MANUFACTURING & QUALITY AUDIT DIVISION
CENTRE FOR DRUG ADMINISTRATION

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GUIDANCE NOTES ON PARAMETRIC RELEASE

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GUIDANCE NOTES

Subject: PARAMETRIC RELEASE

1 DOCUMENT HISTORY

This document originates from PIC/S and was adopted by PIC/S Committee on 22 May 2001.

2. GENERAL INTRODUCTION

2.1 The definition of Parametric Release used in this document is based on that proposed by the European Organisation for Quality: "A system of release that gives the assurance that the product is of the intended quality based on information collected during the manufacturing process and on the compliance with specific GMP requirements related to Parametric Release."

3. PURPOSE

3.1 The purpose of the document is to provide guidance for GMP inspectors to use for training purposes and in preparation for inspections of company premises where Parametric Release has been approved or applied for. In addition the document provides a framework for GMP inspectors and Marketing Authorisation assessors to work together and jointly approve an application for Parametric Release.

4. SCOPE

4.1 This guidance attempts to cover a wide scope that includes a reduction or elimination of routine finished product testing. Within the Finished Product testing group the elimination of routine sterility testing is a primary focus of interest. The document is organised to accommodate this focus of interest.

4.2 At the time of issue, this document reflected the current state of the art. It is not intended to be a barrier to technical innovation or the pursuit of excellence. The advice in this recommendation is not mandatory for industry. However, industry should consider this recommendation as appropriate.

5. DEFINITIONS / GLOSSARY

Failure Mode Effect Analysis - FMEA
An analysis of the process that assigns a numerical value on a defined scale (1 to 5 or 1 to 10 are most commonly used) to the following:

- probability of failure of a defined stage,

- probability that the failure will be detected before the product is released,
- severity of consequence if the product is released.

The numerical values are multiplied to produce a score. The magnitude of the score determines the priority with which the failure mode has to be prevented or controlled. More information can be found in R.G. Keiffer and A. Borgmann 'Applications of Failure Mode Effect Analysis in the Pharmaceutical Industry' Pharmaceutical Technology Europe, September 1997.

Hazard Analysis and Critical Control Points--HACCP
A systematic documented analysis of the process that identifies pivotal points of control and provides the details of methods of control with defined tolerances.

Parametric Release
A system of release that gives the assurance that the product is of the intended quality based on information collected during the manufacturing process and on the compliance with specific GMP requirements related to Parametric Release.

Reduction of human error
An analysis of the process from the point of view of the people operating it that takes into account known human fallibility's and provides ways to minimise their effects. The analysis should also include automated processes, software creation and use etc.

Sterility Assurance System
The sum total of the arrangements made to assure the sterility of products.
For terminally sterilized products these typically include the following stages:

(a) Product design.
(b) Knowledge of and, if possible, control of the microbiological condition of starting materials and process aids (e.g. gases and lubricants).
(c) 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.

(d) Prevention of mix up between sterile and non-sterile product streams.
(e) Maintenance of product integrity.
(f) The sterilization process.
(g) The totality of the Quality System that contains the Sterility Assurance System e.g. change control, training, written procedures, release checks, planned preventative maintenance, failure mode analysis, prevention of human error, validation calibration, etc.

Bioburden
The total level of microbiological contamination present.

Presterilization count
The estimate of the number of microorganisms present just prior to sterilization based on a validated method of determination.

Revalidation
A repetition of work carried out in the initial validation or subsequent change control process in which specific equipment/sterilization cycle/load configuration combinations are tested to show compliance with the same acceptance criteria that were used in the initial validation protocol or subsequent change control protocol.

6. PART I ELIMINATION OF ROUTINE STERILITY TESTING FOR PARAMETRIC RELEASE

6.1 Introduction

6.1.1 This section is only concerned with that part of Parametric Release which deals with the routine release of finished products without carrying out a sterility test. Elimination of the sterility test is only valid on the basis of successful demonstration that the sterility assurance system is fully robust and capable. Appendix I provides general recommendations for a sterility assurance system for terminally sterilised products. Specific guidance about eligibility for consideration for parametric release is also provided. All sterile products must be manufactured using an adequate sterility assurance system, and in those cases where the system is fully capable and robust parametric release may be authorised.

6.1.2 It is generally recognised that a sterility test only provides an opportunity to detect a major failure of the sterility assurance system which should be more reliably detected by other means. An alternative view is that the sterility test does provide the last chance to detect a failure and a decision to eliminate the test should not be taken without careful consideration.

6.1.3 Elimination of the routine sterility test may become acceptable with the application of technological advances and the commitment to maintain a rigorous quality system. This aspect of Parametric Release can take place if the data demonstrating correct processing of the batch provides sufficient assurance, on its own, that the process designed and validated to ensure the sterility of the product has been delivered and providing the following Principles have been respected.

6.2 Principles

6.2.1 At present elimination of routine sterility testing can only be approved for products terminally sterilized in their final container.

6.2.2 Sterilization methods according to Euro. Ph. or other relevant pharmacopoeia using steam, dry heat and ionising radiation may be considered.

6.2.3 Once parametric release has been granted, decisions for release or rejection of a batch should be based on the approved specifications. Non-compliance with the specification for parametric release cannot be overruled by a pass of a sterility test.

6.2.4 Authorisation for elimination of routine sterility testing should be given, refused or withdrawn jointly by those responsible for assessing products together with the GMP inspectors.

6.2.5 This document only addresses the aspects that the GMP inspectors will consider. The features that are clearly the business of the assessors include the following aspects of product and process design and their initial validation.

(a) The assurance of product integrity under all relevant conditions.
(b) The capability of the sterilization agent to penetrate to all relevant parts of the product.
(c) The choice of a suitable sterilization process.
(d) The compliance with microbiological limits.

6.2.6 These factors would also be checked by GMP inspectors on site.

6.2.7 It is unlikely that a completely new product would be considered as suitable for Parametric Release because a period of satisfactory sterility test results will form part of the acceptance criteria. There may be cases when a new product is only a minor variation, from the sterility assurance point of view, and existing sterility test data from other products could be considered as relevant.

6.3 The general basis for authorisation by the GMP Inspectorate

6.3.1 The safe elimination of routine sterility testing as part of a company's quality system will depend on the commitment of the company to maintain compliance to GMP at a high level. This should be a matter of general policy and not just be limited to the sterility assurance system. The evaluation of the historical compliance to GMP, as well as current compliance, would form one of the first steps carried out by the Inspectorate. An evaluation as good to excellent is necessary for the approval of parametric release. If the judgement of compliance to GMP is not clear, the decision should be taken by more than one inspector.

6.3.2 The history of non-sterility of product and of results of sterility tests carried out on the product in question together with products processed through the same or a similar sterility assurance system should be taken into consideration.

6.3.3 The sterility assurance system should be evaluated by inspection and review of documents and found to be fully capable and robust and this is elaborated in Appendix I.

6.4 The mechanism of authorisation

6.4.1 An application to vary a marketing authorisation or a group of similar authorisations should be evaluated as agreed between assessors and inspectors.

6.4.2 The inspectors involved in evaluation and inspection should have specific training in inspecting and evaluating sterility assurance systems. It may be of value to include an appropriately qualified assessor on the inspection.

6.4.3 Upon satisfactory evaluation by the inspector the Inspectorate may recommend that sterility testing be eliminated for a product or group of similar products.

6.4.4 With the approval of the Inspectorate and positive evaluation by the assessors a licence varied to authorise elimination of routine sterility testing can be issued.

6.4.5 If the assessor's or Inspectorates' confidence in the elimination of sterility testing for a company's products is reduced, either group should have a mechanism to withdraw approval. Reduction in confidence may follow an inspection, or on receipt of other information.

7. PART II REDUCTION OR ELIMINATION OF OTHER FINISHED PRODUCT TESTING FOR PARAMETRIC RELEASE

7.1 Introduction

7.1.1 This section is concerned with Parametric Release other than the elimination of routine sterility testing which is covered in Part I.

7.1.2 The results of a comprehensive set of in-process tests and controls may constitute sufficient grounds for batch release and provide greater assurance of the finished product meeting certain criteria in the specification without the tests being repeated on a sample of the finished product. Examples from tablet manufacture could be in-process testing of uniformity of mass, hardness, friability and disintegration. Other examples are the use of process analytical chemistry test methods, such as near-infrared spectrometry (NIR) and Raman spectroscopy, by which in line monitoring particle size, content of active substance, homogeneity, water content or film thickness can be achieved.

7.2 Principles

7.2.1 Authorisation for the reduction or elimination of finished product testing should be given, refused, or withdrawn jointly by those responsible for assessing products together with the GMP inspectors.

7.2.2 This document only addresses the aspects that the GMP inspectors will consider. Matters that were defined in the product licence prior to the

application for Parametric Release will require specific review by the assessors.

7.3 The general basis for authorisation by the GMP Inspectorate

7.3.1 The secure application of reduced frequency or elimination of specific tests will depend on the commitment of the company officers to maintain compliance to GMP at a high level.

7.3.2 The evaluation of the historical compliance to GMP as well as current compliance would form one of the first steps carried out by the Inspectorate.

7.4 The mechanism of authorisation

7.4.1 An application to vary a product licence or a group of similar licences should be evaluated as agreed between assessors and inspectors.

7.4.2 Upon satisfactory evaluation by the inspector the Inspectorate may recommend that the application for a product or group of similar products be accepted. Approval may be qualified by requiring a running in period of reduced testing. Even after full Parametric Release is operational occasional testing may be required.

7.4.3 With the approval of the Inspectorate and positive evaluation by the assessors a licence varied to authorise reduction or elimination of testing for Parametric Release can be issued.

7.4.4 If the assessor's or Inspectorate's confidence in the reduction or elimination of testing of a company's products is reduced, either group should have a mechanism to withdraw approval. Reduction in confidence may follow an inspection, or on receipt of other information.

REFERENCE

PI005-1 Guidance on Parametric Release. Pharmaceutical Inspection Co-operation Scheme (PIC/S).

APPENDIX I

RECOMMENDATIONS FOR A GENERAL STERILITY ASSURANCE SYSTEM FOR TERMINALLY STERILISED PRODUCTS AND PROVISIONS FOR PARAMETRIC RELEASE

1. INTRODUCTION

1.1 This appendix provides the basis for the inspection of a sterility assurance system on site and a checklist of documents that should be reviewed. The appendix should be viewed as an expansion in detail of some aspects, rather than addition to published GMP. Therefore manufacturers of sterile products should comply with the principles expressed, whether or not they are successful in their application for Parametric Release.

1.2 Some of the items stray into the field of investigation originally covered by the assessor of the product licence. This is necessary to confirm continued compliance and reassessment in the full context of manufacture and the possibility of change within the constraints of the licence.

1.3 The objective of the review of the sterility assurance system is to determine whether it is fully capable and robust. That is, can it achieve the objective of assuring the sterility of the product without the additional challenge of the sterility test and in addition withstand variations that may reasonably be expected.

2. OVERALL CONSIDERATIONS

2.1 A clear description of the sterility assurance system should be documented and available for review. Ideally this document should refer to or incorporate a detailed breakdown of each element with a formal risk analysis including potential failure modes of equipment and procedures and the potential for human error. Having identified these risks the document should describe how features of design, procedures and training have reduced them to acceptable levels. In addition there should be assurance that all critical failure modes that do occur will be routinely detected.

2.2 The disciplines of Hazard Analysis and Critical Control Points (HACCP) Failure Mode Effects Analysis (FMEA) and the Reduction of Human Error can provide the formal basis for such analyses. (See Definitions/Glossary)

3. PERSONNEL

3.1 A sterility assurance engineer with knowledge of automated systems, if applicable, and a microbiologist should normally be present on the site of production and sterilization. The continued presence of these sterility assurance experts provides a familiarity with the day-to-day operations together with informal supervision and availability that is unlikely to be provided by remote experts. The engineer and microbiologist should hold formal qualifications in engineering and microbiology respectively and have at least two years experience in relevant sterility assurance systems. A degree in Pharmacy may be adequate if there is evidence of specialisation in microbiology. It is recognised that experience may compensate for the formal qualification, but this can only be judged on a case-by-case basis. These people should have sufficient seniority and authority to enforce compliance for matters related to sterility assurance. There may be circumstances when the presence of just one of the two sterility assurance experts is sufficient provided the other is readily available.

3.2 All personnel involved in activities connected with sterility assurance should have a clear understanding of their part in the system with documented training, training reviews and retraining.

3.3 The number of people involved should be sufficient to cover normal absences due to holiday or sickness without having to work routine overtime.

4. CONTROL OF PRODUCT

4.1 The design and original validation of the manufacturing process should ensure that the integrity of the product can be maintained under all relevant conditions.

4.2 Review of routine in process and finished product integrity testing methods and results should demonstrate that product into which microorganisms could penetrate will not be released for sale. One of the advantages that may be lost by not carrying out the sterility test is the often functional manipulation of the product during the test which may, in the past, have revealed faults of integrity or other faults not detected by other tests. If there is evidence of product faults being detected in this way then additional testing to compensate for this should be operational before approving Parametric Release.

4.3 The change control system should require review of change by the sterility assurance engineer and microbiologist; small changes may have an effect on the sterility assurance system that are not apparent to other reviewers.

5. CONTROL OF PRESTERILIZATION BIOBURDEN

5.1 The control of presterilization bioburden is a component of most sterility assurance systems and in order to be eligible for parametric release there should be a system to control bioburden in product streams and thus control presterilization count (see Definitions/Glossary). If the history of batch-by-batch presterilization count and the rigour of the bioburden control system is satisfactory a case can be made to reduce the frequency of testing of presterilization count. All relevant parts of Annex 1 "Manufacture of Sterile Medicinal Products" of the GMP Guide should be reviewed for compliance.

5.2 Environmental control and its associated monitoring play a part in product bioburden control, but it is often a relatively small part. Hence, the primary focus of attention should be on the details of determining and controlling presterilization bioburden.

5.3 The sampling of filled units for presterilization bioburden determination should be based on worst-case scenarios, or be representative of the batch, and the following should be considered:

(a) their storage conditions before testing,
(b) the time of testing in relation to the start of sterilization,
(c) the suitability of the method of testing, which should include tests for microorganisms resistant to the sterilizing agent, should be reviewed.

5.4 The validation of the tests, the interpretation of results and the way in which batch release depends on satisfactory results should also be reviewed.

5.5 With regard to the methods used to assess bioburden there should be evidence that the company has evaluated any advantages that new technology may offer particularly in the detection of types of organism that may be resistant to the sterilization process.

5.6 For aqueous or otherwise microbiologically unstable products the time lag between dissolving the chemical starting materials, product fluid filtration and sterilization should be examined. These time lags should be set to minimise the development of pyrogens (if applicable) and bioburden.

5.7 The microbiological state of the container and closure should be controlled and meet limits based on sound microbiological rationale.

5.8 The microbiological state of the fluid contact parts of the filling system should be controlled. Note that this may include the following:
(a) Gases.
(b) Solvents.
(c) Lubricating fluids.
(d) Details of pipework.
(e) Sanitary connecting joints.
(f) Welds.
(g) Internal structure of valves, turbine fillers etc.

5.9 The following elements should be carefully reviewed as they are often involved in loss of control of bioburden:
(a) Design.
(b) Cleaning.
(c) Sanitation.
(d) Microbiological monitoring.
(e) Planned preventative maintenance.
(f) Breakdown repair.
(g) Change control and validation.
(h) Operator error or non compliance with procedure.

5.10 With regard to the product filter the following should be reviewed:
(a) The grade of product filter.
(b) The effect of product on the filter.
(c) Its initial microbiological condition.
(d) Its period of use.
(e) Whether it is washed, sterilized, and reused (the 'validation' of washing and prevention of build up of pyrogen should be investigated in detail).
(f) The method of integrity testing, off line or on line.
(g) Storage in between integrity testing and the next stage.
(h) At which stage in the process it is integrity tested.
(i) What decisions are taken if it fails the test.
(j) The microbiological state of the test equipment-particularly product contact surfaces on the clean side.
(k) Microbiological monitoring of product fluid after the filter.
(l) Method of sampling and holding conditions.

5.11 The relevance of environmental control of the filling area and the details of microbial control of stages prior to filtration, to the sterility assurance system should be evaluated and inspected accordingly. These areas still need review for pyrogen control and general aspects of GMP.

5.12 In the event of the loss of control of presterilization bioburden, particularly if this is due to a type of micro-organism resistant to the sterilization process, clues as to the root cause of the problem may be found in parallel loss of control in more peripheral areas.

5.13 There should be evidence of some level of monitoring and, if possible, control further back into the chain. This should extend to monitoring chemical starting materials particularly for the presence of microorganisms that may be resistant to the sterilizing agent. As an example, if a chemical is contaminated with heat resistant bacterial spores the mixing area will become contaminated and it is only a matter of time before cross contamination or a weakness in one of the control systems results in contaminated product and a challenge to the sterilization process.

5.14 The way in which monitoring limits are set and acted upon and the consideration of the need for trend analysis should be documented with a valid rationale.

6. STERILIZATION PROCESS

6.1 Only terminal sterilization processes that incorporate large safety margins will be considered for parametric release. If pharmacopoeial reference cycles are not used for moist heat processes, each unit of product should receive a minimum F_o of 8 together with a SAL of 10 -6 or better.

6.2 The sterilization process should be adequately validated initially and revalidation (see Definitions/Glossary) should take place at least annually with all combinations being revalidated within two years. The data should demonstrate that a specified minimum process is delivered to each unit and the sterility assurance level (SAL) can be achieved throughout the load.

6.3 Routine monitoring of the sterilizer should demonstrate that the validated conditions necessary to achieve the specified process and SAL are achieved in each cycle.

6.4 The expectation of detailed system analysis to discover all failure modes discussed in the **Overall considerations** section above is particularly relevant to sterilizers.

Each step of the often complex cycles should be known, the ways in which the step could deviate, the effect of this, and the ways in which the deviation could be detected or better, designed out, should all be available for inspection.

6.5 The loads validated should be precisely defined including position of product on the truck or carrier, and position of carrier in the sterilizer. They should also reflect loads that are routinely processed.

6.6 The validation studies should demonstrate that the sterilizing agent is homogenous or follows a predictable pattern inside the chamber.

6.7 Penetration of the sterilizing agent throughout all the necessary parts of the product should be demonstrated directly i.e. temperature for heat and radiation for irradiation processes.

6.8 Where there is no alternative, for example in microenvironments inside the product for heat processes, biological indicators may have to provide the only source of information confirming sterility assurance.

6.9 Appropriate sterilizer validation guidelines should have been consulted and the details of validation should have a properly documented rationale. For irradiation process EN 552: 1994 "Sterilization of Medical devices -Validation and routine sterilization by irradiation" may be applicable.

6.10 The tolerances that will be used to define the acceptance of routine cycles should be derived from the data generated during initial validation with a documented rationale.

6.11 The cooling phase of a heat based cycle should not offer any opportunities for recontamination of product that may transiently have lost integrity i.e. the cooling medium should be sterile. In the case of autoclave cooling water, the water should have been sterilised, and not subsequently been exposed to recontamination, before contacting the product. If the water is tested it should show no growth. Parametric release of the sterilized cooling water is appropriate providing the equipment that contacts the water is also assured to be sterilized and retain its integrity.

6.12 The principles of sterilizer validation for review during the inspection include the following, but the list is not exhaustive:

(a) The sterilizer should be in exactly the same mechanical, electrical and software state as it was during the validation or last change control protocol.
- This focuses attention on the drawings and specifications defining that state and the change control system.
- The planned change control should be approved by both the sterility assurance engineer and microbiologist.
- Unplanned repairs should also be subject to the same level of review and approval prior to being carried out or reviewed sufficiently soon afterwards to prevent possibly compromised product being released.
- The assumptions that 'like for like' replacements are truly 'like for like' and do not require confirmatory testing should be investigated.

(b) Routine planned preventative maintenance programmes should be documented and be completed by the programmed date.

(c) Sterilizer and services start up checks should be confirmed as having been carried out successfully prior to sterilizing the product each day.

(d) The state of the services should similarly be as in the validation stage. For example the steam pressure and volume available can have an effect on the heat up time so this should be a constant controlled service.

(e) The instrumentation in routine use should be sufficient to confirm the delivery of the validated cycle. It should be independent of the control system instrumentation.

(f) The routine sensing probes should be sufficient to map the chamber or product, be in the same position as for the validation and be calibrated.

(g) The accuracy of standards used to calibrate process measurement instruments should be specified and the calibration should be traceable to national standards.

7. THE SEGREGATION OF NON-STERILE PRODUCT FROM STERILIZED PRODUCT

7.1 A gross failure of the sterility assurance system that may be detected by the sterility test is a mix up where product appears in the final packing area or, in the case of sterilization by contractor is sent to the customer or finished goods storage without having been subjected to the sterilization process. It follows that product that has not been exposed to the sterilization process must be rigorously segregated from the flow of product coming out of the sterilizer and moving to the next stage in the process.

7.2 In order to prevent mix up of sterilized product by non sterilized product, there should be a system in place to prevent the movement of product to the stage of processing following sterilization without passing through the sterilizer and having been confirmed as having been exposed to a valid cycle. The following arrangements to prevent this should be inspected:

(a) Physical barriers that ensure entry to the sterilizer should be used. These may be quite complex and comprise metal fencing, one way gates, swinging barriers, overhead trackways with controlled points like railway tracks, and carefully positioned posts to prevent carriers turning at cross over regions. The objective of these barriers is to prevent non-sterile product entering the flow of sterile product. Such barriers are best used in conjunction with double ended sterilizers although well designed swinging barriers or other arrangements can secure a sterilizer with only one door.

(b) Well designed and validated electronic systems may provide a substitute for physical barriers. Such systems would be GMP critical and would require an independent second system to confirm the correct functioning of the primary system.

(c) Both physical and electronic systems should be supported by comprehensive contingency procedures to control breakdown situations of even the most minor type. Each failure mode should have a clear method of securing product already in the system defined together with all the necessary steps to correct the problem.

(d) The main flow of product may be secured by these means, but there are other streams of product that may escape control. The obvious ones are samples that may be inadvertently returned to the batch, such as presterilization bioburden samples and samples for marketing purposes. Rigorous tracking and reconciliation is essential for all samples removed from the batch. Rework may also be another product flow that presents a risk. The company's analysis of failure modes and risks should clearly address these issues.

(e) In assessing all these systems, it should be born in mind that deliberate attempts to by pass them cannot always be anticipated and neutralised. The company should still take into account the human element and be able to show that risks of human error have been considered and that the motivation to avoid a control system, for example by the presence of an easier pathway, is designed out as far as possible.

(f) On completion of the sterilization cycle the checks carried out by the operator before moving the load out of the sterilizer should be as comprehensive as possible to assure that the validated process has

been delivered. The steps to be taken if the cycle is not correct should be clearly defined. This may include resterilization (if this has been validated) or placing the product under quarantine without moving the load out of the sterilizer on the sterile side of the barrier system.

8. THE PROCESS OF STERILITY ASSURANCE RELEASE

8.1 The following sterility assurance related items should be confirmed at the appropriate level of authority prior to recommendation for release of each batch of product.

(a) Details of product integrity and compliance to specification.

(b) All presterilization micro biological release criteria have been met. These should include presterilization bioburden in limits with no signs of adverse trends or associated batches out of limits. All other microbiological indicators should show a process in control. (See also 5.1)

(c) If applicable, filter integrity test data passes.

(d) The sterilizer used had completed all planned maintenance and routine checks

(e) There were no unplanned repairs or modifications that have not been reviewed and released by the sterility assurance engineer and microbiologist.

(f) All instrumentation was in calibration,

(g) The sterilizer was qualified for the product load processed.

(h) The number of units of product produced, the number of units of product presented for sterilization, the number of units of product placed into the sterilizer and removed on the sterile side of the sterilizer, the number of units of product presented to subsequent stages and the number of units of product being considered for release are reconciled.

8.2 The sterilization cycle records should have been reviewed and released by production personnel ref. 7.2.f.

8.3 The way in which the sterilizer load is labelled should result in documents that clearly provide a record of each carrier of product with a corresponding activated process indicator (such as autoclave tape that has shown exposure to heat).

8.4 Elimination of routine sterility testing may have been authorised subject to the use of more sophisticated process monitors such as thermochemical indicators which degrade in a way that demonstrates that a full process has been delivered. In this

case, records of their testing in clear association with corresponding cages trucks or other product carriers should be present.

8.5 It should be confirmed that the sterilization cycle that will be used to release the product was started within the bioburden control time constraints, for example the filtration to sterilization time.

8.6 The sterilization cycle records comply with specification, this is usually confirmed by QA and is additional to the production release in 8.2.

8.7 In case of an atypical cycle, a recommendation to release is approved by the sterility assurance engineer and microbiologist. Product should only be recommended for release if the cycle parameters are within tolerances that were accepted during the validation and in compliance with written procedures. The Qualified Person may reverse a release decision, but should not reverse a reject decision in this situation.

8.8 When release involves computer systems all relevant aspects of Annex 11 of the EC Guide to GMP and current good practice should be addressed.

9. INSPECTION WHEN ELIMINATION OF ROUTINE STERILITY TESTING HAS PREVIOUSLY BEEN AUTHORISED

9.1 In addition to confirming continued operation of the approved system, particular attention should be given to the company's handling of out of limit or other atypical situations. It is recognised that the desire to maintain the advantages of the elimination of routine sterility testing may place stress on those responsible for assessing the significance of atypical situations. The process of assessing product or process deviations should be based on the facts and on sound objective decisions. This process should be documented.

9.2 It would also be appropriate to review the rigour with which the company's self inspection programme is adhered to, the qualifications of the auditors and that the scope of the self inspections include all areas related to sterility assurance.

APPENDIX II

DETAILED GUIDANCE CONCERNING THE REDUCTION OR ELIMINATION OF OTHER FINISHED PRODUCT TESTING

1. GENERAL

1.1 The general basis upon which authorisation may be granted should include the following.

(a) The demonstration that the test is redundant, i.e. it has not detected any out of alert limit situations, failures or other anomalies not already detected by the remaining system.

(b) The product quality being assessed is assured, or directly tested by the remaining system.

2. SPECIFIC CONSIDERATIONS

2.1 When the test in question is being made redundant due to adequate testing elsewhere in the system, the company should provide the following.

(a) Relevant process validation.

(b) A concise analysis of the production process showing that any events that could be reasonably predicted, near misses drawn from history and expert risk analysis relevant to the quality being tested for are prevented or their occurrence detected.

2.2 If reduced testing is being sought based solely upon the assurance provided by the process then the case should clearly demonstrate that the output of instruments or other data demonstrates unequivocally that the validated process has been delivered.

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