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

GUIDANCE DOCUMENT

Process Validation :
Irradiation Sterilization for Pharmaceuticals

Supersedes

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1. FORWARD

While radiation processing technology has been in existence since the 1950's and has now evolved to its present 'state-of-the-art' availability, most of the literature regarding validation of the process, has been written for the application of this process to medical devices (See Reference 19.1).

The reader should understand that it is impossible to state in one document all of the specific elements required in the validation of a manufacturing process. The goal of validation is to demonstrate that a process, when operated within established limits, produces a product of consistent and specified quality. During validation, the critical process parameters should be identified, and, based on sound scientific principles, appropriate studies should be performed to demonstrate that the parameters can be met on a consistent basis.

Process validation should be considered as early in the development of a new product or a new or modified process as is practical. In this way, data required for validation can be collected during development studies, and also during the production of clinical batches. This "prospective" validation approach is preferred by the Branch since it demonstrates a well thought-out product production process. It is also cost effective as the data is collected while doing work which is necessary for reasons other than just validation.

In preparing this document, we have assumed that the reader is familiar with radiation processing in general, and its application to and effects on their product(s) in particular. For background reading on these subjects, the reader is referred to references 19.1-19.10.

Radiation processing, in the context of this guide, is considered to mean the exposing of the product to ionizing radiation (i.e. gamma radiation generated by an isotopic source such as Cobalt 60, or electron beams, or the photons generated from electron beam machines) in a controlled manner to ensure that a pre-determined dose is delivered to the product.

The objective is to reduce the bioburden to a desired level.

There are significant differences between the two technologies which affect process validation. For instance, gamma radiation delivers a specified dose relatively slowly, (over a period of minutes to hours), to a large volume of product. Conversely, an electron beam machine can deliver the same dose in a fraction of a second to a very small volume of product. These and other factors make it imperative that a product be validated independently for each source of radiation.

If the procedures and recommendations of this guide are followed it should result in the generation of acceptable documentation for submission to the Health Products and Food Branch Inspectorate for approval to utilize ionizing radiation for the purpose of treating a pharmaceutical raw material or finished product to improve its microbial quality.

It is important that the level of microbial quality be critically evaluated first, in order that the use of ionizing radiation may be rationally applied. A knowledge of the microbial quality of the raw materials and the manner in which it was achieved may have significant implications. Reduction of the microbial bioburden of raw materials will, in general, allow a reduction in the radiation dose to

the final product. It thus reduces the effects of ionizing radiation on the product. At the same time, attention must be paid to the formulation in order that the most stable form of the product is manufactured. This will allow a greater radiation dose and provide for a greater degree of Sterility Assurance.

It is important to track the species as well as the number of organisms in order that the radiation dose delivered to the product continues to provide the same Sterility Assurance Level.

2. INTRODUCTION

The purpose of this document is to provide guidance to manufacturers of pharmaceutical dosage forms regarding how to establish the scientific effectiveness, as required by the Health Products and Food Branch Inspectorate, of radiation sterilization processes when used to produce pharmaceutical products. It includes both the type of information which needs to be gathered and the supporting documentation which should be submitted to the Branch for approval of the process and for inclusion in the GMP's for the manufacture of that pharmaceutical.

This guide will **not** detail specific procedures or define elaborate mathematical principles which may be critical to the validation process as this information is available through other sources. It is intended to provide: an outline of those elements of product manufacture and radiation processing when applied to pharmaceuticals, which require evaluation; and a description of approaches to evaluation which are acceptable to the Health Products and Food Branch Inspectorate.

Section 17 of the guide specifies the documentation required to enable certification that the irradiation process has been thoroughly evaluated for a given product, and is capable of being adequately controlled. This documentation, aside from being invaluable to the manufacturer, will be essential to the specialists of the Directorate for the purpose of drug submission evaluation.

This guide is applicable to radiation processing only. While the principles outlined in this document are shared with other processes 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.

Sample-based, end-product testing does not guarantee a consistent or high quality product; it can only effectively identify and statistically quantify the incidence of substandard product. Therefore, the manufacturing process must be designed to deliver optimum product consistently, and the Process Validation Program must test this.

Radiation sterilization is used mainly for the sterilization of heat sensitive materials and products. In that many medicinal products and packaging materials are radiation-sensitive, this method is permissible only when the absence of deleterious effects on the material/product has been confirmed prior to use. Ultraviolet irradiation is not normally an acceptable method of sterilization.

Prior to beginning a Process Validation Program for any product-specific radiation sterilization process, the following should exist and/or be done:

a. the desired end-product (the pharmaceutical and its packaging) should be defined (specifications), in terms of its physical, chemical, microbial and pharmacological properties

b. specifications should be established for all raw materials and components

c. the required level of sterility assurance should be established based upon the indicated use of the product

d. assays used to determine product purity should be validated

e. the sensitivity of the analytical test methods should permit accurate detection and quantification of the product of interest, as well as impurities, prior to the initiation of radiation processing, so that the effects of radiation on the product can be determined.

As in all scientific testing, it is important that validation tests and challenges be repeated enough times to assure reliable and meaningful results. Demonstrating that the manufacturing process consistently produces the desired product may eliminate the need for testing every production batch or lot. Revalidation may be required in the event that a process step is removed, added or modified. Radiation process validation will usually cover the following major elements: raw materials, manufacturing area bioburdens, radiation dose limit determinations, product loading pattern (for treatment), dose delivery determinations, and vendor qualification (if the radiation facility is external to manufacturing facility).

3. VALIDATION APPROACHES

The validation of a product-specific radiation sterilizing process may be performed using one of the three approaches outlined below. The most appropriate approach should be selected, and this selection must be justified/defended in any submission to the regulatory authority.

3.1 **Prospective Validation** applies when new products or new formulations of existing products are being developed, or when a change of sterilization process (to radiation sterilization) is intended.

The validation is conducted, documented and evaluated, and the validation process and end-product is "certified" (by in-house or regulatory authorities as required), prior to starting toxicological or clinical trials (if these are required).

3.2 **Concurrent Validation** applies when existing products and/or raw materials and/or supplies (e.g. bottles, septa), are routinely being produced using a radiation sterilization process, but for which accurate and complete materials, process and test data do not exist.

The validation program is conducted concurrent with product/material/supply production and/or use.

3.2.1 This approach should only be considered in situations where there exists a clear history of consistently high quality product/material/supply production. It would be wasted effort to attempt to validate an inconsistent "situation".

3.3 **Retrospective Validation** applies when existing products and/or raw materials or supplies (e.g. bottles, septa), are routinely being produced using a radiation sterilization process, and for which accurate and complete materials, process and test data exists. In this unlikely case, the validation could be based entirely on historic data. Note the following:

3.3.1 It must be established that the product/material/supplies were consistently treated by the same process (i.e. with the same dose) and that the radiation sterilization equipment was operated according to relevant GMP's.

3.3.2 The historic data should be capable of demonstrating that the irradiated product/material/supplies were clinically effective.

3.3.3 Data related to periods in which different sterilization processes were employed should be used to compare the effects of these different processes on the product/material/supplies. Differences in the product/material/supplies attributable to the different processes used during the data collection periods should be evaluated and reported.

4. VALIDATION 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.

Process validation documentation encompasses, but is not limited to the following documents.

4.1 A process validation protocol (Sec. 5).

4.2 Reference documents (e.g. standard test methodologies, instrument calibration data, measurement device use procedures, change control procedures) (Sec. 8 & 9).

4.3 Product qualification protocol (Sec. 11).

4.4 Equipment qualification protocol (Sec. 12).

4.5 Personnel documentation (Sec. 6).

4.6 Process validation data: gathered as part of the various validation activities; (e.g. tests, studies, reference searches)(Secs. 13 & 14).

4.7 A process validation Summary Report (Secs.7 & 18), including specific process validation activity reports/evaluations as attachments.

Each of these documents is discussed in subsequent sections which describe in more detail the development of the protocol, the data which need to be collected, and the information to be summarized for submission to the Branch in cases where approval is being sought to use radiation processing as part of the GMP's for a particular product.

5. PROTOCOL DEVELOPMENT AND CONTROL

5.1 Each activity of a process validation program for a product-specific sterilization process should be based on pre-established and pre-approved detailed, written methods and procedures. The collection of specific-activity methods and procedures, generic-activity methods and procedures, process/product/materials/supplies information, relevant logistics and administration information, and relevant reference documents, constitutes the Process Validation Protocol.

5.2 For all process validation programs that are based on validation approaches which require the conduct of new data-generating activities, (Prospective and Concurrent Validation approaches), it is recommended that a "generic" Change Control Procedure be created, documented and enforced. The purpose of the Change Control Procedure should be to reduce the risk of unauthorized deliberate, or inadvertent change(s) being made to the protocol, methods and/or procedures, the sterilization process, and the product/materials/supplies. Such changes could invalidate large bodies of data. The absence of a Change Control Procedure for a given process validation program could create doubt about the validity of new data generated by the program.

5.3 The Process Validation Protocol should be consistent in content and form with the validation approach (see Section 3) selected. It should contain:

5.3.1 a detailed description of the process being validated and the product involved including the physical context/environment in which the process will function;

5.3.2 the process objectives in terms of the required Sterility Assurance Level of the processed product;

5.3.3 pre-established specifications for the process such as: temperature limits (if relevant), minimum dose requirement, maximum/not-to-exceed dose

requirement, dose rate (if relevant), maximum acceptable product bioburden of product prior to treatment, etc.;

5.3.4 a description of the equipment and relevant support systems which will be used to deliver the "process". This description should include relevant performance characteristics of each system, sub-system or piece of equipment;

5.3.5 a description of the process control "system" (components of, sensitivity of, methods and practices);

5.3.6 a list and description of all of the activities (tests, studies, data collection etc.) which form the process validation program;

5.3.7 the methodology for monitoring the performance of the equipment, relevant support systems, and the entire process during the process validations studies (if different from 5.3.5);

5.3.8 all laboratory testing methodology;

5.3.9 a listing of the personnel responsible for coordinating, performing, evaluating and certifying each activity of the protocol, and for conducting the final evaluation prior to the "in-house" certification of the process or prior to regulatory submission;

5.3.10 a process and protocol Change Control Procedure, if appropriate (see 4.2); and

5.3.11 a plan of action which explains/defines the sequence and timing of activities.

5.4 Once the protocol is approved, specific process validation activities can begin. The bureaucratic objective of the program is to produce a Process Validation Summary Report, and a body of Validation Documentation. If the process is found to be "acceptable", then the process is deemed to be "validated".

6. PERSONNEL AND PERSONNEL DOCUMENTATION

A documented statement (including appropriate evidence) of the experience and training of key personnel involved in validation studies should be maintained. For process validations intended for submission to the Branch, this personnel documentation will be required.

6.1 Qualified personnel should ensure that the protocol and in particular the testing methodologies are developed in a sound engineering and scientific manner, and that all studies are professionally evaluated and certified.

6.2 All personnel conducting tests should be trained and experienced in: the use of the equipment and measuring devices; the handling of the product; and the test methodology.

7. DATA REVIEW AND STUDY "CERTIFICATION"

7.1 All information and data generated as part of the validation program should be evaluated by qualified individuals against protocol requirements, and judged as meeting or failing these requirements. Written evidence supporting the evaluations and judgments should be available.

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

7.1.2 If evaluations show that protocol requirements were not met, the impact on the sterilization process, or the validation activity and program, and the suitability of the protocol requirements should be investigated and documented.

7.1.3 Lack of adherence to protocol requirements always requires that a critical evaluation of the impact on the test/study/activity and the program be conducted and documented.

7.2. The final "certification" (positive judgement) of a process validation program will specify the specific process parameters (refer to Sections 4.7 and 5.4).

8. LABORATORY CONSIDERATIONS

8.1 All laboratory tests, including D10 Value determinations of microbial species (when required), should be performed by a competent "contract" laboratory if not available "in-house".

8.2 Detailed methodology covering all laboratory tests should be available in writing.

8.3 A suitable system for verifying and documenting the appropriateness and competency of both "contract" and "in-house" laboratories should be included in the study protocol.

9. INSTRUMENTS

9.1 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.

9.2 All process controlling and recording instruments associated with the sterilizer and support equipment must be calibrated before any process validation can be performed. The standards used for calibration must be traceable to a national or international standard. Written calibration procedures should specify the methods to be used and be included in the validation documentation.

9.2.1 Dose measurement instruments common to both electron beam and gamma radiation processing technologies, and which require calibration include: spectrophotometer, thickness gauges, and temperature recorders (when required).

9.2.2 Recalibration should be required and documented after any maintenance of instruments and, in the case of dose measurement instruments, before and after each validation "run" conducted as part of dose distribution studies.

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

9.2.4 Dosimeters, while not an "instrument", are a critical item requiring calibration and certification. This should be traceable to a recognized national or international standard.

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

9.2.6 Process-controlling instruments are specific to each radiation sterilization system, and as such should be specified in the documentation describing that system. Reference should be made to this document for details describing the frequency of need for calibration and the methods to be used for recalibration.

10. RECOMMENDED SEQUENCE OF ACTIVITIES

10.1 A successful "product qualification program" is a pre-requisite to process validation, and product qualification documentation should be an integral part of process validation documentation. Product qualification demonstrates the effects (or lack thereof) of ionizing irradiation on the product and establishes key treatment parameters. The term 'product' in this section refers to either raw materials or

finished goods, and includes all packaging materials with which the product comes into intimate contact during the radiation process.

10.2 It is also necessary to demonstrate that the irradiation system (the controls and equipment) is adequate for the process, and is being maintained and operated in accordance with GMP's. Therefore a successful "equipment qualification program" is a pre-requisite to process validation, and equipment qualification documentation should also form part of the process validation documentation.

10.3 Consequently, the next three sections describe in some detail how each of these "programs", namely the qualification of the product, the qualification of the equipment, and lastly the validation of the process should be performed.

11. PRODUCT QUALIFICATION

11.1 A product qualification program demonstrates the effects of ionizing irradiation on the product. The most important outcome of product qualification is the determination of the product's **Maximum Tolerated Dose** (D_{maxT}) for the product. In addition the **Maximum Process Dose** (D_{maxP}) and the **Minimum Process Dose** (D_{minP}) will also be set.

The **Maximum Tolerated Dose** is that dose of radiation which induces an unacceptable change in the analytical profile of the pharmaceutical. It may be possible to select a radiation dose at which no radiation induced changes in the analytical profile can be detected. It is important in the initial product qualification steps to test the product using widely separated radiation doses. This will quickly assess the ability of the product to withstand radiation and to "zero-in" on the most appropriate radiation dose for further testing.

11.2 Prior to commencing any determination of D_{maxT} for the product, it is essential to determine if any of the components of the product have received prior radiation treatment. Radiation effects are cumulative. Therefore, any prior radiation treatment will affect the interpretation of dose-effect experiments. The effects of variations in density of the packages are also a consideration to be looked at.

11.3 The **Maximum Process Dose** (D_{maxP}) for a product must not exceed its D_{maxT}. It is determined by judgment. It is usually set below the **Maximum Tolerated Dose** to ensure that the product is not overexposed. It is dependant upon the product loading, and the physical parameters of the irradiator, such as source strength.

11.4 A third factor is the **Minimum Process Dose** (D_{minP}). The **Minimum Process Dose** is determined by the product loading pattern, density, and the operating characteristics of the irradiator. The ratio of the **Maximum Process Dose** to the **Minimum Process Dose** is known as the D_{max}/D_{min} Ratio. This **Ratio** is the key to successful radiation processing.

11.5 PRODUCT QUALIFICATION APPROACHES

11.6 **Prospective Qualification**: For prospective qualification, the D_{maxT} will be that dose which achieves the greatest SAL provided the product does not lose its "fitness for use" properties, (i.e. there is no loss of potency). This is because all toxicologic and clinical studies will be performed using the irradiated product.

11.6.1 **Concurrent Qualification**: Concurrent qualification would be undertaken for an existing product where there is a need to increase the SAL of the product. The D_{maxT} will be the highest dose which produces no disturbance to the analytical profile and to the physical properties of the product. In this case the achievable SAL will be limited because of a desire to cause no change in the analytical profile of the product, thus avoiding having to retest the product for toxicity.

It will be necessary here to carefully note changes in the analytical profile and to use a level of radiation in the test program which will produce changes and demonstrate the ability of the analytical techniques to detect these changes. [Comment: Because drugs are usually administered for short periods of time, long-term effects of minor changes will be less significant for some drugs. However, for those drugs with protracted administration periods it may be necessary to consider toxicological/testing. In this case it would be better to use the prospective validation approach.]

11.6.2. **Retrospective Qualification**: A retrospective qualification is only relevant for raw materials which have a history of being treated with ionizing radiation. It would be undertaken as part of an effort to standardize the properties of incoming raw materials. The D_{maxP} and D_{minP} will be important values to have documented.

[Comment: Specifications with microbial limits can be met in a number of ways. Different suppliers of a raw material may use different methods to achieve these limits. The same supplier might choose a different method depending upon price/availability of methodologies. It is a certainty that each method will have its own peculiar impact upon the properties of the raw material, which in turn may affect its behaviour in the product formulation/manufacturing process.]

12. EQUIPMENT QUALIFICATION

Prior to commencing any studies it is necessary to qualify, the irradiation equipment. Normally this should be done/provided by the operator of the irradiation equipment. In the event that the irradiation equipment is operated by the pharmaceutical company, this documentation should already be available. Equipment qualification focuses on two discrete topics; design and installation, and operation.

12.1 Equipment Design and Installation

12.1.1 New Facilities: For new facilities, qualification begins with the establishment of design, and installation requirements.

12.1.1.1 Design: Included in these written requirements are : the key construction materials, the source of ionizing radiation, product transportation system through the irradiator, support services and power supplies, control systems, monitoring and alarm systems with response tolerance and accuracy requirements, and performance specifications. All of these requirements must be compatible with the product, the product format, and the established process specifications.

12.1.1.2 Installation of Equipment: Installation qualification (commissioning) of new equipment should be based on a written procedure, and the results documented. The procedure should ensure that design changes are documented in the "as built/as installed" drawings and in all manuals, and that the performance specifications are met. Failure of the equipment to meet the required performance specifications may invalidate the use of this equipment for processing.

12.1.1.3 All design/installation parameters should be documented and certified prior to operational qualification of the equipment.

12.1.2 Existing Facilities: For existing facilities, it is not necessary to establish design and installation requirements. The "job" has already been done. However "Qualification" requires the defining of the existing equipment design, and confirmation that it meets the stated performance specifications. In most cases, this should be "do-able" from existing records and documentation.

The equipment is then evaluated for its capability of satisfying the defined process specifications, and for determination of any upgrading or procedural modifications needed to meet the process requirements.

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

12.2 Equipment Operation

Operational qualification consists of testing the equipment over its full, relevant, operating range using actual or simulated product in its specified packaging and loading configuration to verify consistent performance.

12.2.1 Three or more test runs should be performed which demonstrate, through documented evidence, that:

- controls, alarms, monitoring devices and operation indicators function
- radiation dose administration is maintained
- written procedures accurately reflect equipment operation
- operation parameters are attained as preset for each test run.

12.2.2 Subsequent studies can only be considered adequate if the equipment has been certified as operationally validated (qualified) for the specific product, its packaging and loading configuration, and for its ability to deliver the treatment required (as defined in the established process specifications).

13. PROCESS VALIDATION

Process validation includes, but is not limited to a consideration of the following subjects; the sterilization approach, dose distribution studies, product loading patterns, biological challenge reduction studies, "cycle" interruptions, and temperature control of the product. These subjects are addressed in the following sections.

13.1. Sterilization Approach

Three basic approaches can be employed to develop a sterilization process for radiation processing: **Overkill, Bioburden-Based**, and **Species-Based Bioburden Sterilization**.

13.1.1 The **Overkill** method has traditionally been used when the product can withstand radiation doses in excess of 25 kGy, without adverse effects. It is based on worst-case bioburden assumptions. Therefore product specific bioburden and resistance data are not required. The irradiator and product loading parameters are selected to assure that the product receives the minimum dose (D_{minP}) of 25 kGy and that the maximum tolerated dose D_{maxT} is not exceeded.

13.1.2 The **Bioburden-Based** approach is well explained and detailed in the AAMI Guidelines (Reference 19.3). In using this approach, it is necessary to demonstrate that the pharmaceutical product's bioburden is similar in nature to that assumed for the AAMI calculations. This approach is only relevant in cases where the product's bioburden (before treatment) is consistent, and can be proven to be so. The result is a treatment dose that is tailored to the actual need (bioburden), and that is less than the very high (for pharmaceuticals) 25 kGy. The reader is strongly encouraged to obtain a copy of Reference 19.3, because an understanding of this approach is also necessary to fully understand the **Species-Specific Bioburden** approach.

13.1.3 The **Species-Specific Bioburden** approach is more particularly suited to the pharmaceutical industry as it relates the radiation dose delivered to the most resistant organism in the bioburden population found in the manufacturing area. This population should be significantly skewed in the direction of radiation sensitive organisms, especially when dealing with aseptic processing areas. This should result in a much lower dose of radiation being needed to achieve sterilization. For this method to be effective it is necessary to conduct dose distribution studies to determine the product loading pattern which achieves the best possible D_{max}/D_{min} ratio. (See 13.2).

Validation studies must confirm that the product in the D_{min} position actually receives the **minimum** dose, and that the product in the D_{max} position does not **exceed** the maximum process dose (D_{maxP}).

13.2. Dose Distribution Studies

Dose distribution studies are performed in order to determine the D_{max} and D_{min} positions in the irradiator transport mechanism for the product in its predetermined loading configuration; and to confirm that the radiation dose delivered to the product does not vary outside the process specification.

13.2.1 These studies should be performed according to written procedures using appropriately placed dosimeters which have been calibrated against a known standard (see 19.1 guidelines).

13.2.2 The location of each dosimeter should be documented. The placement of the dosimeters should ensure that a uniform distribution is achieved throughout the transport/irradiation system.

13.2.3 The dosimeters should be capable of measuring the dose over the desired range.

13.2.4 The data from all runs should be collated into a dose-map profile for each product transfer/irradiation device.

13.2.5 Dose distribution studies must be performed for each different product loading configuration, and each product size.

13.2.6 The studies should prove that the dose uniformity requirements, as contained in the process specification, are consistently achieved.

13.2.7 Failure to demonstrate operational consistency within the chosen criteria for acceptable dose uniformity precludes the validation of the process. Each test run performed should be evaluated. The completed studies should be certified.

13.3 Product Loading Patterns

The configuration of the product in/on the transport mechanism for conveyance through the irradiator is critical to achieving the specified D_{max}/D_{min} ratio and the specified doses which are essential to the maintenance of product integrity and the desired SAL. A detailed 'map' of how the product is to be placed in/on the transport mechanism forms a part of the process validation documentation. It is important to address the possibility of and effects of improperly loaded product.

13.4. Biological Challenge Reduction Studies

13.4.1 Studies of biological challenge reduction are to be performed initially to ensure that the product does not demonstrate a radioprotective effect on the microbial population.

13.4.2 The level of biological challenge selected for the study should consider product lot-to-lot variation in the bioburden (species and number).

13.4.3 A worst-case bioburden challenge using *B. pumilus* is acceptable, if the product is radiation resistant. In all other cases the microorganism with the highest D_{10} value, occurring in the natural population as determined by sampling of the environment, should be used.

13.4.4 The biological challenge should be performed as described in ISO 11131 as a guideline (see 19.1).

13.4.5 The biological challenge may be run in conjunction with dose distribution studies.

13.4.6 The placement of biological challenges should be defined in writing. The challenge should be located as close as possible to the D_{min} position and placed as close as possible to any dosimeters if run concurrent with dose distribution studies.

13.4.7 A minimum of three cycles should be performed for each load configuration under evaluation.

13.4.8 Records of the organism type, D_{10} value, challenge level, lot number, placement, and growth result should be available.

13.5 "Cycle" Interruptions

13.5.1 For the Gamma Process

13.5.1.1 It is necessary to specify for each product, the maximum permitted length of time from the completion of the filling cycle to the commencement of the sterilization treatment. Normally, all of a production lot of a pharmaceutical would be simultaneously exposed to the gamma radiation source. (There will be some exceptions for larger volumes/bulkier drugs.) For products treated by electron beam, where each unit is individually exposed, this period would be from the start of processing the first unit until the last unit has been sterilized.

13.5.1.2 For mechanical, safety or operational reasons, the radiation source may need to be turned off during the course of a "treatment", thus interrupting the sterilization treatment. For those products which are capable of sustaining microbial growth, it will be necessary to define the maximum length of time permitted for an interruption in relation to the treatment received at the time of interruption. [e.g. **For gamma radiation processing**; if the interruption occurs before 50% of the dose has been delivered, and the interruption is of sufficient length to allow for microbial growth, then a procedure must be in place to define how the product will be handled; i.e. allowed to continue, to restart, or to reject. If more than 50% of the dose has been delivered then it may be permissible for the cycle to be continued as there would be insufficient bioburden to support growth. **For electron beam processing**; it will be necessary to determine if a particular unit was completely irradiated at the moment of shut down. The delay factor for the remaining units has already been defined.]

[Comment: One could consider doing this work as part of the product qualification activity, if it was felt that a cycle interruption would be crucial to the successful sterilization of the product.]

13.5.2 For the Electron Beam Process

It is necessary to specify for each product the maximum permitted length of time from the completion of the filling cycle to the **end** of the irradiation treatment. This is because each unit within a batch (unit here can mean an individual vial or a carton), is sequentially exposed to the electron beam. Thus product unexposed could permit microbial growth, while awaiting treatment. Note the contrast here between gamma and electron beam processes.

13.5.3 For Both Processes

For both processes it will be necessary to have the appropriate procedures in place to direct the operator as to the appropriate person to contact in the event of a "cycle" interruption or a delay in the commencing/completion of the irradiation "cycle".

13.6 Temperature Control

For those products which are temperature-sensitive, it will be necessary to document the permitted temperature range of the product upon arrival at the irradiation facility and the time available for irradiation before the product temperature rises to the maximum tolerated level. It may be necessary to provide cooling of the product during the irradiation process. The manner in which this is to be done must be specified. This type of information will form part of the process validation documentation.

14. POST VALIDATION PROCESS MONITORING

14.1 The sterilization process must be monitored routinely to ensure that the process conditions are routinely met as specified. These results should be documented in the processing records.

14.1.1 The requirement for, the existence of, and adherence to effective, routine process-monitoring procedures should be included in the validation protocol.

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

14.1.3 Deviations from defined processing conditions must be documented, investigated and assessed regarding the impact on the product, and on process objectives. In the absence of qualified evaluators, the sterilization process should automatically be considered to have been compromised.

14.2. For sterilization approaches based on either of the two Bioburden-Based methods, samples for ongoing bioburden testing and data collection should be obtained from each batch of drug product for an initial period of time sufficient to define the limits of species and number of organisms for seasonal/operational variations to be adequately documented and controlled.

14.2.1 Samples collected at the beginning and at the end of the filling operation should be used to determine the most resistant product isolates.

14.2.2 For any validated sterilization process a maximum microbial count and a maximum microbial resistance for the work area should be established.

14.2.3 Microbial counts or resistance exceeding the levels established in paragraph 14.2.2. should be judged as compromising the sterilization.

14.3 In order to ensure that the equipment and support systems function consistently within the process (as documented in the protocol) there should be a written program for the ongoing maintenance of each piece of equipment defined in the protocol. The execution of these maintenance programs should be monitored routinely.

14.3.1 The maintenance program should detail the items to be checked, the frequency of maintenance and calibration of monitoring devices, and require detailed written records of all maintenance performed.

14.3.2 The execution of the program and its records should be routinely reviewed by a qualified person on a schedule which will ensure that the process has not been compromised.

15. PRODUCT PROCESS CLAIMS

The Sterility Assurance Level is to be set based on the anticipated/indicated use of the final product, and on its ability to withstand a terminal treatment. While a media fill provides a **rate** of contamination (e.g. 1 x 10-3), that particular contaminated unit may contain more than one organism. Therefore for final products in unit of use form (i.e. other than bulk), it is preferred that, as a starting point, each unit be considered to contain **one** organism.

15.1. **Sterility Assurance Levels**: From bioburden studies, the organism with the highest D_{10} value should be used as the most probable contaminant. From the D_{minP} determination, the dose of radiation delivered will determine the sterility assurance level achieved.

Terminal sterilization: - the $D_{minP}/D_{10} => 6$

Enhanced Sterility Assurance: - the $D_{minP}/D_{10} < 6$

For example, the D_{minP} is 3 kGy, and the D_{10} of the most resistant organism is 0.3 kGy; 3/.3 = 10 therefore a claim of terminal sterilization may be made. If however the D_{10} value is 1 kGy, then 3/1 = 3; therefore a claim of enhanced sterility assurance may be made.

15.2 **Non-pyrogenicity**: It should be recognized that for those products where this attribute is critical, treatment by gamma radiation can provide some enhancement over aseptic processing (see 19.8 and 19.9).

It is essential to establish that the initial levels of pyrogens are low, and that if organisms are present, that the opportunities for growth (and thus the production of endotoxins) are severely restricted during the period from the end of manufacture to the time of irradiation. (This is most critical for unpreserved liquid products.) This latter requirement may place restrictions on the mode of transport and/or storage conditions from the time of manufacture to the time of irradiation.

Gamma radiation is **not** recommended as a method for depyrogenation **per se.**

16. REQUALIFICATION

16.1 All changes to the sterilizer system or process must be pre-authorized through the Change Control Procedure or be required as part of a pre-established maintenance program.

16.2 Requalification is the activity(ies) which establishes that changes to parts of the sterilizing system have not invalidated the conditions outlined in the validation protocol.

16.3 The requalification protocol will define those changes to the system or its components which necessitate a requalification exercise. Certain components that may require replacement as defined in the pre-established maintenance program may be deemed **not** to affect the process and therefore requalification of the process is not required.

16.4 Requalification is performed according to detailed written procedures which require that the original validation parameters and limits be used as evaluation criteria.

16.5 Changes which require requalification include but are not limited to:

- replacement or replenishment of ionizing radiation source
- replacement of cycle timers
- modifications to the transport mechanism(s)
- new lot of dosimeters or a change in the type of dosimeters.

16.6 Product loading should be requalified when changes to the transport mechanism equipment may affect the dose distribution.

16.7 Changes to loading patterns, new container/closure systems or "cycle" parameters require that validation be performed since the conditions of section 16.3 would not apply.

16.8 Requalification studies must be documented in detail. The documentation should be compared to the original validation results and evaluated to the same extent. If the results are satisfactory, the system or process may be recertified. If the results are

not satisfactory, the modified system or process will require a new validation program.

17. DOCUMENTATION REQUIRED IN SUBMISSIONS TO THE BRANCH FOR RADIATION PROCESSING BY IONIZING RADIATION

17.1 Microbial Documentation

17.1.1 **Raw materials**: List the organism which will be used as the basis for assessment of radiation dose selected. Seasonal/source variations should be on file to justify selection of the organism. Data should be collected on an ongoing basis for each lot/batch/shipment of materials received.

17.1.2 **Finished product**: List the organism which will be used as the basis for the assessment of final SAL achieved. Facility/plant/seasonal variation data should be on file to justify the selection of the organism. This data could be enhanced by data from media fills.

17.1.3 **Processing Area**: List the organism which will be used as the basis for the assessment of final SAL achieved. Data should be on file for the formulation area, the fill/seal area, or any other manufacturing area where the product is exposed to the environment before passing through a filter or undergoing a process which would of itself lower the bioburden. Data should be available as follows:

17.1.3.1 **Existing facilities** - minimum of 1 year but preferably up to three years, and to be ongoing;

17.1.3.2 **New facilities** - start-up plus ongoing data.

17.1.4 Procedures to adjust radiation processing requirements/SAL if there are changes in the normal bioburden pattern (i.e. species variations). This could result either in a dose reduction because less-resistant species are now found, or an increase in the dose required due to the presence of species with a higher D10 value.

17.2. **Product Documentation**

17.2.1 **Raw Materials**: - If specifications for these materials include microbial limits, it is important to determine what process (or processes), is currently being used to treat the material so that it meets these specifications. This may require some effort on your part to trace the origin of your supplies as many materials originating 'off-shore' are treated to reduce the bioburden, but the method of treatment is not specified. Residues from EtO or other fumigants may introduce their own unwanted impurities in the product or cause the formation of others when exposed to radiation. This information

must be available but need not be submitted. The method of bioburden reduction should be part of your raw material specification as different methods may impart different properties to the materials.

A statement that all materials, other than the active drug, have been tested alone and in conjunction with the drug and shown to be unchanged using current analytical techniques for these materials is required.

17.2.2 **Finished Product**: Documentation will be required showing the analytical profiles of the product before and after exposure to irradiation. It would be advisable to include a profile of the drug as obtained when the D_{maxT} has been exceeded, in order to show the location of radiation-induced changes in the analytical profile. This will provide some indication of the safety factor involved in exposing the product to the selected radiation dose.

17.2.2.1 **Old Drugs**: If the product after irradiation , shows changes in any analytical profiles, these changes need to be analysed/evaluated for their impact on the "fitness-for-use" of the product. Some changes will have little or no significance, others will require further investigation. Summary document should indicate what, if any, impact these analytical changes will have on the performance of the product. The data to back up this conclusion must be on file and available upon request.

17.2.2.2 **New Drugs**: Documentation identical to that presently submitted. All toxicological/clinical trials will be done with irradiated material. Documentation must be on file to show the effects of irradiation on all components incorporated into the final product; final product in final container.

18. EXPERT SUMMARY

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 radiation process to achieve the SAL desired, without adversely affecting the properties of the pharmaceutical.

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.

19. REFERENCES

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19.2 E-Beam Processing in the Medical Device Industry. Barnard, J.W., Medical Device Technology (June): 34-41, 1991.

19.3 Gaining the Competitive Edge with Gamma Sterilization. Brinston, R., Medical Device Technology (June): 28-33, 1991.

19.4 Radiation in the Sterilization of Pharmaceuticals. Jacobs, G., In; Sterile Pharmaceutical Manufacturing. Interpharm Press, 1991.

19.5 Radiation Processing Technology for Pharmaceuticals: ed. Reid, B.D., (Authored by PDA Subcommittee on Irradiation Sterilization of Parenterals). Available through the PDA office One Penn Center, 1617 JKF Boulevard, Suite 640, Philadelphia, PA 19103.

19.6 Genova, T.F., *etal.*, A Procedure for Validating the Sterility of Individual Gamma Radiation Sterilized Production Batches. J. Parenteral Science and Technology 41(1):33-36, 1987.

19.7 Genova, T.F., *etal.*, A Procedure for Supplementing the AAMI B1 Method for Validating Radiation Sterilized Products. J. Parenteral Science and Technology 41(4):126-127, 1987.

19.8 Guymomard, S. *etal.*, Defining the Pyrogenic Assurance Level (PAL) of Irradiated Medical Devices. Int. J. Pharmaceutics 40:173-174, 1987.

19.9 Guyomard, S. *etal.*, Effects of Ionizing Radiations on Bacterial Endotoxins: Comparison Between Gamma Radiations and Accelerated Electrons. Radiat. Phys. Chem. 31(4-6):679-684, 1988.

19.10 El-Bagory, I., Reid, B.D., and Mitchell, A.G., The effect of gamma radiation on the tableting properties of some pharmaceutical excipients. Int. J. Pharmaceutics (1994) in press.

GLOSSARY

The definitions given below apply to the words as used in this guide. They may have different meanings in other contexts. We have used the ISO 11137 document as a guide.

Batch: Defined quantity of bulk intermediate, or finished product, that is intended or purported to be uniform in character and quality, and which has been produced during a defined cycle of manufacture.

Bioburden: The total number of viable microorganisms on or in a pharmaceutical product or in the manufacturing environment prior to sterilization processing.

Sterility Assurance Level (SAL): Expected probability of a surviving microorganism on each individual product after exposure to a valid sterilization process. Note: SAL is normally expressed as 10-n.

D10: Radiation dose required to kill 90 percent of a homogeneous microbial population where it is assumed that the death of microbes follows first order kinetics.

kGy: The Gray (Gy) is the international unit for measuring the radiation dose delivered. 1 kGy=100,000 rads or 0.1 MRad (old terminology).

Product: A term used to refer to either raw materials, packaging components or the final pharmaceutical. The context will clarify which material is being referred to.

DmaxT: The maximum dose tolerated by the product before product degradents increase to significant levels.

DmaxP: The maximum process dose allowed. This dose is a judgment call. It is set below the DmaxT, to prevent damage to the product, but is large enough to ensure that the DminP will achieve the desired SAL.

DminP: The minimum process dose. This dose is determined by the configuration of the irradiation facility and the loading pattern/density of the product.

Cycle: An irradiation cycle is the irradiation of the product. It may consist of more than a single pass past the source.

GMP Committee members

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

** Bureau of Pharmaceutical Assessment now part of Therapeutic Products Directorate (TPD).

*** Bureau of Biologics and Radiopharmaceuticals changed to Biologics and Genetic Therapies Directorate (BGTD).

**** Office of Compliance, Planning and Coordination now National Coordination Centre (NCC).

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