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TO: ASSOCIATIONS

I am pleased to inform you that a revised version of Guide 0006 entitled "Process validation: Aseptic Processes for Pharmaceuticals" is now available on the Health Products and Food Branch Inspectorate website at the following address:

www.hc-sc.gc.ca/hpfb-dgpsa/inspectorate

This document has been revised to harmonize its content with version 2 of the Good Manufacturing Practices (GMP) Guidelines, 2002 Edition. No major changes to the requirements were made, therefore, consultation is not deemed necessary.

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GUIDE

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Aseptic Processes for Pharmaceuticals

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1. INTRODUCTION

This document is intended to provide pharmaceutical dosage form manufacturers with guidance on the validation of aseptic manufacturing processes, as required in Division 2, Part C (Good Manufacturing Practices) of the Food and Drug Regulations, and in a manner which is acceptable to the Health Products and Food Branch Inspectorate.

Sterile Products may be broadly classified into two main categories, according to the manner in which they are produced: those which are sterilized after the product has been filled and sealed in the final container(s) ("terminally sterilized" products) and those where the sterilization stage (or stages) takes place before the bulk product is filled. In this latter instance, all subsequent processing (typically, the filling and sealing operations) must be conducted aseptically in order to prevent recontamination of the sterilized product.

It is recognized that aseptic processes play an important role in rendering sterile formulations which cannot be terminally sterilized. However, terminal sterilization, in particular using moist heat processes, is considered to be the method of choice in the manufacture of sterile products due to the enhanced sterility assurance which it affords. Manufacturers who choose to manufacture a sterile product without terminal sterilization must be prepared to justify this decision by demonstrating that the product cannot be terminally sterilized, even under less severe autoclave cycles tailored to the bioburden of the batch (Probability of Survival approach).

The two most common pharmaceutical applications of aseptic processing methods are (a) the filling of liquid products following sterilization by filtration and (b) the filling of previously sterilized bulk powder products. Both are covered in this guide. The final section of this guide outlines documentation required to provide acceptable evidence that a given process has been thoroughly evaluated and is adequately controlled.

It is assumed that, throughout, manufacturing and control operations are conducted in accordance with the principles of Good Manufacturing Practice, both in general and in specific reference to Sterile Products manufacture.

The steps recommended in this guideline may be summarized as follows:

- As a pre-requisite, all studies should be conducted in accordance with a detailed, pre-established PROTOCOL, or series of protocols, which in turn is subject to formal change-control procedures.
  (See Section 3).

- Both the personnel conducting the studies, and those running the process being studied should be appropriately TRAINED and QUALIFIED and be suitable and competent to perform the tasks assigned to them (See Section 4).

- All data generated during the course of the studies should be formally REVIEWED and CERTIFIED, as evaluated against pre-determined criteria (See Section 5).

- Suitable TESTING FACILITIES, EQUIPMENT, INSTRUMENTS and METHODOLOGY should be available (See Section 6).

- Suitable CLEAN ROOM FACILITIES should be available, in terms both of the "local" and "background" environments. Assurance that the Clean Room environment is as specified should be secured through initial commissioning ("Qualification") and subsequently through the implementation of a program of re-testing, in-process control and monitoring (See Section 7).

- All processing equipment should be properly INSTALLED, QUALIFIED and MAINTAINED (See Section 8).

- When appropriate attention has been paid to the above, the aseptic process may be validated by means of "MEDIA FILL", (or "PROCESS SIMULATION") studies (See Sections 9 and 10).

- The process should be REVALIDATED at intervals (See Section 11).

- Comprehensive DOCUMENTATION should be available to define, support and record the overall validation process (See Section 12).

Whilst this Guide is concerned only with the validation of ASEPTIC PROCESSES, it is crucial to the success of any such process that the product, materials, components etc. that are being handled/processed aseptically (e.g. bulk solution or powder; containers and closures) plus any equipment, vessels or surfaces (e.g. holding tanks, pipework, filling machines) which will or can come into contact with sterilized products/materials have themselves been previously sterilized by appropriate and validated sterilization processes. In any aseptic filling process, assurance of container/closure integrity is, of course, vital. Evidence that all this is so should be provided as part of the overall Validation Documentation (see Section 12).

2. VALIDATION - GENERAL/TERMINOLOGY

2.1 In the context of this guide, Process Validation is defined as:

> The action taken to demonstrate, and to provide documented evidence that a process will, with a high degree of assurance, consistently achieve the desired and intended results.

2.2 Before Process Validation can commence there must be what may be termed an essential Prevalidation phase. This phase, in addition to such considerations as equipment specification, equipment design and equipment purchase, requires attention to Equipment Qualification.

2.3 Equipment Qualification in turn has two main phases :

2.3.1 Installation Qualification, that is demonstrating and certifying that a piece of equipment is properly installed, is provided with all

necessary services, subsidiary equipment and instruments, and is capable of performing in accordance with its basic design parameters.

2.3.2 Operational Qualification, consists of demonstrating that the equipment will perform consistently, and within pre-defined limits, as specified and installed.

2.4 None of these various phases need to be considered as entirely "water-tight" compartments. The divisions have been defined as a matter of convenience in discussion. In practice there is likely to be some overlap, or merging, between the various components of Validation/Qualification. In addition, there are quite wide-spread variations in terminology and conception. Some consider "Qualification" and "Validation" as two separate, yet related activities. Others use the term "Validation" to embrace the overall activity of Prevalidation/Qualification PLUS Process Validation.

The relationships between these various phases may be summarized as follows:

<table>
<tr><td rowspan="2">Specification
Design
Purchase</td><td colspan="2">Equipment Qualification</td><td rowspan="2">Process
Qualification</td></tr>
<tr><td>Installation
Qualification</td><td>Operational
Qualification</td></tr>
<tr><td colspan="3">Sometimes termed “Prevalidation”</td><td></td></tr>
<tr><td colspan="4">The overall activity of Validation</td></tr>
</table>

2.5 Validation has also been considered to have three aspects, or possible strategies - Prospective Validation, Concurrent Validation, and Retrospective Validation.

2.5.1 Prospective Validation applies to new processes and new equipment, where studies are conducted and evaluated, and the overall process/equipment system is confirmed as validated before the commencement of routine production.

2.5.2 Concurrent Validation applies to existing processes and equipment. It consists of studies conducted during normal routine production and can only be considered acceptable for processes which have a manufacturing and test history indicating consistent quality production.

2.5.3 Retrospective Validation applies to existing processes and equipment, and is based solely on historical information. Unless sufficiently detailed past processing and control records are available, retrospective validation studies are unlikely to be either possible or acceptable. For example, it would be

necessary to establish that the process had not been modified and that the equipment was still operating under the same conditions of construction and performance as documented in the historical records. Maintenance records and process change control documentation would be necessary to support any such claim. Furthermore, the incidence of process failures, and records of rejects and/or reworking would need to be carefully evaluated for evidence of inconsistency in the process. Manufacturing, maintenance, testing and calibration data would all need to demonstrate process uniformity, consistency and continuity.

2.5.4 Concluding Note on Validation Terminology. While there is considerable variation in the understanding and use of the various terms discussed above, there is general agreement that the critical validation concepts are the following:

- the overall process is understood
- equipment is appropriately specified and designed
- equipment is properly installed and maintained and is demonstrably operating as specified and designed
- the process is validated to ensure that it does achieve the desired and intended result.

3. PROTOCOL DEVELOPMENT AND CONTROL

3.1 Each stage in the validation of the overall process should proceed in accordance with a pre-established and formally approved, detailed, written protocol, or series of related protocols.

3.2 Prior to the commencement of the studies, written change control procedures should be established, which will prevent unauthorized changes to either the process itself, or to the study protocol, and restrict change during any stage of the study until all relevant data are evaluated.

3.3 Protocols should have a Title, Date and a unique Identification or Reference Number. They should be formally authorized/approved by person(s) with the competence and authority to do so.

3.4 Protocols should specify the following in detail:

3.4.1 The objectives and scope of the study. That is, there should be a clear Definition of Purpose.

3.4.2 A clear and precise definition of the process, equipment, system or sub-system which is to be the subject of the study, with details of performance characteristics.

3.4.3 Installation and qualification requirements for new equipment.

3.4.4 Any up-grading requirements for existing equipment, with justification for the change(s) and a statement of qualification requirements.

3.4.5 Detailed, step-wise statement of actions to be taken in performing the study (or studies).

3.4.6 Assignment of responsibility for performing the study.

3.4.7 Statements on all test methodology to be employed, with a precise statement of the test equipment and/or materials to be used.

3.4.8 Test equipment calibration requirements.

3.4.9 References to any relevant Standard Operating Procedures (SOPs).

3.4.10 Requirements for the content and format of the report on the study.

3.4.11 Acceptance criteria against which the success (or otherwise) of the study is to be evaluated.

3.4.12 The personnel responsible for evaluating and certifying as acceptable each stage in the study, and for the final evaluation and certification of the process as a whole, all as measured against the pre-defined acceptance criteria.

4. PERSONNEL

As with all Process Validation studies, documented evidence of the relevant experience and training of the personnel involved in conducting the studies should be maintained. However, because the personnel actually performing the aseptic processing (both during the course of any validation studies, and in routine operation) can, and do, have so crucial an effect on the quality of the end-product, it is appropriate and necessary to consider both these aspects of personnel involvement.

4.1 Appropriately qualified personnel should ensure that the protocol and the testing methodology are based on sound scientific principles and that all studies are properly evaluated and certified.

4.2 All personnel conducting tests should be trained and experienced in the use of the instruments, measuring devices and materials used.

4.3 Engineering/maintenance personnel should be fully trained and competent in the operation and maintenance of the machines, equipment, and air control systems involved.

4.4 Although modern automated and barrier techniques may reduce contamination risk, the significance of the "human factor" in all aseptic processing operations cannot be over-stressed. For the results of any validation studies themselves to be valid, it is

essential that the risk represented by so potentially random a variable as a human operator is kept as much under control as is possible. That is, steps must be taken to reduce the risk and to minimize the variability.

4.5 This in turn means that any operators involved in performing an aseptic processing operation which is the subject of a validation study should adopt the same techniques, disciplines, and standards of hygiene, clothing and behaviour as in normal routine manufacture. The converse also applies: if operators conduct themselves, during routine production, in manner which is different from their behaviour etc. during the validation studies, then conclusions drawn from the validation will be invalid.

4.6 It is therefore vital that all personnel involved in aseptic processing operations are trained in, and fully understand, the concepts and principles of GMP, and the relevant elements of microbiology. They must understand the importance of personal hygiene and cleanliness, and be made fully aware of the possible hazardous consequences of product contamination.

4.7 Operators should be provided with suitable Clean Room clothing and trained in appropriate gowning technique. The type of clothing to be worn, and the "scrub-up" and gowning process should be defined in written procedures, available to the operators, and preferably displayed in the changing room. The same clothing/gowning standards should be observed during validation studies as in routine production, and vice versa.

4.8 The maximum number of personnel permitted in the Clean Room during normal routine production should also be present in the Clean Room during any validation test runs.

4.9 At all times, operators should be encouraged to report any infections, open lesions or any other conditions which could result in the shedding of abnormal numbers of particles or microorganisms. As with routine manufacture, no person thus affected should be present in the Clean Room during validation test runs.

4.10 As in routine production, Clean Room operators involved in validation studies should be microbiologically monitored by taking test samples from gloves, gowns and facemasks.

4.11 Normal routine process documentation should specify and record the numbers and types of operator interventions that are permitted during processing, and in what circumstances. A similar series of interventions should occur during any validation test runs. Details should be provided as part of the overall validation documentation (See Section 12).

Note: As stated in the Introduction it is assumed that all routine manufacturing and control operations are conducted in accordance with Good Manufacturing Practice, and this includes a requirement that all personnel are trained and competent to carry-out the tasks assigned to them.

5. DATA REVIEW AND STUDY CERTIFICATION

5.1 All information or data generated as a result of the study protocol should be evaluated by qualified individuals against protocol criteria and judged as meeting or failing the requirements. Written evidence supporting the evaluation and conclusions should be available.

5.1.1 These evaluations should be made as the information becomes available.

5.1.2 If such an evaluation shows that protocol criteria have not been met, the study should be considered as having failed to demonstrate acceptability, and the reasons should be investigated and documented.

5.1.3 Any failure to follow the procedure as laid down in the protocol must be considered as potentially compromising the validity of the study itself, and requires critical evaluation of the impact on the study.

5.1.4 The final certification of the validation study should specify the pre-determined acceptance criteria, against which success or failure was evaluated.

6. LABORATORY

6.1 All laboratory tests (including physical, chemical and microbiological determinations) should be performed by a competent laboratory, suitably equipped, and staffed with personnel properly trained and qualified to carry-out the test procedures assigned to them.

6.2 Detailed authorized, written procedures defining the relevant, validated methodology should be available for all laboratory tests which are to be carried out during the course of the study. These procedures should be referenced in the study protocol.

6.3 If any external laboratory facilities are used, a system should be in place for determining the competence of these laboratories to carry out the tests required. This requirement should be referenced in the study protocol.

6.4 All measuring/recording/indicating instruments employed in the studies should be adequate for the purpose, in terms of range, accuracy, reproducibility, etc... They must be calibrated in accordance with pre-defined written procedures before any validation studies are commenced.

6.5 Records of each calibration should be maintained, and should form part of the overall validation documentation.

6.6 For the conclusions drawn from any qualification/validation studies themselves to remain valid during routine production, all controlling and recording instruments must be subjected to a written maintenance and calibration program.

7. ENVIRONMENTAL CONSIDERATIONS: CLEAN ROOM STANDARDS, QUALIFICATION AND MONITORING

7.1 Although prior to their being sterilized, products, materials, containers, components, closures etc. may be handled/processed in a lower (for example, Grade C) Clean Room environment, subsequent to the sterilization stage(s) all aseptic processing operations should be conducted under local Grade A ("work station") protection, within a general (or "background") Grade B Clean Room environment. However, if certain specialized automated or barrier techniques are employed to provide the localized protection, a lower background environmental standard may be acceptable, provided that process validation studies demonstrate the attainment of an acceptable level of sterility assurance. (Grades A, B and C are as defined in the table for the "Basic Environmental Standards for the Manufacture of Sterile Products" in the Sterile Products section of the current version of the "Good Manufacturing Practices".

7.2 For the results of any validation studies to have valid relevance to routine production, they must be conducted under precisely the same environmental conditions as used, or intended to be used, during normal routine production.

7.3 Confirmation and Certification that the room and the work station(s) do, in fact conform to the specified Environmental Standard may be considered as forming part of the Installation Qualification phase. To this end, the following basic work should be carried-out on the initial commissioning (or "Qualification") of a new Clean Room installation:

- Room air filter integrity tests.
- Determination of air velocity at the face of each air inlet filter.
- Room air change rate.
- Room air particle counts.
- Room air pressure differentials and air flow patterns.
- Lighting, heating, humidity.
- Work station(s) air filter efficiency tests.
- Determination of air velocity at face of work station air filters.
- Particle counts within work station areas.

7.4 Following the initial commissioning, a regular re-test program should be adopted, e.g.:

7.4.1 Room and Work Station Air Filter Tests: Repeat at least annually, unless results of normal in-process monitoring indicates a need for more frequent, or additional testing.

7.4.2 Air Velocity and Room Air Changes: Repeat at least twice a year.

7.4.3 Air Particle Counts: Determine as part of regular in-process monitoring, with formal certification by a competent specialist agency 3 times per year.

7.5 Room pressure differentials should be monitored on a continuous, on-going, basis.

7.6 Walls, floors, work stations and surfaces generally should be subject to a pre-determined program of cleaning and disinfection.

7.7 In order to ensure that, during routine manufacture, products remain within the quality parameters established during the overall validation process, it is necessary to design and implement a program of in-process control and monitoring. Similarly, as part of the over-all assurance that process validation studies are conducted under comparably normal processing conditions, a similar in-process control and monitoring program should be operated during the process validation runs.

7.8 In-process monitoring and control may be considered under three headings:

- Environmental Particulate
- Microbiological
- Filter Integrity Testing

7.9 As appropriate to the type of manufacturing process, consideration needs to be given to the following Microbiological Monitoring and Control Procedures:

- Bioburden check on bulk solution, prior to sterile filtration.
- Exposure of "Settle Plates" (Petri dishes of nutrient agar) at critical positions within the general Clean Room environment and at the controlled work station(s).
- Use of Air Sampling devices to determine the number of viable organisms per cubic metre (or cubic foot) of air in the room, and within the work station(s).
- Use of Contact Plates, or Swabs, to check the microbiological quality of surfaces.

7.10 Environmental Particulate monitoring should be carried out using appropriate air Particle Counting devices to check that the general environmental and work station air remain in conformity with specification.

7.11 Filter integrity testing of the filter(s) used to sterilize the product is critical in sterile product manufacturing. If the product cannot be sterilized in the final container, solutions or liquids can be filtered through a sterile filter of normal pore size of 0.22 micron (or less), into a previously sterilized container. The integrity of the sterilized filter should be verified before use and should be confirmed immediately after use by an appropriate method, such as a bubble point, diffusion, or pressure hold tests.

7.12 This in-process monitoring and control should be conducted in accordance with a written, pre-determined program, which includes specified test limits and standards, and with all results formally reported and evaluated against those limits. This requirement applies as much to validation studies as routine manufacture.

8. EQUIPMENT QUALIFICATION AND MAINTENANCE

8.1 A wide range of different types of mechanized equipment may be used in various aseptic processing operations. Before any process validation studies may be commenced, it is necessary that all such equipment be properly qualified, in both Installation and Operational terms (see 2.2 and seq.), and that this qualification be certified. It is clearly outside the scope of these guidelines to detail Installation and Operational requirements for every possible item of equipment. The essential requirements are that the equipment be:

- Confirmed as having been constructed as specified.
- Properly installed and provided with all necessary functioning services, ancillary equipment and instruments.
- Confirmed as capable of operating consistently, within pre-determined limits, over its defined operating range.

8.2 Processing equipment must be confirmed as Qualified before any subsequent studies can be considered valid.

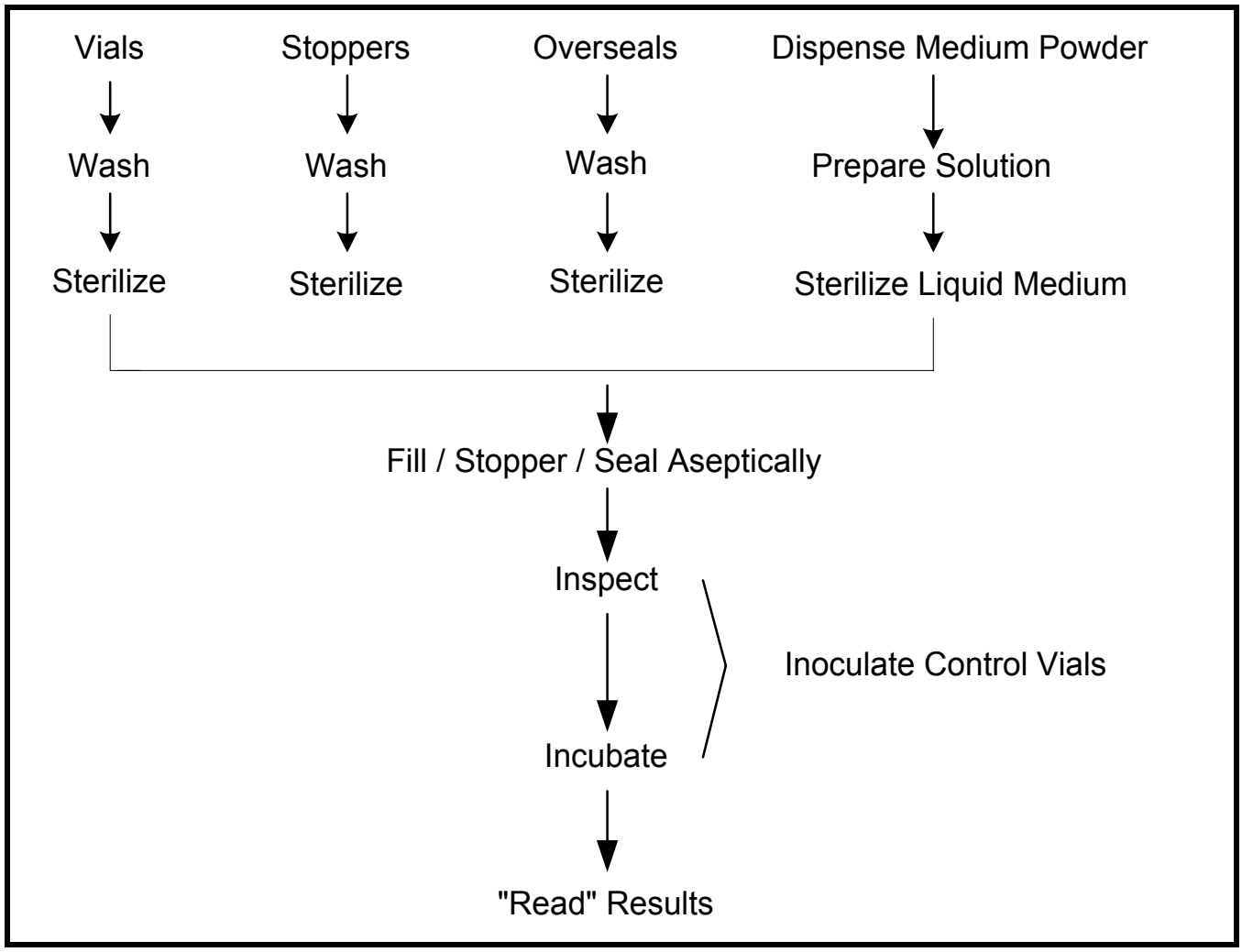
8.3 For the results of any validation studies themselves to remain valid in routine manufacture, a comprehensive routine maintenance program should be developed, setting out each activity in detail along with the frequency in terms of real time, machine time or other time base. The time base should be clearly defined for each procedure.

8.4 Unless such a program is developed and implemented, and the manufacturing equipment and attendant instruments remain in the same state as during the validation studies, then any assurance derived from those studies could be considered to be negated.

9. MEDIA FILL STUDIES (SOLUTION PRODUCTS)

9.1 The "Media Fill", or "Broth Fill", technique, is one in which a liquid microbiological nutrient growth medium is prepared and filled in a simulation of a normal manufacturing operation. The nutrient medium processed and handled in a manner which simulates the "normal" manufacturing process as closely as possible with the same exposure to possible contamination (from operators, environment, equipment, and surfaces) as would occur during routine manufacture. The sealed containers of medium thus produced are then incubated under prescribed conditions and examined for evidence of microbial growth, and thus of an indication of the level of contaminated units produced. The process is summarized in Figure 1

Figure 1: Process Flow Diagram of Liquid Media Filling of vials



NOTES:

- Different types of containers will require different methods of sterilization. For example glass vials are likely to be dry heat sterilized, plastic vials may be sterilized by irradiation or ethylene oxide.

- Any other components, e.g. teats/droppers will also need to be pre-sterilized by some suitable validated method.

– The process flow for liquid media filling of ampoules will be analogous to the above, without the operations involving stoppers, overseals etc...

9.2 It is important to recognize that, in many instances, media fills are, amongst other things, a test of the human operators' aseptic techniques. In this test situation these operators can hardly remain unaware that nutrient medium is being filled, and that they themselves are, to an extent,"under test". There is, therefore the possibility that they will take more than their usual care, and thus the normal process will not be precisely simulated. Every effort should be made to ensure that the operators do behave normally during the media fills, and conversely (and perhaps importantly) that during routine production they do not deviate in any way from the high standards adopted during those simulation studies.

9.3 A further difficulty which needs to be noted is the possibility of contamination of the facility and equipment by the nutrient medium. If the process is well controlled and the media-fill is promptly followed by cleaning and disinfection, and (as necessary) sterilization of equipment, contamination should not occur. Nevertheless, it is important to recognize the potential hazard, and to respond accordingly.

9.4 It must also be emphasized that the filling of a nutrient medium solution alone does not constitute an acceptable aseptic process validation. The whole manufacturing cycle must be simulated, from the dispensing and reconstitution of the powdered medium under normal manufacturing conditions, to the filling and sealing process itself. Operators (and numbers of operators), numbers and types of filtrations etc. should all be "as normal", as should holding times in any mixing vessels, interim holding tanks etc. General activity should be at a normal level, and no attempt should be made to take any "special" precautions to ensure that the test run is successful. If any deviation from the normal is permitted, it should only be in the direction of presenting a greater, rather than a lesser, microbiological challenge to the process.

9.5 Before any meaningful aseptic process validating media-fills can be carried-out, all necessary Equipment Qualification and Instrument Calibration must be completed, together with the appropriate certification (see e.g. Sections 6 and 8). The Clean Rooms used for all processing stages should also have been confirmed and certified as complying with the required environmental standards. (See Section 8).

9.6 Normal routine in-process control and monitoring procedures (see Section 8) should be operated during the media-fills.

9.7 The liquid Nutrient Medium used should meet the following criteria:

Selectivity: The medium should have low selectivity, that is, it should be capable of supporting growth of the widest range of micro-organisms that might reasonably be encountered.

Clarity: As "made-up", it should be clear, so as to allow for the observation of any evidence of growth following incubation.

Filterability: Where the process being simulated includes a filtration stage, the liquid medium should be capable of being filtered through the same grade and type of microbial retentive filter as that through which the actual product is, or will be, filtered. Liquid Soybean Casein Digest (SCD), also termed "Tryptic Soy Broth" (TSB) is perhaps the liquid medium most frequently employed. However, other formulations (for example, liquid Tryptone Glucose Yeast Extract, Brain Heart Infusion etc.) may be used, provided they meet the criteria set out above.

9.8 The liquid medium should be either sterilized by filtration (if such a stage is part of the normal operation being simulated) or pre-sterilized by heat and cooled to ambient temperature before proceeding.

9.9 The Number of Units to be filled per run should be sufficient to provide a high probability of detecting a low incidence of microbial contamination. For example, in order to give 95% confidence of detecting a contamination rate of 1 in a thousand units filled (i..e. 0.1%) with sterile nutrient media, 3000 units need to be filled and no contaminated unit should be found after the incubation period. (However, see 9.19).

9.10 For the initial validation of a new process or facility, sufficient consecutive media fill runs should be performed to provide assurance that the results obtained are consistent, meaningful and provide an acceptable level of sterility assurance. At least 3 separate, consecutive, successful runs per operator team, or shift, should be performed to acceptable initial validation of a given process line (For Revalidation, see Section 11).

9.11 The Volume to be Filled per unit should be the normal production fill-volume where possible. In the case of high volume containers, a lesser quantity may be used, provided steps are taken to ensure wetting of all the inner surface of the container, and any closure, by the medium, e.g. by shaking or inversion, and/or by inverting the containers part-way through the incubation period. It is good practice to take similar steps to ensure complete inner surface wetting when normal full volumes are filled as well.

9.12 Immediately following filling, all units filled should be examined for leakers and/or damage. In this context, any leak-test method in which heat is employed should obviously not be used. Any leakers or damaged units should be rejected.

9.13 Incubation of the filled units should follow immediately after filling and leak-testing, and should be for a period of 14 days.

9.14 The Incubation Temperature should be 30ºC to 35ºC. Incubation temperatures should be carefully monitored and maintained throughout the incubation period.

9.15 Test Controls: Media used in the evaluation must pass a growth promotion test where a challenge with between 10 - 100 organisms per container is suitable to show the growth characteristics of the organism.

9.16 Reading of Results: All units filled and incubated should be visually examined for microbial growth after 14 days incubation. Any contaminated units will be identifiable by the turbidity of the medium. Any contaminated units that are found should be examined in the laboratory, and the contaminating organisms identified, to the species level where possible, so that appropriate preventative action may be taken. For the results of the media fill run to be considered valid, all the inoculated control units should display growth.

9.17 The contamination rate found in a media fill run should be calculated as follows:

Observed number of failures	0	1	2	3	4	5	6	7	8	9	10
Upper 95% confidence limit	3.0	4.74	6.3	7.75	9.15	10.51	11.84	13.15	14.43	15.71	16.96

$$\text{Contamination Rate} = \frac{\text{Upper 95 \% contamination limit}}{\text{Number of filled units}} \times 100$$

9.18 Acceptance Criteria: A currently accepted limit is 0.1% at a 95% confidence level.

9.19 It is however important to recognize that, for example, a media fill run of 3000 units will usually represent only a simulated sample of a normal production run. Actual production runs are likely to be much larger. The contamination level determined from a media fill will therefore be subject to sampling error, such that (for example) 3 contaminated units in a media fill of 3000 may be indicative of a potential contamination rate in actual production significantly greater than 0.1%.

9.20 The following table indicates the maximum permitted number of contaminated units per various Media-Fill "run sizes" to indicate a 0.1% contamination limit with a 95% Confidence Level.

Media Fill Units	Contaminated Units Permitted
3 000	0
4 750	1
6 300	2
7 750	3
9 150	4

10510	5
11840	6
13150	7
14430	8
15710	9
16960	10

Thus for example, to provide confidence (95%) of complying with the 0.1% limit, 4750 media-filled units would be required with no more than one unit found contaminated, or 6,300 units with no more than 2, and so on.

9.21 If batches smaller than 3,000 units are produced, the minimum number of containers used for process simulation with sterile nutrient media should be equal to the commercial batch size and no contaminated unit should be found after the incubation period.

9.22 To demonstrate compliance with a contamination limit of one in 10,000 (0.01%) notably larger numbers of units would need to be filled with "broth". For example, in relation to a normal production run of 50,000 units, over 46,000 units would need to be filled with medium, with no more than one unit found contaminated.

9.23 These statistical considerations reveal a distinct practical problem with regard to the number of units which may need to be filled with medium and incubated, particularly in any attempt to demonstrate a probability of a low (for example, less than 0.1%) level of contamination in "standard" production batch sizes. Manufacturers should determine (according to their particular circumstances and production batch sizes) media-fill run sizes, with permitted contamination levels, which will provide adequate confidence in sterility of actual production batches. Purely on the basis of the practical limitations of the test procedure itself, a contamination level in a media fill of 0.1%, detected infrequently, may be considered to be acceptable. Regular, or common, contamination levels (in media fills) of 0.1% or above should be regarded as unsatisfactory.

9.24 Whilst it may be statistically unsound to sum in a simple fashion data from a series of discrete events, and then treat these data as if they had been derived from a single event, a series of "good" media fill results over a period of time (assuming reasonable comparability of conditions etc.) may be regarded as confidence-strengthening, if not in any precisely quantifiable fashion.

10. MEDIA FILL STUDIES (NON-SOLUTION PRODUCTS)

The same general principles, conditions and statistical considerations as set-out in Section 9 apply, but the various types of non-solution Sterile Products require various adaptations to the approaches already described. In all procedures involving the use of growth media it is vital to control any contamination by the media of equipment, surfaces etc. All media fill studies should be promptly followed by application of thorough cleaning, disinfecting and sterilization procedures.

10.1 Sterile Powders

The use of the media fill technique in the validation of the filling of sterile powder products presents certain special problems, arising from the probable necessity to employ additional equipment, techniques or manipulations which are different (or additional) to those used in routine production. In such circumstances the media-fill cannot unequivocally be said to be a precise process simulation. This inevitable shortcoming may, however, have to be accepted. A number of different approaches have been proposed and used, as follows:

10.1.1 The normal process is simulated as closely as possible, but instead of filling a powder, a sterile liquid medium is filled. This approach is virtually the same as that described for a solution product (Section 9 above) and fails to simulate the actual powder fill.

10.1.2 The normal process is simulated as closely as possible, with a sterile, dry inert powder filled in place of the normal product or material. Lactose, mannitol and polyethylene glycol 8000 are examples of "simulation" powders which have been used. There are two possible variations on this approach:

a) Fill the chosen inert powder into the containers (e.g. ampoules/vials) which are already filled with sterile liquid medium.

b) Fill the inert powder first, and then add the sterile liquid medium. In both these variations, a powder fill is simulated, but an additional, non-routine step (i.e. the filling of the liquid growth medium) is involved.

10.1.3 Fill sterile dry powdered medium into the containers, in simulation of the normal powder filling operation, aseptically adding sterile aqueous diluent on-line, to form liquid medium solution. As in 9.1.2, a powder fill is simulated, but an additional operation is involved.

10.2 Whichever approach is adopted, it is important to ensure that any powder/medium/diluent combination used does not cause growth inhibition through hyperosmolar or other antimicrobial effects.

10.3 Suspension Products: Simulate the entire normal process as closely as possible, using a sterile inert powder in place of the normal powder product. Micronize etc. (if this

is part of the normal process) and form suspension, using sterile liquid growth medium in place of the normal liquid phase of the suspension product. Fill as normal and incubate. (Comments as in 10.2 above similarly apply.)

10.4 Freeze-dried Product: Simulate the entire normal process (i.e. preparation of bulk solution, filling of solution, loading of freeze-dryer, running of freeze-drying cycle, sealing/closing of containers, inspection) but using a liquid growth medium (dispensed as a powder, dissolved and sterilized) in place of normal product. Actual freeze-drying of the medium solution is not practicable, but exposure, holding times in the freeze dryer should be as normal.

10.5 Semi-solid Products (e.g. Sterile Ointments and Creams): Simulate the normal process cycle as closely as possible, filling a sterile liquid growth medium made to similar consistency as the normal product by the addition, for example, of agar (approximately 4 g. per litre) or carboxymethylcellulose.

11. REVALIDATION

11.1 Following initial aseptic process validation, media-fills and process simulations should be repeated to an extent, and at a frequency, which will depend on the occurrence of events or changes which may bear upon the potential microbial hazard to the process and product. Significant modifications to equipment or facilities, changes in personnel, undesirable trends in environmental monitoring results, and sterility test failures may all indicate an immediate need to implement a full process validation protocol (i.e. minimum of 3 consecutive successful media-fill runs) with the facility in question taken out of service until any problems have been resolved, and the results of the three media-fills have been evaluated and found acceptable.

11.2 In the absence of any significant changes, or of any other events giving cause for concern, then a minimum re-test frequency should be twice per year per operator shift or team, for each process line. For single shift operations, the minimum frequency should be 3 times for each process line per year.

12. DOCUMENTATION

The following information should be prepared in summary form for the purposes of inspection and evaluation by the appropriate authorities.

12.1 Overview

A comprehensive outline of the protocol followed in the validation of the process should be prepared. The overview should indicate the steps performed, in proper sequence, and should encompass:

a) the approach taken;

b) justification of the approach based on the product factors;
c) summation of any modifications to the equipment required; and
d) any modifications to the protocol resulting from the study.

12.2 Prevalidation

12.2.1 A full description of the aseptic fill equipment and ancillary systems and report(s) confirming successful installation in accordance with the Installation Qualification Procedures and certifying that the equipment and systems, as installed, will perform consistently within defined limits.

12.2.2 Statement of the Environmental Standards designated for each stage of the manufacturing process and certification of the conformity of any controlled environment with the designated standard(s) during the studies (see Section 7).

12.3 Process Qualification

12.3.1 A summary of the procedures and controls for the following, as applied routinely and during the validation studies:

- dispensing ingredients
- water quality and supply
- cleaning/disinfection/sterilization (as appropriate) of all equipment, surfaces and services
- sterilization of equipment, vessels and pipelines
- filter integrity testing
- equipment set-up, start-up and adjustment
- clothing and gowning of personnel

12.3.2 Full Process Qualification Report, including:

- medium used
- volume filled
- number of units filled
- number of leakers rejected
- number of units incubated
- incubation temperature
- incubation time
- control organisms used
- filter integrity test results
- record of all in-process monitoring and control results

- summary of number and qualifications of personnel involved in the studies
- policy and records relating to permitted operator interventions (see 4.11)
- written procedures for all laboratory tests and formally recorded results of all laboratory tests, with an evaluation of those results against criteria established in the study protocol(s).

12.3.3 If retrospective validation was conducted, the details of the lot analysis and process condition evaluation, including results of in-process controls, should be compiled for the time period being assessed. Evidence of the equivalence of the manufacturing conditions used for these lots to the current process conditions, including calibration and maintenance history, is required. Evidence that process/product failures and discrepancies were included in the evaluation should be available.

12.4 Expert Evaluation

An evaluation of the entire study against the protocol requirements as outlined above should be prepared and the conclusions drawn at each stage stated. The final conclusions should reflect whether the protocol requirements were met.

The evaluation should include an assessment of the ability of the planned calibration and maintenance programs for the equipment and instrumentation to maintain the validated conditions (see Sections 6, 7 and 8). In addition, all process monitoring and control procedures required to routinely ensure that the validated conditions are maintained should be reported.

The evaluation should be signed by duly authorized officers of the organization who were members of the team establishing the protocol, and who have appropriate expertise in the area assigned to. Overall approval of the study should be authorized by the head of the validation team and the head of the Quality Control Department.

GMP Committee members

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