Health Canada
Health Products and Food Branch

OUR MANDATE:

To promote good nutrition and informed use of drugs, food, medical devices and natural health products, and to maximize the safety and efficacy of drugs, food, natural health products, medical devices, biologics and related biotechnology products in the Canadian marketplace and health system.

Health Products and Food Branch Inspectorate

Guide

Process Validation: Moist Heat Sterilization for Pharmaceuticals

Supersedes

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Canada

TABLE OF CONTENTS

1. INTRODUCTION

The Health Products and Food Branch Inspectorate (HPFBI) of Health Canada recognizes that terminal moist heat sterilization, when practical, is presently considered the method of choice to ensure sterility. For the purpose of ensuring sterility, all aqueous-based sterile products are subject to terminal moist heat sterilization, with the following exceptions: Instances where terminal moist heat sterilization is not practical, e.g., product degradation. Such instances are fully evaluated and documented. And for aseptic processes that exclude human intervention e.g., robotics, form-fill-seal and barrier system, may be employed in lieu of terminal moist heat sterilization providing that validation data demonstrated equivalence.

This document is intended to provide manufacturers of pharmaceutical dosage forms with guidance to establish the scientific effectiveness of moist heat sterilization processes, as required in Sections C.02.004, C.02.005, C.02.007, C.02.011 and C.02.029 of the Food and Drug Regulations. The intent of this document is not to detail specific procedures or define elaborate mathematical principles which are critical to the validation process, as such information is readily available from other sources; rather, this guideline is intended as an outline of the elements in moist heat sterilization processes requiring evaluation, and describes approaches to effectively accomplish this goal in a manner which is acceptable to the HPFBI of Health Canada. Other approaches which achieve equivalent results may also be acceptable.

The section 17 of this guideline specifies the minimum documentation required to certify that moist heat sterilization processes have been thoroughly evaluated and are adequately controlled and validated. Such documentation, aside from being invaluable to the manufacturer, is essential to the specialists of the HPFBI for the purpose of inspection and submission evaluation.

This guideline is applicable to moist heat sterilization processes only. While the principles outlined in this document are shared with other methods of sterilization, those processes require control and assessment of different parameters. It must be recognized that, regardless of the sterilization process, the control of manufacturing environments and good manufacturing practices which provide barriers to microbial contamination remain of utmost importance.

Environments for the manufacture of drugs subject to terminal sterilization:

Drugs subject to terminal moist heat sterilization may be formulated in a grade C environment, provided that the formulated bulk is immediately subjected to its subsequent processing step, e.g., filtration, sterilization, so as to maintain low microbial and particular counts. Formulating may take place in a grade D environment if additional measures are taken to minimize contamination, such as the use of closed systems of manufacture.

Parenterals are filled in an aseptic area of at least a grade B environment or in a grade A zone with at least a grade C background before terminal moist heat sterilization.

Non-parenterals may be filled in a grade C environment before terminal moist heat sterilization.

Note: The limits for the microbial contamination and for the maximum number of particules, in the "at rest" and "in operation" states, in relation to different grades of air standards, are defined in the HPFBI Revised Guidance for section C.02.029 (Sterile Products) of the Good Manufacturing Practices Regulations.

2. VALIDATION APPROACHES

The validation of moist heat sterilization processes may be performed using any of the three strategies outlined below. The approach selected should be appropriate and adequately supported. It should be stressed that the integrity of the container/closure system be established prior to validating the sterilization process to ensure that an appropriate container/closure system has been selected.

2.1 Prospective Validation

This approach applies to new or modified processes and new equipment. The studies are conducted, evaluated, and the process and equipment system certified prior to initiating routine production.

2.2 Concurrent Validation

This approach applies to existing processes and equipment. Concurrent validation studies are conducted during regular production and should only be considered for processes which have a manufacturing and testing history indicating consistent quality production. Reworks and failures indicate potential inconsistencies in the process and should be evaluated for effect on the reproducibility of production prior to establishing validation protocols.

Although suitable records may not be available for the installation of equipment, lack of this data may not compromise the balance of the studies.

2.3 Retrospective Validation

This approach can only be applied to existing products, processes and equipment and is based solely on historical information. Normal processing records generally lack sufficient detail to permit retrospective validation.

a) It must be established that the process was not modified and that the sterilizing equipment is operating under the same conditions of construction and performance as documented in the records to be considered. Maintenance records and process change control documents should be available to support these claims.

b) Periods in which failures occurred should not be excluded. The incidence of failures or reworking attributed to unsatisfactory processing indicates inconsistency in the process. There should be an evaluation of these conditions for the period to be used for validation.

c) The manufacturing, maintenance and testing data should be capable of demonstrating calibration of equipment and devices, and establishing uniformity and consistency of sterilizing conditions equivalent to those required in Sections 7 through 14.

Note: Additional detailed information in relation to different validation approaches is provided in the HPFBI Validation Guidelines for Pharmaceutical Dosage Forms.

3. VALIDATION PROTOCOL DEVELOPMENT AND CONTROL

Each stage of the evaluation of the effectiveness and reproducibility of a sterilization process should be based on a pre-established and approved detailed written protocol, developed in accordance with the validation approach chosen as outlined in Section 2. A written change control procedure should be established to prevent unauthorized change to the protocol or process and restrict change during any phase of the studies until all relevant data are evaluated.

The protocol should specify the following in detail:

3.1 the process objectives in terms of product type, batch size, container/closure system, and probability of survival desired from the process;

3.2 pre-established specifications for the process which include the cycle time, temperature, pressures and loading pattern;

3.3 a description of all of the equipment and support systems in terms of type, model, capacity and operating range;

3.4 the performance characteristics of each system, sub-system or piece of equipment in Section 3.3; performance characteristics including pressure gauge sensitivity and response, valve operation, alarm systems functions, timer response and accuracy, steam flow rates and/or pressures, cooling water flow rates, cycle controller functions, door closure gasketing, and air break systems and filters;

3.5 for new equipment: installation requirements and installation check points for each system and sub-system;

3.6 for existing equipment: the necessary upgrading requirements or any compensatory procedures; justification for alternate procedures should be available;

3.7 methodology for monitoring the performance of equipment and of the process as outlined in Sections 7 through 14;

a) all laboratory testing methodology;

3.8 the personnel responsible for performing, evaluating and certifying each stage of the validation protocol and for final evaluation prior to certification of the process.

4. PERSONNEL

Documented evidence of the experience and training of all personnel involved in validation studies should be maintained.

4.1 Qualified personnel should ensure that the validation protocol and testing methodology are developed in a sound engineering and scientific manner 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 equipment and measuring devices.

4.3 Engineering/mechanical personnel should be qualified in the operation and maintenance of sterilizers and support systems.

5. DATA REVIEW AND STUDY CERTIFICATION

All information or data generated as part of the validation protocol should be evaluated by qualified individuals against protocol requirements and judged as meeting or failing the requirements. Written evidence supporting the evaluation and conclusion should be available.

5.1 The evaluations should be performed as the information becomes available.

5.2 If evaluations show that the validation protocol criteria were not met, the impact on the process and the suitability of the protocol parameters should be investigated and the conclusion documented.

5.3 Failure to adhere to the procedure as laid down in the validation protocol must be considered as potentially compromising the validity of the study itself, and requires critical evaluation of the impact on the study.

5.4 The final certification of the validation study should specify the established process parameters. This information is required for post-validation monitoring as described in Section 15.

6. LABORATORY CONSIDERATIONS

6.1 All laboratory tests, including "D" value analysis, should be performed by a competent laboratory. The laboratory should have detailed methodology and procedures covering all laboratory functions available in writing.

6.2 In cases where outside laboratories are utilized, a suitable system for determining the competency of such laboratories should be included in the study protocol.

7. INSTRUMENTS

The range, accuracy, reproducibility and response time of all controlling and recording instruments associated with the sterilizer and support equipment must be adequate to demonstrate that defined process conditions are met.

7.1 Instruments requiring calibration include:

- temperature recorders and sensors;
- thermocouples;
- pressure sensors for jacket and chamber pressure;
- timers;
- conductivity monitors for cooling water, if applicable;
- flow meters for water/steam;
- water level indicators when cooling water is used;
- thermometers including those for thermocouple reference, chamber monitoring and all laboratory testing.

These instruments must be calibrated against traceable standards before any operational qualification can be performed. Written calibration procedures should specify the methods to be used, and records of each calibration, including actual results obtained, should be maintained.

7.2 Recalibration should be required in writing after any maintenance of instruments and, in the case of temperature sensing devices, before and after each validation run conducted as part of heat distribution or penetration studies.

7.3 The instruments should be included in a written preventive maintenance program.

8. INDICATOR CALIBRATION

Indicating devices used in the validation studies or used as part of post-validation monitoring or requalification must be calibrated.

8.1 Physical and chemical indicators should be tested to demonstrate adequate pre-determined response to both time and temperature.

a) Detailed written test procedures and records of test results should be available.

b) The indicators should be used before a written expiry date and stored to protect their quality.

8.2 Biological indicators should be tested according to detailed written procedures for viability and quantitation of the challenge organism and for the time/temperature exposure response. This applies to indicators either prepared in-house or obtained commercially.

a) For commercial indicators, a certificate of testing for each lot indicating the "D" value of the lot should be available. The quantitation is acceptable if the supplier's count has been qualified and periodically confirmed.

b) If biological indicators are prepared in-house, "D" value determinations and organism characterization are also required (refer to Sections 10 and 14). In conducting "D" value studies, the choice of media (pH, electrolytes, carbohydrates, etc.) and sample carriers (suspension in ampoules, paper strips, inoculated products and inoculation on solid carriers) should be consistent with the materials used in the sterilizer validation.

Records of the testing should be available.

c) The biological indicator should be used before expiry and adequately stored.

9. STERILIZATION CYCLE DEVELOPMENT

Two basic approaches are employed to develop sterilization cycles for moist heat processes: Overkill and Probability of Survival. The "F" and "D" terms used below to describe these methods are defined in Section 10.

9.1 The Overkill method is used when the product can withstand excessive heat treatment such as an $F_0 \geq 12$ without adverse effects. Bioburden and resistance data are not required to determine the required "F_0" values. Cycle parameters are adjusted to assure that the coldest point within the load receives an "F_0" that will provide at least a 12-log reduction of microorganisms having a "D_{121}" value of at least one minute (i.e.: $F_0 \geq 12$). The rationale for the Overkill approach is discussed in references 1, 2, 3, 4, 5, 6, 7.

9.2 The Probability of Survival approach is used primarily for heat labile products. In this approach, the process for the terminal sterilization of a sealed container is validated to achieve the destruction of pre-sterilization bioburden to a level of 10^0, with a minimum safety factor of an additional six-log reduction ($1x10^{-6}$). The probability that any one unit is contaminated is therefore no more than one in a million; this is considered to be an acceptable level of sterility assurance.

a) The probability of survival is determined using a semi-logarithmic microbial death curve, where a plot of the log of the number of survivors versus time at a fixed temperature yields a straight line. After the line has crossed below 10^0 (less than one survivor), the y-value corresponding to a given time value is expressed as the probability of survival.

b) The determination of the minimum "F_0" value for the Probability of Survival approach is based upon the number of microorganisms (bioburden) found in a given product and their heat resistance, as described in Section 10.3.

c) Methods for conducting bioburden studies, estimating microbial heat resistance and determining the minimum required "F_0" value for sterilization are described briefly in Section 10, and in more detail in reference 1, 2, 3, 4, 5, 6, 7.

9.3 For both the Overkill and Probability of Survival approaches, methods for the determination of the process time of a sterilization cycle required to impart the minimum required "F_0" values are described in reference 1, 2, 3, 4, 5, 6, 7. For both methods it is necessary to conduct heat distribution and heat penetration studies to determine the amount of heat delivered to the slowest heating unit in each load. These are discussed in Sections 12 and 13. Validation studies must assure that this unit receives the minimum required "F_0" value.

10. "F_0" AND "D" VALUES

10.1 "**F_0**", or the Lethality Factor, is the amount of time in minutes, equivalent to time at 121°C, to which a unit has been exposed during a sterilization process.

a) One method of calculating the "F_0" is to integrate the time the unit is exposed to heat in terms of equivalent time at 121°C. For more information, refer to reference 1, 2, 3, 4, 5, 6, 7.

b) A second method is based on data obtained by the use of calibrated biological indicators. See reference 1, 2, 3, 4, 5, 6, 7 for a discussion of how biological indicators can be used during a sterilization cycle to obtain an estimation of "F_0" values.

10.2 The "D" value is the time, in minutes, required to reduce a microbial population by 90% - or by one log value - under specified test conditions (i.e. fixed temperature, single species, specified medium, etc.). When heat labile products will not withstand excessive heat treatment, "D_{121}" value studies of product isolates are necessary to determine the minimum Lethality Factor (F_0) that will provide an acceptable assurance of sterilization.

10.3 The minimum "F_0" value required by a process can be related to the "D" value of the bioburden by the following equation:

$F_0 = D_{121}$ X (log A - log B)

where:

- "D_{121}" is equal to the time required at 121°C to reduce the population of the most heat resistant organism in the unit by 90%;
- "A" is the microbial count per container; and
- "B" is the maximum acceptable probability of survival ($\leq 1 \times 10^{-6}$ for pharmaceutical dosage forms).

10.4 Laboratory studies which determine the number and resistance of microorganisms associated with a product (bioburden) serve as the basis for calculating the required minimum "F_0" value required for sterilization. See reference 1, 2, 3, 4, 5, 6, 7 for approaches when using such data to estimate the minimum "F_0" value.

10.5 A more conservative approach assumes a "D_{121}" value of 1 minute ("D" value of a highly heat resistant spore forming organism such as Bacillus stearothermophilus) for the bioburden of the product.

11. EQUIPMENT QUALIFICATION

Prior to commencing heat distribution, heat penetration and/or biological challenge reduction studies, it is necessary that the equipment be checked and certified as properly installed, equipped and functioning as per its design.

11.1 Installation Qualification

a) For new equipment, qualification begins with the establishment of design, purchase and installation requirements. These requirements must be specific to the type and model of units (such as saturated steam, water immersion, water cascade, air-steam mixtures, gravity air displacement, vacuum air displacement). Included in these written requirements are all the construction materials, the sizes and tolerances of the chamber, support services and power supplies, the alarm systems, monitoring systems with response tolerance and accuracy requirements, and the

operational parameter requirements as governed by the established process specifications.

Installation qualification of new equipment should be based on written requirements and documented. The requirements should ensure that the pre-determined construction and installation requirements are assessed as soon as installation permits, and that these requirements are met (correct piping materials, wiring types, alarm hookups, recorders and gauges, chamber levelling, all piping is sealed and door gasketing effects proper sealing). All installation parameters should be documented and certified prior to operational qualification of the equipment.

b) For existing equipment, subject to concurrent or retrospective validation approaches, installation qualification requires defining the existing equipment design and installation parameters from records and direct assessment. The equipment is then evaluated for its capability to satisfy the defined process specifications, and for determination of any upgrading or procedural modifications needed to meet the process requirements.

Modifications should be documented as being performed according to pre-determined requirements and certified as rendering the equipment suitable for validation testing.

11.2 Operational Qualification

Operational qualification consists of testing the equipment over its pre-defined and installed operating range to verify consistent performance. Three or more test runs should be performed which demonstrate through documented evidence that:

- controls, alarms, monitoring devices and operation indicators function;
- chamber pressure integrity is maintained;
- chamber vacuum is maintained, if applicable;
- written procedures accurately reflect equipment operation;
- operation parameters are attained as pre-set for each test run.

Equipment should be certified as operationally qualified for any subsequent studies to be considered adequate.

12. HEAT DISTRIBUTION STUDIES

Heat distribution studies are performed in order to determine temperature variation throughout the sterilizer chamber and should be performed prior to heat penetration studies. These studies should encompass empty chamber and loaded chamber evaluation and should

be performed according to written procedures using temperature measuring sensors or probes which have been calibrated before and after use for each run.

The temperature uniformity requirements based on the type of sterilizer and specific processing parameters should be specified.

12.1 Heat distribution runs using an empty chamber may be performed during equipment operational qualification (see Section 11.2). These runs should be performed using the maximum and minimum cycle times and temperatures specified for the equipment.

Test runs should be repeated at each pre-set cycle time and temperature required in the protocol, in order to identify the heat distribution pattern of the chamber, including the slowest heating points. The studies should demonstrate that the uniformity of the sterilizing medium throughout the empty chamber is within the temperature variation limits established in the protocol.

Multiple temperature sensing devices should be used in each test run. The devices should be capable of simultaneous data generation within pre-established time intervals in order to permit determination of the slowest and fastest heating zones in the chamber.

The location of each device should be documented. The placement of the devices should ensure that a uniform distribution is achieved throughout the sterilizer chamber.

The data from all runs should be collated into a temperature profile of the chamber.

12.2 Heat distribution studies should also be performed on maximum and minimum chamber load configurations with consideration to the following:

a) Multiple temperature sensing devices are placed throughout the chamber but not inside the units of the load to determine the effect of any defined loading pattern on the temperature distribution within the chamber.

b) The test runs should be performed using the different container sizes to be processed using the sterilization parameters specified for the normal production process.

c) The position of each temperature sensor in each test run must be documented.

d) The slowest heating point(s), or cold spot(s), in each run should be determined and documented.

e) Repeat runs must be performed to establish whether, for a given load configuration, the location of the cold spot(s) is fixed or variable.

f) A temperature distribution profile for each chamber load configuration should be developed and documented.

12.3 Failure to demonstrate operational consistency within the chosen criteria for acceptable temperature uniformity precludes validation to be demonstrable for the specified sterilization cycle.

12.4 Each test run performed should be evaluated. The completed studies should be certified prior to beginning heat penetration studies.

13. HEAT PENETRATION STUDIES

In order to verify that the sterilizing temperature has been reached in each load subjected to moist heat sterilization, it is necessary to conduct heat penetration studies. These studies are conducted to ensure that the coolest unit within a pre-defined loading pattern (including minimum and maximum loads) will consistently be exposed to sufficient heat lethality (minimum "F_0"). Refer to Sections 9 and 10, respectively, for procedures to determine the minimum required process time when the Overkill approach is used and the minimum required F_0 value when the Probability of Survival approach is used. Discussions on the use of "bio-indicators" for estimating "F_0" values of autoclave cycles for heat labile and heat stable products are presented in reference 1, 2, 3, 4, 5, 6, 7.

13.1 Heat penetration studies should be performed according to detailed written procedures using temperature sensing devices which have been calibrated before and after each validation run which are capable of simultaneous data generation within pre-established time intervals in order to permit determination of the slowest and fastest heating units in the chamber.

13.2 The validation protocol should make provision for such variables as container size, design, material, viscosity of solution and fill volume. The container should have the maximum fill volume of a solution with heating characteristics as slow as the slowest-to-heat solution sterilized by the specified cycle.

13.3 Heat penetration studies should be conducted with the maximum and minimum loading configurations for each sterilization cycle using the sterilization parameters specified for the normal production cycles.

13.4 Depending on the size of the container, it may be necessary to perform initial container mapping studies with temperature sensing devices placed inside the product container to identify its heat penetration characteristics and to determine the container "cold spot". During heat penetration studies, sensors should be placed in the containers at the slowest heating point in the containers, where practicable. The majority of these containers should be located at the slowest heating point in the loading pattern as determined by the heat distribution studies.

13.5 Heat delivered to the slowest heating unit of the load is monitored and this data is employed to compute the minimum lethality ("F_0" value) of the process. Once the slowest heating units of the load have been identified, at least three replicate runs should be performed to verify that the desired minimum process "F_0" value can be achieved reproducibly throughout the load. The process is considered acceptable once such consistency in lethality has been adequately established.

14. BIOLOGICAL CHALLENGE REDUCTION STUDIES

Introducing a known quantity of specific microorganisms with established "D" values and assessing the level of reduction with time is appropriate when the Probability of Survival approach is used. These biological challenge reduction runs may be done in conjunction with heat penetration studies.

14.1 The level of biological challenge selected for the study should consider seasonal as well as lot-to-lot variation in the product bioburden (quantity and "D" value) and should be such that a probability of survival of 1 in 10^6 is confirmed in all cases. A worse case bioburden using B. stearothermophilus spores is acceptable.

14.2 The placement of biological challenges should be defined in writing. The challenge should be placed in containers where practicable, so as to reflect the desired processing conditions. In addition, they must be located in direct relation to any temperature sensors when run concurrent with heat penetration studies. A minimum of three runs should be performed for each load configuration under evaluation.

14.3 Positive controls should be run with each load to verify the viability of the challenge organism.

14.4 Records of the organism type, "D" value, challenge level, lot number, placement, and growth result should be available. Growth of any challenge following any of the runs indicates that sterilization has not been achieved. The process parameters should be evaluated. If no processing error is discernable, the process is judged unacceptable.

14.5 When change evaluation indicates a potential adverse effect on heat penetration, the biological challenge studies should be repeated.

15. POST-VALIDATION MONITORING

Post-validation monitoring consists primarily of routine checking of sterilization cycle conditions against the validated cycle, routine bioburden sampling, and ongoing equipment maintenance.

15.1 Each sterilization cycle must be monitored to ensure that the cycle conditions were set as specified and that the time, temperature and pressure parameters were attained as per the validated cycle. These checks should be documented in the processing records.

a) The requirement to perform monitoring should be a detailed written procedure referenced in the validation protocol.

b) Biological challenges should be documented when performed in routine monitoring procedures. The location, number, type and lot number of the challenge must be included in the records along with the actual test results.

c) Deviations from defined processing conditions must be documented, investigated and assessed for compliance with the protocol. Deviations below any pre-established conditions should be judged as compromising the sterilization process.

15.2 For sterilization cycles based on the Probability of Survival approach, samples for bioburden testing should be obtained on each batch of drug product prior to sterilization.

a) Samples collected at the beginning and at the end of the filling operation should be used to determine the microbial count and heat resistance of the most resistant product isolates. Routine sampling may vary according to the accumulated product testing history.

b) For any validated sterilization process a maximum microbial count and a maximum microbial heat resistance for filled containers prior to sterilization should be established. Microbial counts or heat resistance exceeding these levels should be judged as compromising the sterilization.

15.3 In order to ensure that the equipment and support systems function consistently within the validation protocol specifications, there should be a written program for the ongoing maintenance of each piece of equipment defined in the protocol. The maintenance program should detail the items to be checked and the frequency of maintenance and calibration of monitoring devices. It should require detailed written records of all maintenance performed. The records should be reviewed by a qualified person to ensure that the process has not been compromised.

16. REQUALIFICATION

All changes to the sterilizer system or process must be pre-authorized through the change control system or be required as part of a pre-established maintenance program. Requalification establishes that changes to parts of the sterilizing system have not invalidated the conditions outlined in the validation protocol.

16.1 Changes which require requalification include:

- replacement of sterilizing medium supply components, exhaust valves or door gaskets;
- modifications to the interior chamber walls;
- modifications to the sterilizing medium generating or cooling system supplies or their control systems;
- modifications to sterilizer carts or unit carriers (trays).

16.2 Heat distribution should be requalified when changes to the equipment may affect the uniformity of sterilizing medium in the chamber.

16.3 Heat penetration should be requalified when changes to the sterilization process system may affect penetration of heat to the units being processed.

16.4 Requalification is performed according to detailed written procedures which require that the original validation parameters and limits be used as evaluation criteria. The requalification studies must be documented in detail and results of the studies should be compared to the original validation results and evaluated to the same extent. If the results are satisfactory, the system should be certified. If the results are not satisfactory, the modified system requires new validation studies.

16.5 Changes to loading patterns, new container/closure systems or cycle parameters do not qualify for requalification but rather require that new validation studies be performed since, the original validation parameters being different, the conditions of Section 16.4 would not apply.

17. DOCUMENTATION

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

17.1 Outline

Information required in relation to the formulation and to the filling stages of sterile drugs:

a) the type of sterile drugs; parenterals or non-parenterals;
b) the batch size;
c) description of the drug and the container/closure system to be sterilized (e.g., size(s), fill volume, or secondary packaging);
d) the air grade where the drug is formulated;
e) the air grade where the drug is filled before moist heat sterilization.

A comprehensive outline of the protocol followed in the validation of the process should be prepared. The outline 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.

17.2 Process Documentation

a) If retrospective validation was conducted, the details of the lot analysis and process condition evaluation for the time period being assessed should be compiled. Evidence that process/product failures and discrepancies were included in the evaluation should be available.

b) The F_0 values required to establish the validation of the process and "D" values used in the calculations should be stated giving the source of the "D" values and calculation applied.

c) The sterilization cycle parameters used along with the load configuration(s) to which the cycle applies should be available. The details of the development of the cycle when a Probability of Survival approach was used must be included, as per Section 9 of this document and Microbiology below.

d) The heat distribution studies conducted should be summarized on a run-to-run and overall basis including an evaluation. Any modifications to the studies should be detailed and study impact evaluations given. The information must encompass the level of testing undertaken, calibration requirements and chamber conditions (empty, max./min. load). Diagrams of loading patterns and sensor placement are recommended.

e) All heat penetration studies undertaken should be summarized on a run to run and overall basis. The data should demonstrate that the study parameters relate to the heat distribution study results. Any modifications to the study should be detailed and process impact assessed. The information available should be similar to that complied for the heat distribution studies.

17.3 Microbiology

a) Bioburden determinations undertaken for the product and environment in Probability of Survival approaches should be detailed. The information should include the materials or areas monitored, media and methods employed and a summary of results by number and species with "D_{min}" and "D_{max}" values. The laboratory conducting the "D" value determinations should be identified.

b) Biological challenge reduction studies, when performed, should be summarized and include the species used, "D" value applied, carrier method, placement, recovery methods and results obtained. Placement

of the challenge should demonstrate relationship to the heat distribution and heat penetration studies.

17.4 Expert Evaluation

A written evaluation of the entire study carried out utilizing the various validation protocols as outlined above should be prepared and the conclusions drawn at each stage stated. In addition, all process conditions and monitoring required to routinely ensure that the validated conditions are being maintained should be provided. The final conclusion should clearly reflect whether the validation protocol requirements were met.

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

18. REFERENCES

1. "Validation of Steam Sterilization Cycles," *Technical Monograph No. 1*, Parenteral Drug Association, Inc., Philadelphia, PA.

2. Ibid., pp. 1-9.

3. Ibid., Section I.J.1.c), p. 9.

4. M.J. Akers, I.A. Attia, K.E. Avis. "Understanding and Utilizing F_0 Values," *Pharmaceutical Technology*, May 1978, pp. iv-vi.

5. *Technical Monograph No. 1,* PDA, pp. 20-22.

6. Ibid., pp. 7-9.

7. Ibid., pp. 19-22 and 27-29.

8. HPFBI Revised Guidance for section C.02.029 of the Good Manufacturing Practices Regulations.

9. "Manufacture of Sterile Medicinal Products" Annex 1, European Union.

10. HPFBI Validation Guidelines for Pharmaceutical Dosage Forms.

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* Bureau of Compliance and Enforcement changed to Health Products and Food Branch Inspectorate (HPFBI).

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