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:
Form-Fill-Seal for Drugs

Supersedes

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1. INTRODUCTION

This document is intended to provide drug dosage form manufacturers with guidance on the validation of Form-Fill-Seal (also known as "Blow-Fill-Seal") processes, as required in Division 2, Part C, of the Food and Drug Regulations (Good Manufacturing Practices), and in a manner which is acceptable to the Health Products and Food Branch.

Form-Fill-Seal (F-F-S) technology is increasingly being used by pharmaceutical manufacturers, most particularly for the manufacture of sterile liquid products, either to produce an ASEPTICALLY prepared product not intended for further sterilization, or to produce a very "clean" product for subsequent terminal sterilization. Although F-F-S machines have been used to produce non-sterile products, this guide concentrates on the use of this technology to manufacture sterile liquid products in plastics containers.

Because of the relative complexity of the Form-Fill-Seal (F-F-S) machines used, what has been termed the "prevalidation" or "Commissioning" phase (i.e. Installation Qualification and Equipment Qualification) is of particular importance. These aspects are covered in this guide, and a brief outline of the basic operation of the machines is given.

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. In addition to providing an invaluable resource and reference for the manufacturer, such documentation is essential to reviewers and inspectors for the purposes of Drug Submission evaluation and inspection.

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.

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 (or phases). 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, provided with all necessary services, subsidiary equipment and instruments, and is capable of performing in accordance with its basic design parameters.*(N.B. with a Form/Fill/Seal machine, and according to the type of product which the machine is intended to produce, the environment in which the machine is installed is an important consideration - see Section 11)*

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 the 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. Although lack of suitable records relating to the Qualification phases may not necessarily compromise concurrent validation of some other processes, evidence of proper machine installation is particularly important in the context of F-F-S.

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. OUTLINE OF THE F-F-S PROCESS

A brief outline of a typical Form-Fill-Seal process to which this guide applies is as follows:

3.1 A Form-Fill-Seal unit is specially built equipment which in one continuous operation forms containers from a thermoplastic granulate, and then fills and seals them.

Originally developed for other purposes, they have for some years been suitably adapted and available for use in the manufacture of pharmaceutical products, specifically sterile products.

3.2 Bulk solution prepared under "microbiologically clean" or aseptic conditions (as appropriate) is delivered to the machine through a bacteria-retaining filter. Pipework, filter housings and machine parts in contact with the product are steam sterilized in place, where practicable.

3.3 Filtered compressed air and granules of a plastic material conforming to a pre-determined specification and known to be compatible with the product to be filled (usually polyethylene, poly-propylene or polyethylene/polypropylene co-polymers) are supplied to the machine.

3.4 Within the machine, the plastic granules are extruded downwards under pressure (up to 350 bar) as a hot hollow mouldable plastics tube (or "parison") or tubes. As a result of the high pressure extrusion process, the parison reaches a temperature of 170° - 230°C. The configuration and internal integrity of the parison is maintained by an internal downward flow of filtered air under pressure.

3.5 The two halves of a mould close around the parison and seal the base. Simultaneously, the top of the parison is cut free by a hot knife-edge. The plastics material is now formed into a container(s) as determined by the design of the mould by vacuum and/or sterile air pressure.

3.6 The container(s) is/are immediately filled with a metered volume of the solution, displacing the sterile air. Both the air and the solution are filtered through bacteria retaining filters immediately before entry into the forming, or formed container(s).

3.7 When the required volume is filled into the container(s) the filling unit is raised and the containers are sealed automatically. The mould then opens, releasing a package formed, filled and sealed all in the one continuous, automatic, cycle which takes a matter of seconds. Meanwhile, parison-extrusion continues, and the cycle repeats. The filled and sealed units usually require "cropping" off excess plastic.

3.8 In versions of these machines adapted for aseptic manufacture, the cycle is conducted automatically within the machine's own internal sterile air flushed environment (or "air shower"). The machines can also be used to fill suspensions, ointments, creams, and liquids other than aqueous solutions, although with such products it is not always possible to employ the final aseptic product filtration prior to filling.

3.9 A "multiblock" version of the machine permits the formation of a number (or set) of containers at each pass from the parison by one mould.

4. PROTOCOL DEVELOPMENT AND CONTROL

4.1 Each stage of the evaluation of the effectiveness and reproducibility of an overall 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 2.5. 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.

4.2 Protocols should specify the following in detail:

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

4.2.2 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 their performance characteristics.

4.2.3 Installation and qualification requirements for new equipment.

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

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

4.2.6 Assignment of responsibility for performing the study.

4.2.7 All test methodology to be employed, with a precise statement of the test equipment and/or materials to be used.

4.2.8 Test equipment calibration requirements.

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

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

4.2.11 Acceptance criteria against which the success of the study is to be evaluated.

4.2.12 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.

5. PERSONNEL

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

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

5.2 All personnel conducting tests should be trained and experienced in the use of the equipment and measuring devices.

5.3 Engineering/mechanical personnel should be fully trained and competent in the operation and maintenance of the F-F-S machines and any subsidiary equipment.

6. DATA REVIEW AND STUDY CERTIFICATION

6.1 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.

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

6.1.2 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.

6.1.3 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.

6.2 The final certification of the validation study should specify the pre-determined acceptance criteria.

7. LABORATORY CONSIDERATIONS

7.1 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.

7.2 All equipment should be serviced and calibrated at suitable intervals; records of these activities should be kept.

7.3 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.

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

8. INSTRUMENTS

8.1 The range, accuracy, reproducibility and response time of all controlling and recording instruments associated with the F-F-S Machine, and all supporting equipment, must be adequate to ensure that defined process conditions will be consistently met, both during the study and during routine production.

8.2 All controlling and recording instruments associated with the F-F-S Machine and supporting equipment must be calibrated before any meaningful operational qualification can be performed.

8.2.1 Written calibration procedures should specify the methods to be used for each instrument.

8.2.2 Instruments which need to be calibrated include:

- temperature recorders and sensor;
- thermocouples;
- pressure/vacuum sensors (for hydraulic/vacuum systems, product lines, pressure differentials across filters, etc.);
- timers;
- flow meters for steam/water/cooling systems;
- level indicators for buffer tank(s);
- thermometers (as used, e.g. in laboratory testing, thermocouple reference etc.).

8.2.3 Recalibration should be carried-out after any maintenance of instruments.

8.2.4 Records of each calibration, including the actual results obtained, should be maintained.

8.3 All controlling and recording instruments must be subjected to a written on-going maintenance and calibration program.

9. MACHINE DESIGN AND SPECIFICATION

Currently, F-F-S machine manufacturers produce machines with a range of modifications (or variations) even within one specified model number. It is therefore essential that purchasers of these machines specify their requirements precisely, and check that their specified requirements are met.

The original machine specification should include statements of requirements for the following:

9.1 Materials of construction for all components, with special attention being paid to all contact parts, for example;

9.1.1 Machine pipework.

9.1.2 Internal components of purchased fittings e.g. automatic valves, including elastomeric and mechanical seals.

9.1.3 Pipeline joint seals.

9.1.4 Welding materials, particularly if any modifications to the manufacturer's specifications are required.

9.1.5 Filters and filter housings, including casing and substrate layers of cartridges, as well as the main medium and all elastomeric seals.

9.1.6 Polymer extrusion equipment.

9.2 Pipework configuration, with attention to sterile fluid pathways, for example;

9.2.1 Elimination of "deadlegs".

9.2.2 Position of thermocouples ("as installed" configuration, verified against the original design configuration - to be confirmed by temperature mapping as part of validation protocol).

9.2.3 Design of filter housings.

9.3 Porosity both of product and air filters. The validation data from the filter manufacturers should be available.

9.4 Design of moulds, considering fill volume range plus ullage, wall thickness, opening characteristics and ease of use, as well as overall shape and other aesthetic considerations.

10. EQUIPMENT QUALIFICATION

10.1 Prior to the commencement of any Process Validation studies it is necessary to demonstrate and certify that the F-F-S Machine and any supporting/subsidiary equipment, sub-systems and services are properly installed and functioning in accordance with their basic design parameters.

10.2 For new equipment, qualification begins with the establishment of design, purchase and installation requirements.

10.2.1 These requirements should be specified in writing and should include those matters relevant to the F-F-S machine itself, in addition to design specifications for ancillary equipment, where relevant.

10.2.2 These design and installation requirements must be specific to the type and model of the equipment required.

10.3 **INSTALLATION QUALIFICATION** of new equipment should be based on written procedures and the results documented.

10.3.1 These written procedures should ensure that the pre-defined construction and installation requirements are confirmed as being met, during the actual installation process.

10.3.2 All key installation parameters should be recorded, and certified as conforming to the pre-determined requirements prior to operational qualification of the equipment.

10.4 For existing equipment, installation qualification may consist of defining existing equipment design and installation parameters from records and from direct assessment.

10.4.1 This equipment should then be evaluated for its ability to meet the defined process specifications and for the determination of any mechanical upgrading or procedural modifications needed to meet process requirements.

10.4.2 Any modification should be documented as having been performed in accordance with predetermined requirements, and certified as rendering the equipment suitable for Process Validation Studies.

10.5 The **Installation Qualification** phase should be designed to ensure that the specified construction and installation requirements are met, including correct provision of, and connection to, all services, power-supplies, drainage systems and all ancillary equipment and instruments. In addition it should also cover all basic functional checks, including:

10.5.1 Operation of all electric motors, pumps etc. (e.g. extruder drive motor, hydraulic vacuum pumps).

10.5.2 Operation of all automatic valves, switches etc.

10.5.3 Operation of automatic systems for each of the pre-defined stages of production. This includes all computerized process control systems associated with the operation of the machine.

10.5.4 Operation of steam traps.

10.5.5 Operation of extruder heaters.

10.5.6 Operation and designation of thermocouples.

10.5.7 Setting and operation of alarm systems. (e.g. Air shower filter blockage, filter damaged switches).

10.5.8 Operation of hydraulic system. (e.g. Mould carriage, mould closing systems).

10.5.9 Positioning of main and head moulds (in relation to each other and to the platen).

10.5.10 Operation of the extruder including position of die and pin.

10.5.11 Fixing of timer settings for each stage of the process.

10.6 **OPERATIONAL QUALIFICATION** consists of checking the equipment (as installed) over its defined operating range in order to verify that it will perform consistently with the pre-determined limits.

10.6.1 Three or more test-runs should be performed in order to demonstrate through documented, certified evidence that:

- operational parameters are maintained as pre-set for each test-run;

- all controls, alarms, indicators, and sensing, monitoring and recording devices function correctly;

- written procedures accurately reflect equipment operation.

10.6.2 Functions requiring attention in the specific context of F-F-S technology include:

- the equipment/pipe-line sterilization process (including steam supply temperature and pressure, temperature mapping for "cold point" determinations; the overall profile of the sterilization cycle should be monitored in order to minimize the use of excessive heating and/or time at elevated temperature to bring the coldest part to the required temperature);

- fluid and air flows, including mould coolant temperature and flow-rate and air supply pressure for each function;

- timer settings for each stage of the process;

- flushing and cleaning of all product and other fluid pathways (in respect of each product manufactured);

- the filter drying process;

- extrusion of polymer and formation of product units to the required specification (e.g. appearance, size, shape, wall thickness, fill volume, opening characteristics etc.; conformance to the specifications should be assessed for each change in variable such as mould shape and size, type of polymer, product formulation, product filter etc.);

- filter testing - to cover the testing of all filters, and to include the establishment of filter test frequency for routine production.

10.7 Equipment must be certified as operationally qualified before any subsequent studies can be considered valid.

11. ENVIRONMENTAL CONSIDERATIONS

11.1 If F-F-S machines are used for the manufacture of non-sterile products, then they should be installed in an environment conforming to normal GMP requirements for non-sterile products, unless the nature/hazards of the product requires special conditions or precautions. However, it is usually advisable to place the machines in segregated air-conditioned areas, in view of the heat and particulate contamination which may be generated.

11.2 If F-F-S machines are used to manufacture products intended for subsequent sterilization, then they may be installed within an environment which would normally be considered appropriate for the manufacture and filling of terminally sterilized products.

11.3 If the machines are to be used for the aseptic filling of sterile products they are usually provided a localized environment at the point of fill, with air of an environmental standard corresponding in particulate and microbial quality to Grade A.

11.4 In such circumstances (11.3) an environmental standard for the area in which the machine is contained, which is lower than that normally required for a room used for aseptic filling, may be acceptable **provided that adequate process validation studies demonstrate an acceptable level of sterility assurance** (see Section 14).

11.5 Confirmation and certification that the room does in fact conform to the specified Environmental Standard should form part of the Installation Qualification phase. To this end, the following basic work should be carried-out in the initial commissioning 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.
- Air particle counts, both viable and non-viable, in the rest condition.
- Room pressure differentials.
- Lighting, heating, humidity.

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

11.6.1 Room Air Filter Test: Repeat at least annually, unless results of normal in-process monitoring indicate a need for more frequent or additional testing.

11.6.2 Air Velocity: Repeat at least twice a year.

11.6.3 Air Particle Counts: Determine as part of regular in-process monitoring with formal certification by a competent specialist agency twice a year.

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

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

12. MACHINE MAINTENANCE

12.1 For the results of any validation studies to remain valid in routine manufacture, a comprehensive on-going maintenance program should be developed and implemented, setting out each activity in detail along with the frequency.

12.2 Matters to be specifically covered in the Maintenance Program should include those items listed under "Equipment Qualification" (Section 10), plus examination and replacement (as necessary) of elastomeric seals, and the condition of moulds, dies and pins.

12.3 The requirements for planned maintenance apply to all supporting equipment and instruments associated with the F-F-S process.

13. ROUTINE IN-PROCESS CONTROL AND MONITORING

13.1 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 which reflects the validation conditions established.

13.2 In-process control and monitoring may be considered under four headings:

- **Environmental Particulate**
- **Microbiological**
- **Filter Integrity Testing**
- **In-process Product Control**

13.3 The amount and type of Microbiological/Environmental monitoring that is required depends on the nature of the manufacturing process (terminal sterilization as compared with aseptic processing) which is adopted.

13.4 **Environmental Particulate** monitoring should be carried-out using an appropriate air Particle Counting device to check that the environmental air remains in conformity with specification.

13.5 Steps should also be taken to ensure that the immediate Air Shower environment remains in conformity with specifications during processing with respect to viable and, where possible, non-viable particulate matter.

13.6 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 delivery to the F/F/S machine.

- Exposure of "Settle Plates" (Petri dishes of nutrient agar) at critical positions within the general room in which the machine is sited.

- Use of Air Sampling devices to determine the number of viable organisms per cubic metre (or cubic foot) of air in the room.

- Use of Contact Plates, or Swabs, to check the microbiological quality of surfaces.

Although, once filling has commenced, operator entry into the machine room should be kept to a minimum, operator "finger dabs" can provide a useful additional microbiological control.

13.7 **Filter integrity testing** of the filter(s) used to sterilize the product, and the filter(s) used to ensure the required air quality within the F-F-S machines internal "Air Shower" and container moulding process is critical in sterile product manufacturing. Filter integrity tests of the product filter should be conducted after each use of the filters in order to detect any leaks or perforations which may have occurred during the filtration process itself. It is recommended that such integrity testing be performed before the filtration of the product commences. It is, however, the integrity test performed after the batch, or lot, has been filtered which is critical.

13.8 **In-process Product Control** checks should include, as appropriate:

- Appearance.
- Fill Volume.
- Wall-thickness of container.
- Check for leakers.

- Container opening characteristics.

13.9 All 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.

14. ASEPTIC PROCESS VALIDATION - MEDIA FILLS

14.1 The usual, and generally acceptable, method of validating a sterile filtration and aseptic filling process is the "Media Fill", - "Broth Fill", or "Process Simulation" technique, in which a liquid microbiological nutrient growth medium is prepared and filled in a simulation of a normal filling operation. The nutrient medium is processed and handled in a manner which precisely simulates the "normal" filling process, with the same exposure to contamination-risk (from operators, environment, equipment and surfaces) as would occur during routine manufacture. Sealed containers of the medium produced during the "media-fills" are then incubated under prescribed conditions and examined for evidence of microbial growth, and thus of an indication of the level of contamination in the units produced.

14.2 It is important to emphasize 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" precaution 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.

14.3 An objection which has been raised concerns the possibility of contamination of the facility and equipment by the nutrient medium. However, if the process is well controlled and the media-fill is promptly followed by cleaning and disinfection, and (as necessary) sterilization of equipment, this problem should not arise. It is nevertheless important to recognize the potential hazard, and respond accordingly.

14.4 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. Section 7, 8 and 10 of this Guide). Rooms used for both bulk solution processing and for the F-F-S process should also

have been confirmed and certified as complying with their respective environmental standard (see Section 11).

14.5 Normal routine in-process control and monitoring procedures (see Section 13) should be operated during the media-fill. Mechanical adjustments which are permitted during production should also be qualified.

14.6 The **Nutrient Medium** used should be capable of supporting the growth of the broadest spectrum of microbial contaminants that might reasonably be expected to be encountered. Liquid Soybean Casein Digest is the medium most frequently recommended and used. Other media may, however, be used provided they meet the required criteria and are demonstrably capable of supporting the growth of the relevant range of micro-organisms.

14.7 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. In order to give 95% confidence in detecting a contamination rate of 1 in a thousand at least 3000 units need to be filled.

14.8 On initial validation of a new F-F-S machine/facility sufficient consecutive runs should be performed to provide assurance that the results obtained are consistent and meaningful and that they provide an acceptable level of sterility assurance. At least 3 separate, consecutive, successful (see later) runs per machine, per mould configuration should be performed to provide acceptable initial validation of a new F-F-S installation. (For Size and frequency of Revalidation runs, see Section 16).

14.9 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 the inner surface of the container by the medium.

14.10 Immediately following filling, all units filled should be visually checked for leakers, possibly with the aid of physical pressure. In this context, any leak testing method in which heat is employed should obviously not be used. Any leakers should be rejected.

15. INCUBATION

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

15.1 The **Incubation Temperature** should be 30° to 35°C. Incubation temperatures should be carefully monitored and maintained throughout the incubation period.

15.2 **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.

15.3 **Reading Results:** All units filled and incubated should be visually examined for microbial growth after 14 days incubation. **Any contaminated units will be identifiable by turbidity of the medium, sediment, or pellicles at the surface of the medium. Any contaminated units should be examined in the laboratory, and the contaminating species identified so that appropriate preventative action may be taken.** In order for the results of the media fill run to be considered valid, the inoculated control units should display growth.

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

16. REVALIDATION

16.1 Following initial aseptic process validation, media-fills should be repeated to an extent, and at a frequency, which will depend on an 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 repeat a full process validation protocol (minimum of 3 consecutive successful media-fill runs). During this time, the machine in question is taken out of service until any problems have been resolved, and the results of the three media-fills have been evaluated and found acceptable.

16.2 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 machine, or where the machines are operated on a continuous 24-hour operation basis, once per shift per year, that is, 3 times per year.

17. DOCUMENTATION

The following information should be prepared in summary form for the purposes of inspection and evaluation by the appropriate Directorate of the Health Products and Food Branch.

17.1 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.

17.2 Prevalidation

17.2.1 A full description of the F-F-S machine and relevant 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.

17.2.2 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 11).

17.3 Process Qualification

17.3.1 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 and services;
- steam sterilization of equipment, vessels and pipe-lines;
- filter integrity testing;
- machine set-up, start-up and adjustment;
- product in-process checks (leaks, fill-volumes, wall-thickness, etc.).

17.3.2 Full Process Qualification report, including:

- medium used;
- volume filled;
- number of units filled;
- number of leakers rejected;
- number of units incubated;
- incubation temperature(s) and time(s);

- control organisms used;
- filter integrity test results;
- record of all in-process monitoring and control results;
- results of examination of incubated units with evaluation of the those results against the criteria of the protocol;
- confirmation of growth in inoculated control units.

17.3.3 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.

17.4 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 maintenance programs for the F-F-S machine and ancillary equipment and instrumentation to maintain the validated conditions (see Sections 12). 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 signed for. Overall approval of the study should be authorized by the head of the validation team and the head of the Quality Control Department.

18. REFERENCES

For additional information on the Form/Fill/Seal processes, see:

H. Berrebi, The bottle-pack system for the pharmaceutical industry, pub. Rommelag AG, Hintere Bahnhofstrasse 78, CH-5001, Aarau, Switzerland.

F. Leo: Chapter in Aseptic Pharmaceutical Manufacturing - Technology for the 1990's. Ed. Olson and Groves. pub. Interpharm Press.

J.R. Sharp, "Manufacture of sterile pharmaceutical products using 'blow-fill-seal' technology," Pharmaceutical Journal, 1987, **239**, 106.

J.R. Sharp, "Validation of a new form-fill-seal installation", Manufacturing Chemist, Feb. 1988, p.22.

L. Zimmerman, "Technical measures for aseptic packaging of liquids with the 'bottlepack-aseptic-system'", Drugs made in Germany, 1984, 41, (2), 56.

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