Reviewing Sterile Products – Examining the Factors Required for Release

White Paper

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Preparing equipment for aseptic processing (Image: Tim Sandle)

Introduction

This white paper provides an insight into the critical microbiological quality attributes required for the manufacture of sterile products, including bioburden and endotoxin control. In doing so, the paper presents a holistic approach for batch release based on ensuring there is an assurance of sterility. In addition, this paper assesses the physical control factors needed to support sterile products manufacture, including those that should be considered as part of batch release. This understanding of control extends to the steps necessary for fill and finish activities, in line with current Good Manufacturing Practices (GMP)[1].

Batch release is the final part of the manufacturing process and it is the last chance to prevent unsuitable product from being released. One of the most important aspects during the review of an executed batch record is the documentation of any unexpected or atypical events that may have occurred. As well as assessing that the product is efficacious, a sterile product assessment brings with it some additional concerns.

The presence of microorganisms in pharmaceutical preparations may reduce their efficaciousness or make them unsafe for the patient. The severity of the consequences of having microorganisms present in pharmaceutical preparations differs according to the purpose of the preparation and its route of administration. It is in relation to the severity from the risk of contamination, and due to the route of administration, that sterile products are at the greatest risk from microbial contamination. Assessing the control factors that could impact upon sterility assurance are therefore of great importance for the batch release process[2].

The prerequisites for sterile products are[3]:

1. They are sterile (in all probability, based on the control of sterility assurance)
2. Pyrogen free (apyrogenic)
3. Free of visible particles

Other key quality attributes for sterile products are:

- Chemical / biological purity
- Correct dose / strength – correctly labelled
- Correct physical form e.g. colour, particle size, viscosity
- No physical contaminants

Batch release is the process of reviewing and approving all pharmaceutical product manufacturing and control records. It is performed by the Quality Unit to determine compliance with all established approved written procedures before a batch is released. The process of batch release, and the authority and training of the persons eligible to do so, varies according to different GMP systems.

Regulations

The important regulations impacting on sterile products manufacture and batch release are:

United States of America (USA):

- Good Manufacturing Practice (cGMP) regulations (Code of Federal Regulations sections CFR 210 and 211).
- US Department of Health and Human Services, Food and Drug Administration, "Guidance for industry: Sterile drug products produced by aseptic processing – current Good Manufacturing Practice"

Europe:

- Euradlex. The Rules Governing Medicinal Products in the European Community, Annex 1, published by the European Commission
- Guideline on the sterilisation of the medicinal product, active substance, excipient and primary container - EMA/CHMP/CVMP/QWP/850374/2015

Pharmaceutical Inspection Co-operation Scheme (PIC/S):

- PIC/S GMP Guide PE 009-9
- Aide-Memoire Inspection of Utilities PI 009-3
- Aide Memoire on Inspection of Quality Control Laboratories PI 023-2
- Validation of Aseptic Processes PI 007-5
- Recommendation on Sterility Testing PI 012-3
- Isolators Used for Aseptic Processing and Sterility Testing PI 014-3
- Technical Interpretation of Revised Annex 1 To PIC/S GMP Guide PI 032-1

World Health Organisation (WHO):

- WHO. "Quality Assurance of Pharmaceuticals: A compendium of guidelines and related materials". Volume 2. Good Manufacturing Practices and Inspection. 2nd edition. WHO Library Cataloguing – in-Publication Data, Geneva

Sterility and Sterility Assurance

A good facility design (ideally including the presence of a barrier system) and the constant control on process critical steps and variables (including sterilisation), together with the continuous monitoring of environmental contamination, can provide a satisfactory degree of confidence level regarding process capability of protecting each and every product unit from microbial contamination. This confidence level has been defined as 'sterility assurance' and it is often assessed through a contamination control strategy[4].

Sterility itself can be defined as 'the absence of all viable microorganisms'. Therefore, something would be deemed sterile only when there is complete absence of viable microorganisms from it. Sterility is an absolute term. Either something is sterile, or it is not. There is no such thing as 'slightly sterile' or 'almost sterile'.

Sterility Assurance System is a term used to describe the sum total of the arrangements made to assure the sterility of products. For terminally sterilised products these typically include the following stages:

1. Product design
2. Knowledge of and, if possible, control of the microbiological condition of starting materials and process aids (e.g. gases and lubricants)
3. Control of the contamination of the process of manufacture to avoid the ingress of microorganisms and their multiplication in the product. This is usually accomplished by cleaning and sanitation of product contact surfaces, prevention of aerial contamination by handling in clean rooms or in isolators, use of process control time limits and, if applicable, filtration stages
4. Prevention of mix up between sterile and non-sterile product streams
5. Maintenance of product integrity
6. The sterilisation process

Central to sterility assurance are the principles of quality risk management (QRM). The QRM concept is an important part of science-based decision making which is essential for the quality management of pharmaceutical manufacturing. ICH Q9, Quality Risk Management5, defines QRM as a systematic process for the assessment, control, communication and review of risk to the quality of drug product across the product lifecycle. Similarly, the FDA's cGMPs for the 21st Century: A Risk-Based Approach[6], states that using a scientific framework to find ways of mitigating risk while facilitating continuous improvement and innovation in pharmaceutical manufacturing is a key public health objective, and that a new risk-based pharmaceutical quality assessment system will encourage the development of new technologies[7]. Where possible as much data as possible should be obtained through real-time monitoring to enable the batch manufacturing to flow between stages. Such a strategy also helps to minimise drug recalls. The sterility assurance assessment should feed into the overall quality management system for the manufacturing site[8].

Aseptic processing

Manufacturing of sterile drugs or active pharmaceutical ingredients by aseptic filling represents one of the most challenging pharmaceutical operations. Aseptically filled products contain molecules that, due to their nature, cannot be terminally sterilised in the final container by the conventional sterilisation processes.

Because of this, sterilisation takes place on the formulated bulk product (typically by filtration) and the subsequent process steps (such as filling, lyophilisation, closing, crimping and so on) must be executed in a manner that prevents any possibility of microbial contamination of the product.

Due to contamination risks coming primarily from personnel, when an aseptic filling takes place, the manufacturing environment represents a key element for the quality of the final product and the manufacturing processes and personnel interactions must be carefully designed and implemented in order to guarantee that no product containers could be contaminated by microorganisms coming from the surrounding environment.

Performing an aseptic filling, there are many variables that must be defined and kept under control. These variables involve different elements in the process, such as personnel gowns and aseptic behaviour (particularly during interventions in the proximity or within the area where the product is exposed to the environment), HVAC and air filtration systems (including pressure differentials between adjacent areas), cleaning and disinfection procedures, materials and personnel flows. In this scenario, monitoring of environmental contamination (viable and non-viable) is a critical activity and regulators have progressively put in place stricter contamination limits in areas where aseptic filling takes place. Understanding whether these variables are in control is essential for the personnel tasked with batch release.

Parametric Release and Terminally Sterilised Products

Parametric release is a system of release based on information collected during the manufacturing process and based on verifiable compliance with GMP. Parametric release is based on evidence of successful validation of the manufacturing process and review of the documentation on process monitoring carried out during manufacturing to provide the desired assurance of quality of the product. It is a system of release that gives the assurance that the product is of the intended quality based on the information collected during the manufacturing process and on the compliance with specific requirements related to parametric release resulting in the elimination of certain specific tests of the finished product. In essence, it has come to mean release of sterile products without recourse to a pharmacopoeial Sterility Test. Parametric release can only be applied to terminally sterilised products; there are differences between regulatory bodies as to the permitted sterilisation methods.

A pre-sterilisation bioburden monitoring program for the product and components must be developed to support parametric release. The bioburden should be performed for each batch. The sampling locations of filled units before sterilisation should be based on a worst-case scenario and be representative of the batch. Any organisms found during bioburden testing should be identified and their impact on the effectiveness of the sterilising process determined. Where appropriate, the level of pyrogen (endotoxins) should be monitored.

In those cases where parametric release has been authorised, a robust system needs to be applied to the product lifecycle validation and the routine monitoring of the manufacturing process.

The principle is normally applied to all terminally heat sterilised products but cannot be applied to aseptically filled products. For a sterilisation process to be eligible for parametric release:

- It should have been validated through thermal and biological qualifications and should demonstrably be capable of achieving 10-6 Sterility Assurance Levels referencing a Biological Indicator of defined resistance to the sterilisation process
- The integrity of the containment system for products proposed for parametric release must have been qualified through microbiological challenges
- The pre-sterilisation bioburden must be tested for each batch of product eligible for parametric release. All spore formers isolated must be identified and have their resistance to the process determined. If any such organism is found to be more resistant than the Biological Indicator used in validation of the process, the steriliser load must be rejected

Some inspectors are wary about parametric release and the company should prepare an appropriate rationale. Furthermore, the parametric release process should not be a static system, and the system needs to be periodically reviewed.

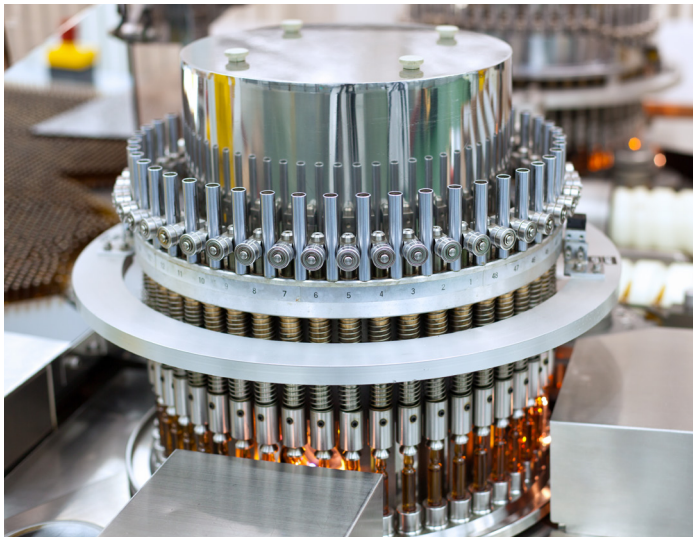
When seeking approval for parametric release, regulators will tend to ask that[9]:

- The manufacturing process is validated adequately
- It is reliably controlled
- The relationship between end-product testing and process monitoring, including justification of acceptance criteria
- In-process requirements chosen for approval/rejection are decided on the basis of the acceptance criteria defined in the validation records
- Clear, specified procedures are in place describing the reporting and actions to be taken on approval/rejection
- Historical batch data

Batches and Batch Processing Records

With pharmaceutical manufacturing, a batch refers to a specific quantity of a drug or other material that is intended to have uniform character and quality, within specified limits, and is produced according to a single manufacturing order during the same cycle of manufacture. Importantly, a batch refers to the quantity of material and does not specify the mode of manufacture. With the production of a batch, Good Manufacturing Practice requires that a detailed record be kept of every stage of the manufacturing, testing and release process. Different terminology is applied to the 'batch record'. Some examples are[10]:

- Batch Manufacturing Record (BMR)
- Batch Processing Record (BPR)
- Batch Processing and Control Record (BPCR)
- Batch Manufacturing Record and Batch Packaging Record (BMR and BPR)



It may sometimes be necessary to divide a batch into a number of sub-batches, which are later brought together to form a final homogeneous batch. In continuous manufacture, the batch must correspond to a defined fraction of the production, characterised by its intended homogeneity. The batch size can be defined either as a fixed quantity or as the amount produced in a fixed time interval.

Batches are often produced with reference to a master formula. This is a document or set of documents specifying the starting materials with their quantities and the packaging materials, together with a description of the procedures and precautions required to produce a specified quantity of a finished product as well as the processing instructions, including the in-process controls.

Batches are assigned a number (or lot number). This is 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. The batch number must be reflected in the batch record. A batch record – either manual or electronic – is based on a 'master record', which refers to a document or set of documents that serve as a basis for the batch documentation (in other words a blank batch record or appropriate database fields). The master record will contain:

- Identification of product name
- Bill of materials detailing the weight, measure or count of each component needed to manufacture the batch
- Equipment list
- Component list
- Statement of theoretical yield at each step in the manufacturing process
- Expected yield of the finished product
- Specific instructions for each state in the manufacturing process
- Sampling and testing procedures
- Instructions for manual operations

The purpose of the master batch record is to ensure that all proper ingredients are added and that each step in the process is completed. Batch records are copies of the master record, enabling the manufacturer to record in documents when, how, by whom, with what tools and in what environment a product was produced. Hence, the batch record provides a history of each batch of product and of all circumstances pertinent to the quality of the final product. In relation to records, the date of manufacture is important. This is the date fixed for the individual batch, indicating the completion date of manufacture. With manufacture, the scope includes all operations of purchase of materials and products, production, quality control, release, storage and distribution of pharmaceutical products, and the related controls.

For the release of finished products, batches require review (normally by the Quality Assurance function). Batch review is not just about review of compliance to Good Documentation Practices (GDPs) – the Critical Process Parameters (CPPs) and the Critical Quality Attributes (CQAs) assigned to the product being manufactured must also be reviewed for compliance to specifications.

Arguably, batch record review can be improved by the transition from manual records to electronic records (provided that such records have been appropriately qualified and meet the data integrity requirements pertaining to computerised systems). An electronic batch record is one that provides evidence that an organisation properly handles and records all critical steps to produce each batch of a product.

The good design of batch processing records is discussed on the next page.

Personnel Tasked with Batch Release

The person responsible for certifying the batch needs to be responsible for ensuring all relevant duties have been met prior to certification in the relevant register. The individual will have responsibility to ensure that no product is released prior to the legal requirements GMP and supply being confirmed as met. Furthermore, the person should undertake their responsibilities in accordance with the Code of Practice and in the knowledge that the relevant quality systems are in place. Such individuals assess all the batch release test results alongside relevant manufacturing monitoring procedures and data (that is everything from spot checks and feedstock analyses to pipeline flow rates). Based on all this operational and analytical information, they decide whether a batch is acceptable for sale on the market or for use in clinical trials as an investigational medicinal product. The responsible person must be satisfied that the product is fit for use, that it complies with the terms of the marketing authorisation and will not put subjects at risk due to inadequate safety, quality, efficacy or quality control. It is a highly responsible position requiring specialist knowledge and experience of the specific chemical and manufacturing processes involved.

The major differences are between the U.S. and Europe. In the U.S., batch release is typically instigated by the person responsible for quality control; in Europe, there is the system for Qualified Persons (as discussed below).

Access to information

Persons responsible for the quality release of sterile products have appropriate access to manufacturing and quality information.

Knowledge, skills and experience

Those involved in the release of sterile medicinal products are required to possess adequate knowledge and experience in the manufacture of sterile products and their critical quality attributes.

This depth of knowledge is necessary, in order to allow such persons to ascertain that the sterile products have been manufactured in accordance with the registered specifications and are of the required quality.

What to Consider When Assessing Sterile Products for Release

Batch review is not just about the review of compliance to Good Documentation Practices - the critical process parameters and the critical quality attributes assigned to the product being manufactured must also be reviewed for compliance to specifications (and the most important critical quality attribute is sterility).

As part of the review, the responsible person should perform the following checks on each batch record[11]:

- Check that all entries are complete, including signatures and dates on attached chits and traces
- Ensure that batch processing limits have been met, or that deviations are identified where limits are not met. Here it is also important to look wider and consider any other batches which might be implicated from the cited error
- Check if calculations have been performed in line with the agreed formulae. Check that the calculation has been correctly performed
- During document review, ensure that approval boxes have been completed
- Confirm that transcriptions are correct
- Confirm that operators have been signed off to identify that a step has been completed but is not an independent verification of a step being completed
- Confirm that temperature readings have been completed
- Ensure that corrections are made in compliance with good documentation practice
- Assess whether specification codes have been checked against the presentation, bottle / vial / bag size and relevant prefix of the product. This will apply to all product streams
- Check each page for comments and satisfactory outcome to deviation reports
- Check printing materials are legible and apparently correct for the dose strength
- Check all checklists are completed and review comments
- Check that intermediates certificates are present when intermediate records are filed elsewhere
- Any controlled changes have been taken account of
- Any additional sampling, tests, checks or investigations have been carried out or initiated
- Check that the finished product test results are in compliance
- That quality department checks have been completed
- That deviations reported in the record have been satisfactorily resolved
- Batch number
- Quantity
- Expiry date
- Date of manufacture (as a technical characteristic)
- Potency, as required

Batch specific investigations need to be closed when the root cause has been determined and the corrective and preventative actions have been assessed and implemented.

Specific Points for Accessing Sterile Products

Raw materials

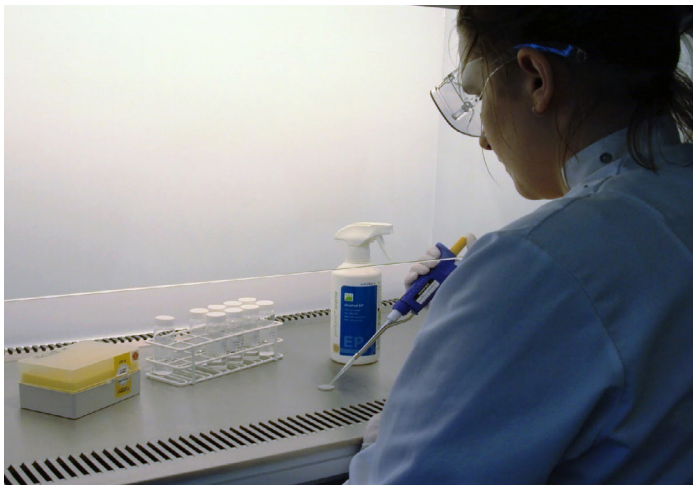
The quality of incoming raw material, active ingredient, and excipients must be assessed as having come from an approved supplier (to an appropriate pharmacopeial grade) and that the material has been properly received, sampled, and put into quarantine by the manufacturer. Typically, quality control testing is performed and reviewed prior to release. In relation to sterility assurance, this will include the Microbial Limits Test. Once the materials are deemed suitable, they should have been released to the manufacturing line for formulating and processing using appropriate documentation.

Other information that should be presented includes:

- The name of the manufacturer
- Identity and quantity of each shipment of each batch of raw materials, intermediates, or packaging materials
- The name of the supplier
- The supplier's control number(s) or other identification number
- The number allocated on receipt
- The date of receipt
- Records tracing the use of materials
- Documentation of the examination and review of materials for conformity with established specifications
- The final decision regarding rejected raw materials, intermediates, or packaging materials

In-process controls

An important feature of the pharmaceutical manufacture of sterile products is the microbiological monitoring of the product, at different stages, as it is being manufactured. Although such monitoring may not relate directly to the probability of sterility or non-sterility, such monitoring is a good indicator of whether something is going wrong or could go wrong.



Testing in-process samples (Image: Tim Sandle)

One important aspect of processing is process hold times. Here, time limits should be established and justified for each phase of processing period between the start of bulk product compounding and final sterilisation.

Such monitoring includes:

- The microbial limits and bacterial endotoxin monitoring of incoming pharmaceutical ingredients and packaging components
- In-process bioburden monitoring using the Total Viable Count (TVC) technique
- Pre-sterile filtration bioburden monitoring
- Disinfectant effectiveness testing, including checks for resistant strains

In terms of batch release, it is necessary to know that sampling has been undertaken to a pre-approved sampling plan and all test methods should be validated. It is also important that the data is regularly reviewed, and this should form part of the batch review. Any out-of-limits or out-of-trend results should be assessed, and the implications on batch disposition assessed.

In addition, the record should detail:

- That the materials were sequenced and combined in the proper order
- That the materials were mixed and stirred for the required length of time
- Any hold times, for equipment or product, to ensure they were within the validated time

The following should also be assessed as part of intermediate manufacturing:

- The name of the intermediate / being manufactured and an identifying document reference code
- A complete list of raw materials and intermediates
- 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

Furthermore, the following should be detailed in the batch record:

- Sequences to be followed
- Ranges of process parameters to be used
- The methods, or reference to the methods, to be used for preparing the critical equipment (e.g. cleaning, assembling)
- 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

Bioburden and endotoxin control of water

Water systems, in terms of generation and distribution, will need to be subject to scrutiny. Suitably controlled means of preparation, storage and distribution must be employed to ensure that endotoxin levels are complied with at point of use. Systems and user points require regular monitoring for endotoxin and bioburden. With endotoxin, the level must be <0.25 EU/mL and with bioburden, the level must be <10 CFU/100mL (with R2A agar used as the culture medium and the membrane filtration method employed).

While non-batch specific water results are not always supplied with batch records, the batch review process should capture any excursions linked to the time of manufacture and the impact should be noted, especially with the risk of endotoxin contamination of the batch.

Controls around water systems should be in place. If there has been any control breakdown, this should be identified, and the risk impact considered. As an example, the temperature range in hot re-circulating systems should be appropriate for the water system (e.g. 65-80°C for water-for-injections) and continuously monitored.

Other quality control tests

The specific types of quality control tests will be product dependent, outside of the sterility assurance controls discussed above. However, there are some important points of compliance which need to be applied to laboratory records supplied to the batch record.

Quality control testing (Image: Tim Sandle)

For example:

- Laboratory control records should include complete data derived from all tests conducted to ensure compliance with established specifications and standards, including examinations and assays
- There should be a description of samples received for testing, including the material name or source, batch number and, where appropriate, the manufacturer and / or supplier
- A reference to each test method used, including version numbers
- A statement of the weight or measure of sample used for each test as described by the method
- Data on the preparation and testing of any reference standards, reagents, and standard solutions must be provided
- A complete record of all raw data generated during each test
- A record of all calculations performed in connection with the test such as units of measure, conversion factors, and equivalency factors
- A statement of the test results and how they compare with established acceptance criteria
- A justification needs to be provided of any modifications to an established analytical method
- Any applicable Out-of-Specification (OOS) investigations

Sterilisation and depyrogenation controls

Different parts of the sterile manufacturing process will require sterilisation or depyrogenation. This is either conducted in-house or in relation to products purchased. With in-coming materials, certificates must be assessed to ascertain that sterilisation has been achieved. In addition, it is a GMP expectation that the manufacturer has the same oversight into the sterilisation process undertaken by a supplier to the same degree as if sterilisation was conducted by the sterile products manufacturer. This degree of confidence is supported by audit.

In terms of sterilisation and depyrogenation conducted in-house, the batch release process must include an assessment of all control parameters. These processes relate to vessels, vials, stoppers and so on.

In addition, for terminally sterilised products, sterilisation is conducted on the finished product. Importantly, sterilisation records should be available for each sterilisation run and they should be approved as part of the batch-release procedure.

With depyrogenation, this process is necessary to inactivate endotoxin. With aseptically filled products using glass vials, depyrogenation using a dry heat tunnel is a key part of the process. The regulatory standard for validation of an endotoxin inactivation (depyrogenation) process is that it should be capable of reducing an endotoxin challenge through 3 log10 reduction.

This is normally performed using a high challenge of endotoxin (>10,000 EU/device), assessed at six-monthly intervals. For routine operation, the temperature of the depyrogenation oven and the time within the oven that devices spend must be within the control parameters (this is normally greater than 250°C).

With steam sterilisation, as conducted using an autoclave, the most important compliance aspect in relation to autoclave operation is in ensuring that all the trapped air is removed from the autoclave before activation, as hot air is a very poor medium for achieving sterility. It follows that failure to sterilise in porous load autoclaves is almost always due to air being trapped

Isolator preparation at RSSL

in the load. Another area that requires assessment is with ensuring that the load is dry; wet loads, which can occur due to problems with steam quality, are a sign of non-sterility.

Autoclaves should be regularly assessed using biological indicators (to show that a sterility assurance level of 10^{-6} is achieved) and thermometrically. The validation of steam sterilisation in autoclaves follows the same pattern as any other validation in the regulated pharmaceutical industry, except for a requirement for more frequent repeat validations (usually at six-monthly intervals). Some of the challenges around sterilisation can be overcome with the use of sterile, disposable plastic devices, although suitable checks are required to the reactivity of such devices in terms of leachables and extractables[12].

Sterile filtration

Filtration will normally occur at different stages of the manufacturing process for sterile products. For aseptically filled products, a final sterilising filtration step is required in order to connect the finished bulk to the filling line. Filtration is a means of sterilising fluids by removing, rather than inactivating, microorganisms. The sterilisation of liquids is used extensively in aseptic manufacturing; sterilisation of gases is used both in terminal sterilisation and in aseptic manufacture.

An important compliance aspect of filtration is pore and integrity testing. The porosity quoted for filters is not obtained by physical measurement of the dimensions of the pores. It is done on the basis of the pressure which is required to displace liquid from the pores – essentially a bubble point value – coupled to a formula which takes account of the pressure required, the surface tension of the liquid and the contact angle between the liquid and the surface of the pore.

The “bubble point test” is also one of several options that the regulators require all users of bacteria-retentive filters to apply to their filters before and after use. In validation, the filter suppliers provide a “bubble point” value for their filters. The user may either test his filter by increasing the pressure on a wetted filter until the wetting liquid is displaced (determination of an actual bubble point) or increase pressure to the level given by the filter supplier as the bubble point. As long as the wetting liquid is not displaced the filter can be safely assumed to meet the requirement.

The main reasons for filter failure are:

- Incorrect assembly in the housing – this occurs more frequently than it ought to
- Flawed or defective cartridges
- Membrane failure – this occurs less frequently than one might imagine
- Grow-through of microorganisms

Biodecontamination

Devices such as isolators used for aseptic filling are ‘biodecontaminated’. The most common (but not only) means to do so is using hydrogen peroxide vapour. This is not classed by EU regulators as a sterilisation process (due to the vapour having no penetrative ability); and there is an additional requirement that product contact parts (such as filling needle manifolds and stopper bowls) are subject to separate sterilisation processes.

Vaporised Hydrogen Peroxide (VHP) is commonly used for isolator technology. One means to produce VHP is by the vaporisation (at 120°C) of liquid hydrogen peroxide to give a mixture of VHP and water vapour. As a ‘dry’ process, the concentration of VHP is maintained below a given condensation point, which is dependent on the area temperature. Its advantage over other gaseous decontamination agents is that hydrogen peroxide decomposes to water and oxygen, which are relatively safe and so-termed ‘residue free’.

The important compliance aspects relate to the physical properties of the item being decontaminated. It must be relatively smooth, impervious to moisture, and be of a shape that permits all surfaces to be exposed to the vapour. Key parameters to assess include chemical (‘gas’) concentration, humidity, temperature, and vapour dwell time.

The importance of operator hygiene (Image: Tim Sandle)

Assessment of environmental monitoring

An important aspect of ensuring that control is maintained within the pharmaceutical facility is through the environmental monitoring programme. Importantly, environmental monitoring is not the same as environmental control. Environmental monitoring should be captured in a formal programme. In the context of this white paper, the programme is designed to describe the particulate and microbiological monitoring undertaken during batch filling[13].

All excursions must be investigated and root causes determined. This will include a corrective action plan when action levels are exceeded. Where Grade A samples exceed the action level, a detailed assessment is required into the batch disposition, to determine if the batch is suitable for release.

As there is little regulatory guidance as to the environmental monitoring programme, the batch release group must be satisfied that monitoring has been conducted to a plan, with samples placed in locations that assess the risk to the product and with a frequency that captures every activity (such as manipulations through glove ports and any interventions).

The environmental monitoring techniques used should be compressive. The viable count aspect of environmental monitoring consists of enumerating the numbers of microorganisms present in a clean room by collection results using the following sample types:

a. Passive air-sampling: settle plates
b. Active air-sampling: volumetric air-sampler
c. Surface samples: contact (RODAC) plates
d. Surface samples: swabs
e. Finger plates (required for staff involved in filling activities)
f. Plates of sleeves / gowns (required for staff involved in filling activities)
g. Particle counting

Alternatively, rapid microbiological methods can be used (provided they have been evaluated to show equivalence or better compared with the conventional methods).

The requirements for batch fill monitoring should be rigorous and must provide assurance that the environment was under control at the time at which the batch fill took place. Batch related monitoring does not only include the period of filling - it consists of the following stages, for each of which a level of monitoring should take place. These stages are:

a. Filling machine set-up
b. The period between the machine set-up and the start of the fill
c. The batch fill activity
d. Post-fill monitoring of the filling machine, which should include critical surfaces such as stopper bowls and filling needles
e. An assessment of the post-fill machine clean-down

The most critical phases are, arguably, the set-up of the machine and the batch fill. Machine set-up provides the potential opportunity for contamination to be introduced into the Grade A / ISO class 5 clean zone.

Other aspects of filling

As well as environmental monitoring, other aspects of the batch filling process need to be considered, especially those which could impact on the sterility assurance assessment, such as downtime logs, line clearance logs, equipment and room cleaning logs, and equipment calibration status.

Sterility test

Sterility testing is a key GMP Microbiology testing requirement for sterile pharmaceuticals, medical devices and materials, to ensure they are safe for use. The test is:

- Always for aseptically produced products
- Terminally sterilised products – discussions are required with the regulator, as discussed above in relation to parametric release

The sterility test has its limitations, based around sample size (number of units tested), locations within the batch from which samples are drawn and with microbial culturability, where some stressed microorganisms may not be recoverable under the conditions of the test, in addition to those organisms regarded as 'viable but non-culturable'.

For some products it may not be possible to perform a sterility test prior to release because the shelf life of the product is too short to allow completion of a sterility test. In these cases, the site's contamination control strategy should clearly capture the identified risks, the additional considerations of design of the process and additional monitoring required to mitigate the identified risks.

Deviations

Other things to take account of are detailed below. Generally, these are items that are in control. If they go out-of-control, notification should be through a deviation report. The deviation should assess the impact (including batch disposition), detail the root causes and propose appropriate corrective and preventative actions. The person undertaking batch review should assess each deviation and be satisfied that the impact on the batch under review does not affect its sterility assurance[14].

General Manufacturing and Environmental Controls

Personnel tasked with manufacturing and testing

In an unusual situation, a supervisor may not think about scope and impact of a potential problem and fail to consider other products or batches that have been made and possibly affected.

Cleaning and disinfection

The cleaning and disinfection of pharmaceutical manufacturing areas is an important part of contamination control. Assurance should be provided that cleaning and disinfection has been performed to the standards expected.

Sterility Testing Isolators at RSSL

Environmental controls

Any variations with environmental controls which might impact on the batch during processing need to be assessed. This includes:

- All air handling systems having been commissioned and qualified
- Airflow velocities for unidirectional airflow devices should be measured at a defined distance proximal to the work surface (that is, at 'working height'). This is a prerequisite for aseptic processing

- Air exchange volumes (expressed as air changes per hour) should be sufficient to maintain the required room air classification and environmental conditions, and to achieve the required recovery time, from the respective cleanroom grade
- Between adjacent rooms of different air classifications (with doors closed), positive pressure differentials should be maintained and sufficient (that is at least 10-15 Pascals)

Media fill failures

The contamination risk associated an aseptic process needs to be evaluated through a simulation capable of including all the different aspects and variables of the whole aseptic process. This is through an aseptic process simulation (or 'media fill').

Here culture media is filled instead of the real product in the actual containers (media fill). Media filled containers can therefore be incubated, then 100% visually inspected and checked for microbial growth. By this 100% containers inspection, contamination rate associated with a media fill can be assessed directly, differently from the actual process where an extremely low and statistically insignificant number of containers (typically 20 or 40) are tested for sterility.

A prompt review of all appropriate records relating to aseptic production since the last successful media fill. The outcome of the review should include a risk assessment of potential sterile breaches in batches manufactured since the last successful process simulation.

It is important that all other batches not released to the market are included in the scope of the investigation. From then on, any decision regarding their release status should consider the investigation outcome.

Packing

While out-of-scope of this white paper, the batch release process needs to be included in an assessment of the batch packaging record, which needs to be in place for each batch or part batch processed. Such a record is based on the relevant parts of pre-approved packaging instructions.

Product Recalls

Recalls can arise through the improper release of batches. To take the example of Active Pharmaceutical Ingredients (API), an assessment of FDA warning letters relating to this activity shows the following common problems:

- Released quarantined API
- Failure to reject APIs contaminated with foreign material
- Released 36 batches with a test method not validated for its intended use
- Failure to ensure that all released lots and lots in inventory meet revised specification
- Issued outdated Certificate of Analysis that did not include the revised purity specification required by Biological License Application
- Failure to control, process, analyse and approve or reject raw materials and finished APIs
- Released product from non-validated processes and no stability testing schedules
- First batch released under concurrent validation with redline changes to process

Regulators will frequently delve into the batch release process. Where processes are very poor, this can lead to recalls being initiated.

Good Design of Batch Processing Records

As with other documents which form part of the quality system, pharmaceutical batch records should meet the principles of 'good documentation design'. This philosophy means the use of clearly written procedures, designed to prevent errors and to permit the tracing of all activities performed relating to the manufacturing, testing and release of the pharmaceutical product. To achieve this, batch records must be designed, prepared, reviewed and distributed with care. Furthermore, documents must have unambiguous contents: title, nature and purpose should be clearly stated. They must be laid out in an orderly fashion and be easy to check. Reproduced documents must be clear and legible. As part of the process, documents must be regularly reviewed and kept up-to-date. When a document has been revised, systems must be operated to prevent inadvertent use of superseded documents (e.g. only current documentation should be available for use).

Where batch records require the entry of data, these entries may be made in clear legible handwriting, in a suitable indelible medium (i.e. not pencil). Sufficient space must be provided for such entries. Any correction made to a batch record must be signed or initialled and dated – the correction must permit the reading of the original information. Where appropriate, the reason for the correction must be recorded. Each entry into the record must be kept at the time each action is taken and in such a way that all activities concerning the conduct of preclinical studies, clinical trials, and the manufacture and control of products are traceable.

It is also important to ensure storage of critical records takes place. That is storage within a system that is secure and with limited access only for authorised persons. The storage location must ensure adequate protection from loss, destruction or falsification, and from damage due to fire, water, and so on.

Why batch records go wrong

Errors invariably occur with batch records and such errors should be captured during the review process. The problem arises when the errors are missed and these errors are then connected with a reason to recall (either identified at a later date by the company or picked up upon re-review as a recall occurs due to another factor). Some of the common snags that frequently delay manual batch operations include:

- Incorrect data entry
- Failure to recognise out of spec entries
- Missing signatures
- Filling out incorrect forms
- Sending the wrong form to the wrong person
- Forms left incomplete

There are different reasons why batch records are not completed properly or contain errors.

Summary

Batch release carries considerable responsibility. It is, after all, the only evidence that remains after a batch has been manufactured to demonstrate that it was manufactured according to procedural and regulatory requirements. Particular care needs to be taken in relation to sterile products, whether these have been aseptically filled or terminally sterilised. This includes evaluating all of the data required to assess that the product is, in all probability, sterile. This is a combination of product related data, process related data and environmental control – which comes together as the sterility assurance system, supported by risk assessment and validation.

It is an important part of the assessment of pharmaceutical products that assurance is obtained and that adequate manufacturing standards and quality control testing measures are employed to assure that the product meets its quality specifications at time of release to market (and at the end of its shelf life). Failure to do so can result in products being recalled from the market.

This white paper has presented and explained many of the key factors that need to be considered when reviewing and releasing sterile medicinal products.

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About the author

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Dr. Tim Sandle has over twenty-five years' experience of microbiological research and biopharmaceutical processing. He is a member of several editorial boards and he has written over six hundred book chapters, peer reviewed papers and technical articles relating to microbiology. Dr. Sandle works for a pharmaceutical manufacturer in the UK, and is a visiting tutor at both the University of Manchester and UCL.

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