed for terminally sterilized pharmaceutical products, the test for sterility may be omitted;
(b) it is very unusual (even though limits may be registered) for batch by batch microbiological release testing to be applied to solid oral dosage forms such as tablets unless they contain high proportions of starting materials of plant or animal origin or known to carry high levels of contamination. This elimination or reduction of testing for specific dosage forms is a matter of professional judgement and risk and should always be justified and documented in the company's procedures;
(c) similarly, it is very unusual for batch by batch microbiological release testing to be applied to nonsterile products containing antibiotics. Once again, the justification for allowing this should always be justified and documented in the company's procedures.

For starting materials, GMP typically requires that there should be appropriate procedures or measures to assure the identity of the contents of each container of starting material. This is typically via an identity test. This applies to material identity but not necessarily to impurities, defects, or other quality characteristics. Testing of these characteristics is a matter of judgement and risk, and justifications should be documented [3].

19.2.2 Batch manufacturing records

Global GMPs are very specific about the contents of batch manufacturing records (BMRs). A BMR is a description of the milestones along the critical path of manufacture against which manufacturing personnel identify who did what, when they did it, what they did it with, and the critical measurements they made.

Traceability is the key element of the BMR. BMRs are controlled documents, one blank copy should be issued for each batch scheduled for manufacture (or released if a computerized system is used) [4]. This document should be completed and returned to the quality department for checking. The documents should be up-to-date and reflect what actually goes on with processes [5].

Pharmaceutical microbiologists are involved with some parts of the BMR. These include:

(a) Sterilization records are generally included in BMRs and in some companies may be diverted to the pharmaceutical microbiologist for checking. If sterilization records are not checked by the pharmaceutical microbiologist, it may well be the microbiologist's responsibility to ensure that whoever is performing this essential function has proper training in sterilization science and technology;

(b) In aseptic manufacture of sterile products, there may be a BMR for media fills. Within this BMR, the microbiologist may be required to complete the sections pertaining to verification of the growth support properties of the media, and to incubation and inspection of the media-filled containers.

Outside of these examples, it is generally only when there are problems, either in environmental microbiology or in failed finished product testing that the pharmaceutical microbiologist would be expected to encounter the BMR as a part of an investigation into potential manufacturing causes of the problem.

19.2.3 Manufacturing standard operating procedures (SOPs)

Whereas BMRs describe the milestones along the critical path, they do not provide the detail required to define adequately how the various tasks making up the manufacturing process should properly be done. For example, consider set up of an aseptic filling machine which may in the BMR detail only:

- names of the personnel undertaking the set up;
- start time;
- finish time;
- sterilization records of the parts installed.

When it is considered that set up may involve two or three personnel and the difference between the start time and the finish time is unlikely to be less than 30 min and possibly as long as 90 min, it can be appreciated that this is in fact a very complex procedure indeed.

Such complex procedures must be defined and decided and agreed by management through standard operating procedures. The pharmaceutical microbiologist should have an involvement in all manufacturing SOPs that impact on hygiene. This could include, for instance, water system operation, clean-in-place cycles, and process water systems.

19.3 Validation

There are varying definitions of validation within the pharmaceutical setting. One of the clearest is provided by Agalloco, who writes [6]:

> *Validation is a defined program, which in combination with routine production methods and quality control techniques, provides documented assurance that a system is performing as intended and/or that a product conforms to its predetermined specifications. When practiced in a lifecycle model, it incorporates design, development, evaluation, operation and maintenance considerations to provide both operating benefits and regulatory compliance.*

Validation is a critical concept in the pharmaceutical manufacturing industry. There are some key quality attributes, which include [7]:

(a) Documented evidence: validation is an activity which must be recorded and be formally documented for inspection;

(b) Consistently: a process that cannot be shown to be capable of performing consistently in the manner intended is of little value to manufacturing. One of the tenets of validation is that before a process is released for routine manufacture, it should have been shown through a sufficient number of replicate trials that it is capable of performing consistently;
(c) Pre-determined: the expression predetermined when applied to specifications and quality attributes indicates that validation is a confirmatory exercise and not an exploratory one. The exploration involved in new manufacturing processes belongs with the concept of development; it can be determination of what works (and preferably why it works), what its bounding limits (parameters) may be, and even process optimization, but it is not validation. Validation follows only when the limits have been predetermined. Hence, validation is confirmatory.

Good validation is well planned. Thus, the validation program should be defined and documented in a validation master plan (VMP) or equivalent documents. VMPs commonly contain [8]:

(a) *Application and scope*. The VMP must describe unambiguously what is being validated (the application) and the scope of the validation. For instance, it might be that the application is validation of blending for a particular tablet product, using a specific blender located in a particular blending room (the scope). It may be that the blender has been in previous use in that location and some qualifications have been already done in connection with other validations. In such a case some, but possibly not all, qualifications may not need to be repeated but may merely be referenced. On the other hand, it may be that the qualifications done previously need to be re-examined and perhaps updated. The definition of these activities belongs in the VMP;
(b) *Qualifications*. In some instances, it may be practical to combine qualifications, and if this is the case, it should be stated in the VMP. It is universally the case that all new processes are prospectively validated (i.e., all qualifications must be complete before the process is released for routine use), but there may be items of equipment or services (e.g., steam generators, compressors, etc.) identified when preparing the VMP that have not been previously qualified. If this is the case, their retrospective qualification should be included in the VMP;
(c) *Standards*. The VMP is not the place for detailing the standards and limits being applied, this would merely amount to a repetition of detail necessarily included in the qualification protocols. However, it might be that the standards being applied differ, and the VMP is the place to state which standards apply;
(d) *Deviations*. Any deviations that occur need to be addressed and signed off before the validation itself is allowed to be completed;
(e) *Disposition of materials*. The VMP should define if product (or intermediates) manufactured as a part of validation trials may be released to market, and under what conditions this might be possible;
(f) *Revalidation*. Validation does not stop with the final sign off on the VMP. The philosophy of validation is that it continues through the "lifecycle" of an item of equipment or a process.

Generally, validation activities are structured in the same way. Here, there are a series of qualifications that must take place sequentially; each qualification must be completed and signed off before the subsequent one is allowed to begin, and all must be completed and in place before the final validation can be approved and the process released for routine use. Each qualification comprises a protocol predetermined and approved before the work is allowed to begin, reflected by a report on which the actual results obtained are recorded.

Validity should be reviewed periodically (validation review) through scrutiny of equipment logs, maintenance records, deviations, out-of-specifications, and periodic product quality review reports to determine if the equipment or process is still operating consistently to the same predetermined specifications and quality attributes. If not there may be some further requirement for process development or equipment modification or even withdrawal from use. The frequency for formal validation review should be defined in the VMP [9].

Mostly "re-validation" in the sense of repeating some aspect of the original validation (usually performance or process qualification) is only required in the event of a significant change, or from something highlighted in validation review [10]. However, there are some processes and items of equipment (notably sterilization processes, autoclaves, ovens, tunnels, etc.) that require a regular periodic re-qualification. Mostly, the processes requiring re-validation have been identified by the regulatory authorities either in guidance documents or through custom and practice at inspection. They have been determined from risk analysis (probably intuitively rather than by formal risk analysis) and are largely in those areas where serious patient risk could arise from undetected or undetectable "slippage" in the performance of a piece of equipment or a process.

19.3.1 Qualifications

As a part of the validation approach, there are a series of qualifications that form a part of the process [11]. These are discussed below.

(a) User requirement specification (URS). For any new project, there has to be a URS. Some URSs may never lead on to validation. This is because the URS is an expression of what a potential user of a new piece of equipment wants, but the item of equipment may never be approved and purchased. The URS predates the VMP.

For instance, when the pharmaceutical microbiologist needs a new laboratory autoclave, they should define the loads that they want to sterilize; the size of the device; and the means of its operation.

Once a URS exists and an approval in principle to purchase is obtained, functional specifications or designs may be obtained from various suppliers for whatever has been identified. Once it is decided what is going to be purchased, a VMP can be launched, and the validation program formally begins [12].

(b) Design qualification (DQ). DQ compares the functional specification or the design to the URS. A DQ protocol can be as little as a "tick list" reflecting the content of the URS.

If the URS has been prepared properly, DQ will reflect the compromises that are necessary in the "real world." Nothing "fits perfectly," but it might fit well enough. The purpose of DQ is to determine where the compromises may have to be made and whether they are acceptable.

(c) Installation qualification (IQ). IQ is the process of verifying that what the user believed they were buying is really what you got. IQ protocols identify the key elements of the specification or design. For instance, if an item of equipment was specified to be made from 316L stainless steel a metallurgy certificate needs to be provided alongside the piece of equipment.

(d) Factory acceptance test (FAT). If the company is purchasing a major piece of equipment, say an autoclave from Italy, it makes no sense to wait until it arrives in the warehouse before verifying that it has been built to the correct specification. For this, FAT is permitted; but

this testing has to be done under the supervision of the purchaser's representatives, using the purchaser's documentation. An alternative option is site acceptance testing (SAT) in which verification is done in an engineering workshop or a warehouse rather than on the manufacturing floor.

(e) Operational qualification (OQ). OQ addresses whether the piece of equipment is capable of performing in the manner intended over the operating range intended, when installed and supported by local services. It also embraces calibration of measuring devices, establishment of maintenance procedures and schedules, training of maintenance operators, establishment of operating procedures, and training of production operators. The OQ may in some cases be conveniently amalgamated with IQ.

It is commonplace that, apart from the qualification of a new piece of equipment, there may also be a need to investigate how it operates best and to "optimize" it. Although this work may be being done on the same equipment and in the same broad timeframe as OQ it should be regarded as a development exercise and recorded as such.

(f) Performance (process) qualification (PQ). The final qualification, PQ, involves production materials or validation batches. It is PQ that calls for replication (as stated above, usually three times up to now, but who knows how many times in the future except that the number should be a function of risk and is unlikely to be less than three).

The process conditions must be defined and complied with during PQ, and the output must comply with its specifications. If PQ fails to comply with its acceptance criteria, either with respect to the process parameters or with respect to the product specification, or both, there is no choice but to re-develop the process through modifications either to the equipment or to the ways of operating the equipment.

19.3.2 Cleaning validation

A specialized area of validation, and of importance to pharmaceutical microbiology and to contamination control, is cleaning validation. This topic acts as a concrete example of how validation and microbiology interact. Cleaning validation is about providing proof of the effectiveness of the ways in which items of manufacturing equipment are cleaned. This presupposes of course that a cleaning process has been defined.

There are various levels of risk associated with cleaning validation [13]:

- Cleaning between different products. The consequence of carrying an active pharmaceutical ingredient into a second product which should not contain it is that the second product becomes adulterated. This is obviously serious and is a major risk in multiproduct equipment;
- Cleaning between batches of the same product. The risks here are lesser than between different products, but impurities and break down products can be carried over;
- Carry-over of cleaning agents. A self-created problem, but a problem nonetheless; indeed one which could be more consequential than carry-over between batches of the same product;
- Presence and survival of microorganisms.

The effort required to be included in cleaning VMPs and protocols is a reflection of the risk level involved.

Cleaning validation customarily requires selection of the "most difficult to clean product" among a range used on multiproduct equipment. Removal by cleaning should be tested for by product-specific methods; limits on residues can be calculated

from advice contained in the various regulatory guides on the topic. Suspensions and emulsions are generally regarded as being among the most difficult to clean products. High solubility in water often makes cleaning easier.

The second important decision to make and document in cleaning VMPs is where to sample for residues—the "most difficult to clean locations." Dead-legs in pipework, areas beneath valve seatings, and so on are amongst typical locations. Direct swab samples are preferred to rinse samples.

Microbiological considerations are required by the regulations to be included in cleaning validation. Arguably, microbiological considerations should consist largely of preventative measure rather than removal of contamination once it has occurred. This points directly to an expectation that the pharmaceutical microbiologist's role extends beyond the laboratory, really to the URS.

Moreover, routine cleaning and storage should not allow microbiological proliferation. Drying after cleaning is perceived to be the most important aspect of preventing proliferation. A good approach emphasizes that even if cleaning is followed at some time later by a sterilization process, there is the attendant risk that microorganisms may have proliferated to the extent that unacceptably high levels of endotoxin/pyrogens may remain on the equipment, and by surviving the sterilization process come to contaminate products manufactured on the equipment.

19.3.3 Other validation exercises requiring the involvement of pharmaceutical microbiology

Potentially, pharmaceutical microbiology could be involved in all validations. This section briefly validates where pharmaceutical validation is important.

(a) Design of new facilities (and modification of existing facilities). Hygiene is a critical quality of all pharmaceutical manufacturing facilities, not just those dedicated to manufacture of sterile products. Pharmaceutical microbiologists should contribute to HVAC design, facility design and to the selection of materials versus disinfectant activity, etc.;

(b) Installation of new water systems (and modification of existing water systems). There are very few problems with water systems meeting the chemical and physical properties of pharmacopoeial grade waters. Microbiological problems are almost inevitable except where high temperature storage and distribution systems have been installed;

(c) Installation of new thermal sterilization processes;

(d) Introduction of new processes involving bacteria-retentive filtration. The microbiological qualification of bacteria-retentive filters is a highly specialized job, generally undertaken by the filter suppliers. Nonetheless, the pharmaceutical microbiologist should be involved in verifying that this has been done and may well be the person who has to explain it at inspection;

(e) Process qualification of all products with a significant water content. Microorganisms need water to grow and increase in numbers. Conversely, wherever there is water, there is also the potential for microorganisms to grow and increase in numbers. The types of microorganisms that grow in aqueous environments generally have extraordinary biochemical properties that allow them to metabolize complex pharmacologically active molecules, have the capability of causing infections in even healthy patients, and have the ability when present as an infection, to resist antibiotic therapy.

19.4 Conclusion

This chapter has examined two important aspects of the modern pharmaceutical plant: documentation and structure of manufacturing, and the steps required with process validation. With each of these, there is a very important role for the pharmaceutical microbiologist, not least in ensuring that adequate steps are being taken in relation to contamination (and that these have been reliably demonstrated). The foremost way to achieve this is through risk assessment, applying the principles and approaches discussed in Chapter 18.

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