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Validation of the Radiation Sterilization of Pharmaceuticals

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The use of gamma irradiation for the sterilization of pharmaceuticals has been a recognized method of sterilization for some 40 years (1,2). However, radiation sterilization may also be carried out using electron beam irradiation or the somewhat innovative application of X-rays.

While high-energy gamma irradiation is used mainly in the healthcare industries for the sterilization of disposable medical devices, there has been over the years a gradual increase in the number of pharmaceuticals being radiation sterilized. Today drugs manufactured by leading pharmaceutical companies are radiation sterilized. These include ophthalmic preparations, topical ointments, parenterals, and veterinary products. Unlike medical devices that are clearly labeled that they are radiation-sterilized pharmaceuticals are not required to be labeled with the mode of sterilization and therefore information on whether a particular drug is radiation sterilized is often unavailable.

Although radiation sterilization may be undertaken using either gamma rays from a radioisotope source (usually cobalt-60) or electron beam or X-ray irradiation, the former is by far the more common.

As with all methods of sterilization, irradiation involves a compromise between inactivation of the contaminating microorganisms and damage to the substrate or product being sterilized. The imparted energy in the form of gamma photons or electrons does not always distinguish between the two.

The usual mechanism for interaction between the high-energy gamma radiation and matter is the formation of ion pairs by the ejection of an electron, leading to free radical formation, and excitation. The free radicals are extremely reactive as a result of the unpaired electron on one of the outer orbitals. Their reactions may involve gas liberation, formation, and scission of double bonds, exchange reactions, migration of electrons and crosslinking. In fact, any chemical bond may be broken and any potential chemical reaction may take place. In crystalline materials, this may result in vacancies, interstitial atoms, collisions, and thermal spurs as well as ionizing effects. Polymerization is particularly common in unsaturated compounds. In microorganisms radiation-induced damage may express itself in various biological changes which may lead to cell death. Although DNA is generally considered the major target for cellular damage, membrane damage may also make a significant contribution to reproductive cell death. In solutions, a molecule may receive energy directly from the incident radiation (the "direct effect") or, for example in aqueous solutions, by transfer of energy from the radiolysis products of water (for example, hydrogen, and hydroxyl radicals and the hydrated electron) to the solute molecule (the "indirect effect").

The process of radiation-induced damage by electrons is similar to that for gamma photons. In electron irradiation, the high-energy electrons produced externally to the target molecule cause ionization of the molecular species as they pass through the medium and release their energy. The ionization process leads to the production of secondary electrons (known as delta rays) with a range of energies capable of bond breakage in the medium in the vicinity of the ionization event. The high-energy electrons are usually produced either by a direct current machine, by accelerating them across a large drop in potential, or by linear or circular electron accelerator.

X-rays are electromagnetic photons emitted when high-energy electrons strike any material and can therefore be produced by an electron accelerator.

For reviews of radiation sterilization the reader is referred inter alia to the Chapters on Gamma Radiation Sterilization (3) and Electron Beam Sterilization (4) in the Encyclopedia of Pharmaceutical Technology.

The advantages of irradiation for sterilization are:

- Its high penetratability, thus allowing the product to be sterilized in its final container—even in its shipping container;
- The very low temperature rise (normally less than 5°C) therefore being compatible with heat-sensitive products;
- Fewer process variables than other methods of sterilization—this improves process control with sterility rejections for radiation-sterilized products being the lowest reported;
- No remaining sterilant residuals.

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Abbreviations used in this chapter: AAMI, Association for the Advancement of Medical Instrumentation; ASTM, American Society for Testing and Materials; cGMP, current good manufacturing practices; EPR, electron paramagnetic resonance; FDA, Food and Drug Administration; FDIS, Final Draft International Standard; GMP, good manufacturing practices; HIMA, Health Industry Manufacturers Association; IAEA, International Atomic Energy Agency; IQ, installation qualification; NDA, new drug applications; NIST, National Institute of Standards and Technology; OQ, operational qualification; PDA, Parenteral Drug Association; PQ, performance qualification; SAL, sterility assurance level; TLD, thermoluminescence-dosimetry; USP, *U.S. Pharmacopeia*.

Electron beam irradiation has the added advantages that the sterilization dose can be delivered in just a few seconds, compared to several hours or even days with conventional gamma irradiation. This has an added advantage of easier control of the environmental conditions of the irradiation process, which may be important in radiation-sensitive products (see the section entitled Materials Compatibility). There is also the advantage of flexibility of allowing individual product treatment when required. X-ray sterilization is not as fast as electron beam irradiation. Since electron beam and X-ray machines are electric powered, there are no disadvantages of handling, shipping and disposal of radioisotopes. A disadvantage of electron beam irradiation has been their low penetrating power, although the more modern machines have overcome this problem. X-ray machines may be even more penetrating than gamma rays.

It is usual for irradiation to be carried out by contract sterilizers [for a list of contract irradiation facilities, see (3,5)]. While, many aspects of the validation of the process are usually undertaken by the contract sterilizer, nevertheless, the drug manufacturer bears overall responsibility for the sterility of the product. Essentially, the contract sterilizer is responsible for guaranteeing the delivered radiation dose.

Validation of the radiation sterilization process, as an integral aspect of GMP, comprises the following components which relate either to the irradiation facility itself or the product being irradiated:

- IQ
- OQ
- PQ
- Materials Compatibility
- Selection of Sterilization Dose
- Routine Process Control

It is common practice, because of economic or feasibility considerations for a manufacturer of a radiation-sterilized product to use an outside contractor to provide the irradiation service. The criteria used in choosing such a contractor must be the same as those used for choosing other outside contractors for pharmaceutical processing. It must be shown that the irradiation facility operates in a manner consistent with cGMP, and that it is registered with the appropriate regulatory authority such as the FDA or local health authority, and that it meets all national (or federal) and local regulations.

IQ

IQ, or irradiator commissioning, is to ensure that the irradiator has been supplied and installed in accordance with its specifications. IQ includes plant commissioning, and defined and documented operating procedures for the irradiator and associated conveyor systems, radiation source configuration, for gamma irradiators—the activity of the source, for electron beam and X-ray irradiators—the characteristics of the beam, correct functioning with design specifications of electromechanical systems and associated software, documentation for any modifications, instrument calibration and recalibration, cycle timer setting, choice of dosimeters (see the section entitled Dosimetry), dosimeter placement (including frequency and rationale), and product handling before, during, and after irradiation (as well as process release) in accordance with process specifications.

Some aspects of IQ may be considered as part of the OQ or PQ.

Dosimetry

The essential parameter that has to be controlled in radiation sterilization, particularly when using gamma irradiation, is the measurement of radiation dose. This is achieved using dosimeters—chemical or physical systems that respond quantitatively to absorbed radiation dose. In irradiation practice, although not necessarily at the operational level, four types of dosimeters are used. Three types are used as standards, namely, primary, reference, and transfer dosimeters, and a fourth group, routine dosimeters, are used for routine measurement.

Primary dosimeters are the highest quality dosimeters and are maintained by national standards laboratories. The two most commonly used primary standard dosimeters are ionization chambers and calorimeters (6).

Reference and transfer dosimeters (or secondary dosimeters) are used for calibration of radiation sources and routine dosimetry. The most commonly used reference standard dosimeters are the ferrous sulfate (Fricke) and dichromate dosimeters for gamma and X-ray use, and calorimetry for electron beam applications. In chemical dosimeters (ferrous sulfate and dichromate) the chemical change in a suitable substrate is measured. For example, the concentration of ferric ions formed from the radiation-induced oxidation of an aerated ferrous sulfate solution is determined spectrophotometrically. Calorimetry, probably the most direct method of determining the amount of energy carried by a beam of radiation, is based on the increase in temperature of a block of material placed in the path of the beam. The material must be such that all the absorbed energy is converted to heat. Graphite or metals are used for this purpose. Other chemical reference standard dosimeters are the alanine, ceric–cerous, ethanol–chlorobenzene dosimeters. Most of these reference standard dosimeters may also be used as transfer standard dosimeters. Transfer reference standard dosimeters are usually sealed, packaged dosimeters that are sent to the irradiation facility for irradiation to nominal agreed-upon absorbed dose levels in a prescribed geometrical arrangement. The unopened packaged dosimeters are then returned to the national standardization institute (for example, NIST) to be read and evaluated thus providing calibration of the client's irradiator. For electron beam irradiation, the commonly used reference standard dosimeters are calorimeters, alanine, ceric–cerous, ethanol–chlorobenzene, ferrous sulfate and dichromate systems. However they may be limited by the energy range being used.

Routine dosimeters are used at the irradiation plant level for monitoring and quality assurance in routine irradiation processing. Examples of routine dosimeters for gamma and X-ray use are dyed or clear polymethylmethacrylate, cellulose triacetate, ceric–cerous sulfate, radiochromic dye and ferrous–cupric systems. Most of these systems may also be used for electron beam irradiation.

In selecting a dosimetry system consideration has to be given to inter alia; suitability of the dosimeter for the absorbed dose range of interest and for use with a specific product stability; and reproducibility; ease of calibration; ability to correct responses for temperature, humidity, and dose-rate deviations; ease and simplicity of use; resistance to damage during routine handling; and inter- and intra-batch responses. It is a requirement that dose measurements are traceable to an appropriate national or international standard, and that their level of uncertainty is known.

Practical information on radiation dosimetry can be found in the following ISO/ASTM and ASTM standards (7):

- ISO/ASTM 51608 Practice for Dosimetry in an X-ray (Bremsstrahlung) Facility for Radiation Processing;
- ISO/ASTM 51261: Guide for Selection and Calibration of Dosimetry Systems for Radiation Processing;
- ISO/ASTM 51400: Practice for Characterization and Performance of a High-Dose Radiation Dosimetry Calibration Laboratory;
- ISO/ASTM 51631: Practice for Use of Calorimetric Dosimetry Systems for Electron Beam Dose Measurements and Dosimeter Calibrations;
- ISO/ASTM 51649 Practice for Dosimetry in an Electron-Beam Facility for Radiation Processing at Energies between 300 keV and 25 MeV;
- ISO/ASTM 51702 Practice for Dosimetry in a Gamma Irradiation Facility for Radiation Processing;
- ISO/ASTM 51707: Guide for Estimating Uncertainties in Dosimetry for Radiation Processing;
- ISO/ASTM 51818 Practice for Dosimetry in an Electron Beam Facility for Radiation Processing at Energies between 80 and 300 keV;
- ASTM E 170 Terminology Relating to Radiation Measurements and Dosimetry;
- ASTM E 2303 Guide for Absorbed-Dose Mapping in Radiation Processing Facilities.

More information on specific dosimetry systems including guidance on dosimetry characteristics can be found in the following standards (7):

- ISO/ASTM 51205: Practice for Use of a Ceric–Cerous Sulfate Dosimetry System;
- ISO/ASTM 51275: Practice for the Use of a Radiochromic Film Dosimetry System;
- ISO/ASTM 51276: Practice for the Use of a Polymethylmethacrylate Dosimetry System;
- ISO/ASTM 51310: Practice for the Use of a Radiochromic Optical Waveguide Dosimetry System;
- ISO/ASTM 51401: Practice for Use of a Dichromate Dosimetry System;
- ISO/ASTM 51538: Practice for Use of the Ethanol–Chlorobenzene Dosimetry System;
- ISO/ASTM 51539: Guide for Use of Radiation-Sensitive Indicators;
- ISO/ASTM 51540: Practice for Use of a Radiochromic Liquid Dosimetry System;
- ISO/ASTM 51607: Practice for Use of the Alanine-EPR Dosimetry System;
- ISO/ASTM 51650: Practice for Use of Cellulose Acetate Dosimetry Systems;
- ISO/ASTM 51956: Practice for TLD Systems for Radiation Processing;
- ASTM E 1026 Practice for Using the Fricke Reference Standard Dosimetry System;
- ASTM E 2304 Practice for Use of a LiF Photo-Fluorescent Film Dosimetry System.

OQ AND PQ

These have been included in one section, as opinions may often vary as to whether a particular operation is classified as OQ or PQ. The essential point is that all aspects of the validation are undertaken. OQ is to demonstrate that the installed irradiator can operate and deliver appropriate radiation doses within defined acceptance criteria. PQ is essentially dose mapping.

OQ and PQ at a practical level include information on the dimensions and density of the packaged product as well as orientation of the product within the package, product loading patterns, the effect of process interruption, and dose distribution mapping for assessment of radiation dose ranges within the product package, and reproducibility within products. During dose mapping the location and magnitude of the minimum and maximum delivered doses have to be identified. More specific details of dose mapping can be found in the appropriate ISO guidelines (for example, in section 9 of ISO 11137-1).

Information generated by IQ, OQ, and PQ have to be reviewed and documented. A process specification for each product should be prepared and documented. Details of such a process specification for gamma, electron beam and X-ray irradiation can be found in ISO 11137-1 (section 9.4).

MATERIALS COMPATIBILITY

Any processing, such as sterilization, in the manufacture of a pharmaceutical product must cause no degradation. This also holds for radiation processing. In the first instance, data on the feasibility of irradiating a pharmaceutical can be obtained from the scientific literature. Reviews on the effects of gamma (and electron beam) irradiation are readily available (8–22). Although many of the cited investigations report only superficial examination of the irradiated drug, the reported data give useful insights into overall radiation stability of these products, and indicate whether more extensive testing of the product is worth undertaking.

It is necessary to examine each new compound for assessing its radiation stability, even though data may be available for closely related compounds. A thorough knowledge of radiation chemistry would be necessary to infer the behavior of one compound from another. Furthermore, with a formulated medication, the stability of an individual component may change when irradiated as part of product.

Although sterilization doses of radiation are usually in the order of 25 kGy (see the section entitled Selection of Sterilization Dose), the use of a higher dose such as 50 kGy is useful for feasibility studies as a means of indicating the type of radiolytic decomposition that may be expected at sterilization dose levels.

A number of different analytical tools should be used to detect radiation-induced degradation. Each technique usually reveals a change in a specific moiety of the irradiated molecule, and it is therefore essential to examine all generated data to obtain an indication of the extent of degradation. Wherever possible stability-indicating assays should be used.

As with all stability studies, assays should be carried out over an extended time period to indicate long-term stability of the product. Accelerated aging, under conditions recommended by the appropriate regulatory authority such as the FDA may be undertaken.

Even when radiolysis products are within acceptable compendial limits, it has to be conclusively established that any products formed are without any adverse effect at the concentration found. However, other studies, for example (23), show that such radiolysis products are generally not unique to irradiation. It would often suffice to show that radiolysis products are the same and at no greater concentration than those found when the drug is subjected to other sterilization procedures. In this connection guidance from the FDA/International Conference on Harmonisation Guideline on Impurities in New Drug Products [Q3B(R), issued 11/2003] is useful. It is noteworthy that the FAO-IAEA-WHO Expert Committee (24) has recommended that food items irradiated at doses of up to 10 kGy pose no danger to the consumer and can be unconditionally cleared. Appropriate inferences can be made to pharmaceuticals.

In cases where radiolysis products are formed, these can sometimes be reduced by appropriate action. For example, irradiation may be undertaken in anoxia or at low temperatures, or by incorporation of suitable additives, providing that degradation pathways are known. Of course, such additives must not be toxic or interfere with the efficacy of the drug. They may include energy transfer systems, –SH containing molecules, scavengers of radiolysis products of water, or reagents that convert radiolysis products to the parent compound. One example of such a radiation tailored formulation is that of urea broth, used for identification of *Proteus* spp., and its differentiation from other gram-negative intestinal bacteria (25).

In some cases radiolysis may be reduced by use of electron beam irradiation rather than gamma irradiation. Here *dose rate* may be an important factor. Although there is no general rule, many drugs show less breakdown at the higher dose rate, that is, with electron beam irradiation. This may be due to consumption of all the oxygen (which generally increases radiation damage) with sterilization being completed before oxygen can be replenished, and possibly due to too short a time for production of long-lived free radicals which may increase radiation-induced damage. On the other hand, the high dose rate, could in some cases cause increased damage due to the "high concentration" of gamma photons close to the substrate.

The packaging of a pharmaceutical is an integral part of the product, and therefore the radiation stability of packaging and container materials must never be overlooked when considering radiation compatibility. Lists of radiation-compatible packaging materials are readily available [for example, (3,10,26–29)]. It should be emphasized that to ensure their stability, these materials are often formulated specifically for radiation processing by inclusion of, for example, aliphatic antioxidants rather than aromatic ones that are often responsible for yellowing following irradiation.

SELECTION OF STERILIZATION DOSE

Selection of a radiation dose for sterilization is an integral part of validation of the sterilization process. Any deviation from the selected dose could result in either compromising the sterility of the product (in other words, the predetermined SAL may not be realized), alternatively, an excess radiation dose could result in chemical damage to the product.

A radiation dose of 25 kGy (2.5 Mrad) has generally been accepted as suitable for sterilization purposes (see the section entitled The USP Procedure for Dose Selection) [for example, (30,31)]. The choice of this dose was based on the radiation resistance of the bacterial spores of *Bacillus pumilus*. However, today the choice of radiation dose is based on initial (pre-sterilization) microbial contamination, or bioburden, and the desired SAL of the product.[a] Such considerations are based in part on extensive studies of the effects of sub-sterilization doses on different microbial populations (32,33).

The following demonstrates the various approaches to the choice of dose by the various regulatory and official authorities. Close examination, however, shows the similarity of the different approaches.

The USP Procedure for Dose Selection

The USP 28 (34) states as follows:

> Although 2.5 Mrad of absorbed radiation was historically selected, it is desirable and acceptable in some cases to employ lower doses for devices, drug substances, and finished dosage forms. In other cases, however, higher doses are essential. In order to validate the efficacy particularly of the lower exposure levels, it is necessary to determine the magnitude (number, degree, or both) of the natural radiation resistance of the microbial population of the product.

The USP suggests estimation of the appropriate sterilization dose by one of the methods contained in the guidelines published by the AAMI in the document Process Control Guidelines for Radiation Sterilization of Medical Devices (35). This document formed the basis for the International Organization for Standardization standard, ISO 11137, first published in 1984, which in turn became the new AAMI/ANSI standard. The current International Standard (ISO 11137:2006), also an AAMI/ANSI Standard, has just recently been revised. It has been published in three sections ISO 11137-1, *Sterilization of health care products—Requirements for the development, validation, and routine control of a sterilization process for medical devices—Part 1: Radiation sterilization*, ISO 11137-2, *Part 2: Establishing the sterilization dose for radiation sterilization*, and ISO 11137-3, *Part 3: Guidance on dosimetric aspects for radiation sterilization.*

Selection of Dose by the AAMI/ANSI/ISO Standard

The basis of the dose-setting methods described in the AAMI/ISO standards owes much to the ideas first presented by Tallentire and his colleagues (32,36,37). Subsequently standardized protocols were developed (38,39).

[a] SAL is defined as the probability of a single viable microorganism occurring on a product following sterilization. SAL is normally expressed as 10^{-n}. While the majority of authorities give n a value of 6, the FDA does allow values of less than 6 for non-invasive products.

The first ISO method, designated Method 1, is certainly the most common method used for dose selection for sterilization of medical devices and those pharmaceuticals that are radiation sterilized. The method essentially requires determination of the average microbial contamination of representative samples of the product. Note that the radiation resistance of the microbial population is not determined, and dose setting is based on the resistance of microbial populations originally derived from data obtained from manufacturers. The assumption is made that the distribution of the resistance chosen represents a more severe challenge than that presented by the natural bioburden on the article to be sterilized. This assumption is verified experimentally by irradiating 100 samples at a given verification dose, and accepted if there are no more than two contaminated samples. The sterilizing dose, appropriate for the average bioburden per sample and the desired SAL for the product, is then read from a table.

The second method (Method 2) does not entail enumeration of the bioburden but relies on a protocol for a series of incremental dose experiments to establish a dose at which approximately one in a hundred samples will be non-sterile. A sterilization dose is then established by extrapolation from this 10^{-2} sterility level, using a dose-resistance factor calculated from observations of the incremental dose experiments that characterize the remaining microbial resistance. This resistance is estimated from the lowest incremental dose at which at least one sample is sterile, and from the dose at which the surviving population is estimated to be "0.01 microorganisms" per sample.

In the original AAMI Guidelines other more elaborate procedures (originally known as AAMI Methods B3 and B4) were described for dose setting. These methods were not commonly used because of the extensive experimentation involved.

In the current AAMI/ISO guidelines a relatively new method (Method VDmax) specifically for substantiation of a 25-kGy dose is included. This method was first officially introduced as an AAMI Technical Information Report (40), and is now part of (ISO 11137–2: 2006) (41, 47). This method, put forward by for substantiation of a 25-kGy dose is similar to dose-setting Method 1. Like Method 1 it requires a determination of bioburden and the performance of a verification dose experiment.

In substantiating a 25-kGy dose, this method verifies that the bioburden on the product is less radiation resistant than a microbial population of maximal resistance consistent with the attainment of an SAL of 10^{-6} at 25 kGy. Verification is undertaken at an SAL of 10^{-1} with 10 items irradiated in the performance of the verification dose experiment. The dose corresponding to this SAL (verification dose, VDmax) reflects both the magnitude of bioburden and the associated maximal resistance. If there is no more than one positive test in the 10 tests of sterility, a 25-kGy sterilization dose is substantiated. This method is applied with some modification to both single and multiple batches.

ISO also allows substantiating a 25-kGy dose using Methods 1 and 2. The new ISO guidelines (ISO 11137-2:2006) do allow dose setting by any other method that provides equivalent assurance to the above methods in achieving the specified requirements for sterility.

In accordance to the ISO guideline, all ISO methods require the performance of a periodic audit to confirm the appropriateness of the sterilization dose.

British Pharmacopoeia/European Pharmacopoeia Procedures

According to the British and European pharmacopoeias (42,43):

"A minimum absorbed dose of 25 kGy is generally used for the purpose of sterilization, although other doses may be employed, provided that they have been validated. If doses of less than 25 kGy are used, additional microbiological monitoring of the product before irradiation will be necessary."

These pharmacopoeias give no guidance on how to estimate doses of less than 25 kGy.

PDA Procedures

The PDA has made its own recommendations for dose-setting procedures specifically for parenteral products (44). These procedures, however, are similar to those already in use for other sterilization technologies.

One method is essentially a biological indicator (overkill) method in which the sterilization dose is at least double a radiation dose needed to achieve a six logarithmic inactivation of *B. pumilus* spores on or in the product. In practice, the sterilization dose does not differ much from the classical "25 kGy."

Another method involves determination of the maximum bioburden. The logarithm of this bioburden (with three standard deviations), plus a six logarithm sterility assurance factor is multiplied by the decimal reduction factor (D_{10}) for *B. pumilus* spores to estimate the sterilization dose. The decimal reduction factor is the radiation dose to reduce the number of surviving microorganisms by 90%.

IAEA Procedure for Dose Setting

The IAEA, following an Advisory Group Meeting on the Code of Practice for Radiation Sterilization of Medical Supplies (Colombo, November 1986), adopted a pragmatic approach to the selection of a sterilization dose. The Guidelines developed at this meeting state:

> It is a basic assumption that the product to be sterilized is manufactured under conditions that comply fully with the requirements of GMP. In the present context, it is particularly important that practices be implemented, and actions taken, which ensure that the number of microorganisms on product items destined for radiation sterilization processing is consequently low.
>
> A dose of 25 kGy (2.5 Mrads) has been found to be an effective sterilizing dose. It is generally believed that this dose provides maximally a SAL of 10^{-6}. Where it is not feasible to generate data on the radiation resistance of the natural microbial population present on product items, a minimum sterilizing dose of 25 kGy (2.5 Mrads) can be used.
>
> It is more rational to base selection of a sterilizing dose on a knowledge of the resistance of the natural microbial population present ion product items to be sterilized and

on a reasoned selection of a maximal SAL. Methods of dose selection using this approach are Methods 1 and 2 in Appendix B of the AAMI Process and Control guidelines for gamma Radiation Sterilization of Medical Devices (corresponding to the current Methods 1 and 2 of the ISO 11137).

While it is this author's belief that the methods of dose selection presented in ISO 11137 are the methods of choice, the IAEA approach some 20 years later is still rational particularly for less developed countries.

OTHER DOSE-SETTING PROCEDURES

Other dose-setting procedures have been proposed in the scientific literature, including those of (39,45,46).

ROUTINE PROCESS CONTROL

This includes process specification, pre-irradiation product handling, product irradiation, product loading and unloading, monitoring during irradiation, processing records and documentation, process interruption, and routine and preventive maintenance.

LEGISLATIVE CONSIDERATIONS

Although radiation sterilization has appeared in the USP since 1965, the FDA regards a radiation-sterilized drug as a "new product" (that is, submission of an NDA, albeit abbreviated) with the manufacturer responsible for proving its safety. The current USP 23, in the section entitled Sterilization and Sterility Assurance of Compendial Articles makes the following observations regarding radiation sterilization of drugs:

The rapid proliferation of medical devices unable to withstand heat sterilization and the concerns about the safety of ethylene oxide have resulted in increasing applications of radiation sterilization. It is however applicable also to drug substances and final dosage forms.

… radiation sterilization is unique in that the basis of control is essentially that of absorbed radiation dose, which can be precisely measured.

In the U.K., sterilization by exposure to ionizing radiation has been a recognized method since 1980, when the Ministry of Health agreed to accept materials exposed to a radiation dose of 25 kGy. Medicines controlled under the Medicines Act 1968 are subjected to individual assessment by the Committee on Safety of Medicines of the Medicines and Healthcare products Regulatory Agency. This committee requires in addition to proof of sterility, proof that the potency of the drug is unaffected by the process, and that any degradation products would not be harmful.

Similarly, although the *British Pharmacopoeia* recognizes gamma irradiation as a suitable sterilization process, it is the responsibility of the manufacturer to prove that no degradation of the product has taken place.

Most European countries allow pharmaceuticals to be radiation sterilized, provided that authorization has been obtained from the appropriate health authorities.

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