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Invited Paper

PROCESS VALIDATION FOR RADIATION PROCESSING

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Abstract

Process validation concerns the establishment of the irradiation conditions that will lead to the desired changes of the irradiated product. Process validation therefore establishes the link between absorbed dose and the characteristics of the product, such as degree of crosslinking in a polyethylene tube, prolongation of shell life of a food product, or degree of sterility of the medical device. Detailed international standards are written for the documentation of radiation sterilization, such as EN 552 [1] and ISO 11137 [2], and the steps of process validation that are described in these standards are discussed in this paper. They include material testing for the documentation of the correct functioning of the product, microbiological testing for selection of the minimum required dose and dose mapping for documentation of attainment of the required dose in all parts of the product. The process validation must be maintained by reviews and repeated measurements as necessary. This paper presents recommendations and guidance for the execution of these components of process validation.

1. INTRODUCTION

Process validation is an exercise that is aimed at obtaining documented evidence that the radiation process leads to an acceptable product. Documentation requirements for the radiation sterilization process are provided in the two sterilization standards EN 552 [1] and ISO 11137 [2]. They describe process validation a little differently, but the goal is the same. The minimum dose that is required for the sterilization process must be established and documented, the maximum dose that the product can tolerate must likewise be documented, and irradiation parameters must be established that ensure that the product is irradiated within these doses. The maximum dose is determined from the testing of the material and product – sometimes published data may be used as a part of the documentation. The minimum dose is based on microbiological experimentation to find the dose that will give the required degree of sterility assurance level (SAL). In order to make meaningful dose measurements, it is necessary to understand how the dose measurements are used – to understand the relationship between the product characteristics and the absorbed dose. The aim of this paper is to give the reader a backgeound for understanding these relationships.

These considerations concern radiation sterilization, but similar considerations can be made for e.g. food irradiation or crosslinking of plastics. A required minimum dose and a tolerable maximum dose must be established, and it must be documented that the absorbed dose stays within these limits.

2. MAXIMUM DOSE

It is difficult to give exact information about radiation tolerance of various polymers, because the property in question is often very product-specific. Guidance in selecting polymers for a specific use may be found in ISO 11137, appendix A [2].

Polymeric materials are influenced by radiation through two main processes, crosslinking and chain scission [3,4]. Which type of process that dominates in a specific polymer type depends on its molecular characteristics. In polyethylene, for example, with its carbon backbone with only hydrogen substitutions, crosslinking predominates, although influences of the bulk properties are typically seen only at doses higher than the doses used for sterilization. The properties are changed only little at room temperature, but at higher temperatures it becomes obvious that the polymer has turned from a thermoplastic to a thermoset polymer, and therefore the crosslinked polyethylene product keeps its shape at elevated temperatures – above the crystallite melting temperature.

In polypropylene, on the other hand, where every other hydrogen is replaced by a methyl group, chain scission is the dominating reaction. The chain scissions in polypropylene can be observed as changes in molecular weight distribution as shown in Fig. 1, where samples have been irradiated with one and five times 17 kGy with electron and gamma radiation, respectively. The decreasing signal for the higher doses is caused by the measurement technique that is most sensitive for high molecular weight molecules.

The chain scission may, however, not happen immediately, but only after some time. Radiation induced free radicals – often peroxy radicals – created in the crystalline regions need time to migrate to locations where they may react with the polymer and create a scission. Therefore measurements of mechanical properties carried out shortly after irradiation do not necessarily give a useful answer. The properties have to be documented over a long time, typically months. The presence of free radicals is an indication of the possibility for late chemical reactions, and the concentration of the radicals can be measured by EPR spectrometry as shown in Fig. 2. EPR is a very sensitive technique, and the measurement of the free radicals can be used to follow in time the decay of the free radical concentration.

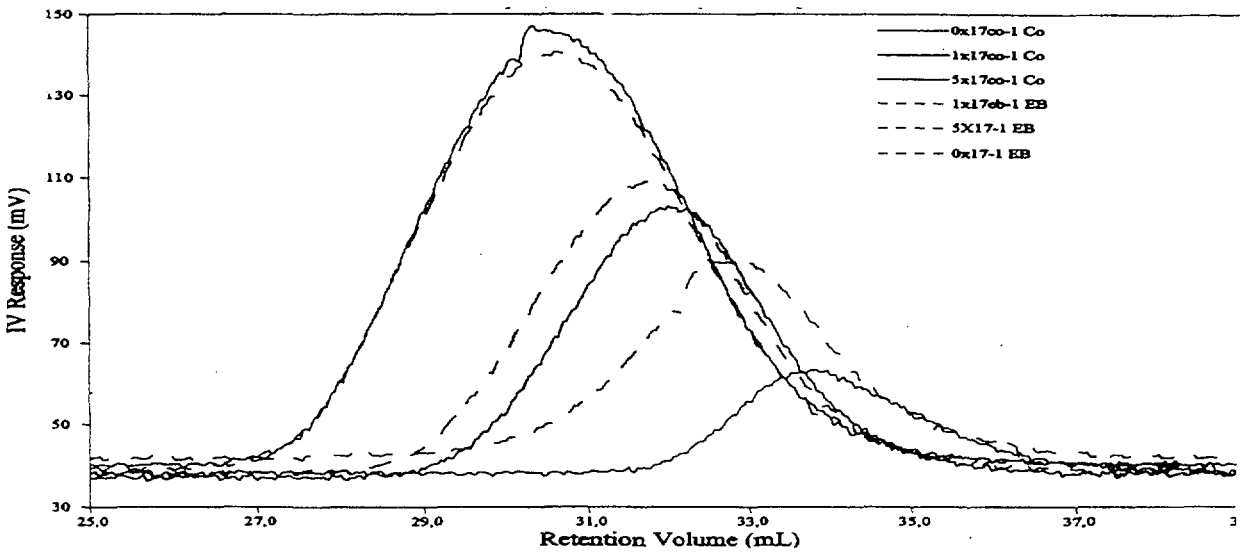

FIG. 1. The molecular weight distributions of irradiated polypropylene films irradiated by electron and gamma radiation (higher retention volume → lower molecular weight).
Full lines: gamma. Dashed lines: electrons.

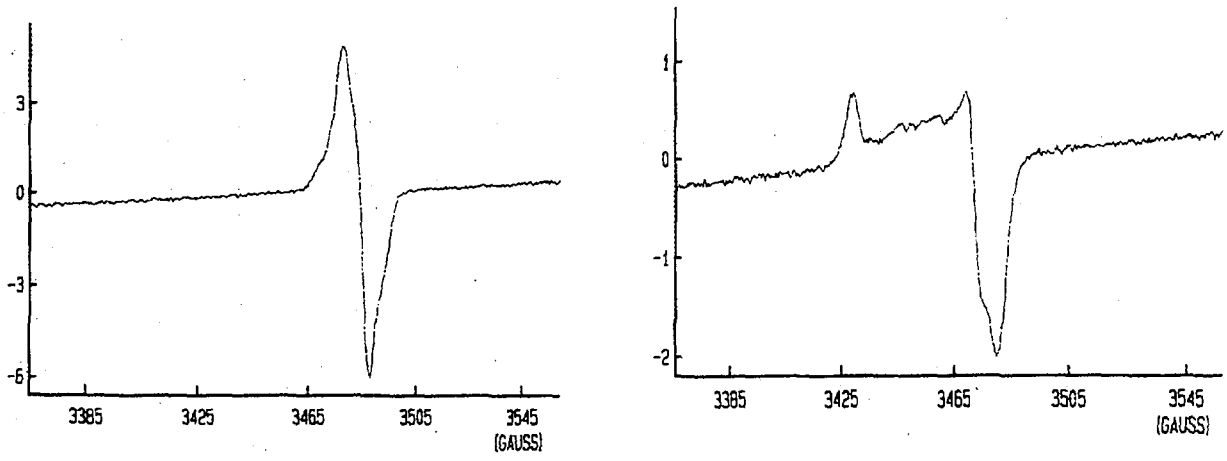

FIG. 2. EPR spectra of free radicals in polypropylene (left) and polycarbonate (right) created by radiation. Both materials were irradiated at a 10-MeV electron accelerator to approximately 50 kGy.

The efficiency of the radiation-induced changes depends to some extent on the dose rate. The free radicals created by the electrons – primary as well as well secondary – may react with other free radicals if the concentration is high as in the case of electron irradiation, thereby reducing the possibility of the free radicals to react with the polymer molecules or to create peroxy radicals that in turn react with the polymer molecules. The duration of the electron irradiation is usually less than a minute and that creates another effect: The oxygen dissolved in the polymer is consumed within a fraction of the total dose, and the remaining irradiation is effectively carried out under oxygen-free conditions thereby reducing the number of radiation induced reactions. The duration of gamma irradiation, on the other hand, is often several hours, and oxygen may diffuse into the polymer. Electron irradiation therefore often produce less changes compared to gamma irradiation at the same dose, and this effect is most visible at the surface of the product [5].

It is the physical, chemical and mechanical properties of the medical device that are of importance for its approval, and these properties, that may be affected by radiation must be tested and documented before the device can be released for use. It is important that the testing is carried out at least at the maximum dose that the product will experience during radiation sterilization, and it is important to realize that it is not possible to irradiate a product to only one dose level. In practice it will be exposed to a range of doses, and at an early stage in the development of a device it may not be possible to know the maximum dose. In stead, testing should be done at a range of doses e.g. 25, 50 and 75 kGy, so that a relationship between dose and the relevant property can be established and used for determination of the allowable *maximum dose.*

3. MINIMUM DOSE

In Europe, before the implementation of the Medical Device Directive, it was an accepted practice to irradiate for sterilization with an absorbed dose of 25 kGy, and the National Health Authorities, that were responsible for the approval of the medical devices accepted that the device was sterile if it could be documented that the device was produced under good manufacturing conditions and that the initial microbiological contamination - the bioburden - was low.

In a parenthesis it might be mentioned that in Scandinavia special rules were in force. The dose required for sterilization depended both on the type of radiation and on the level of contamination, with a minimum dose of 35 kGy for electron and 32 kGy for gamma radiation.

The implementation of the Medical Device Directive means that the primary manufacturer has become responsible for producing evidence for compliance with EN 556[6], i.e. for obtaining and maintaining an SAL of 10^{-6}. An absorbed dose must be determined that can produce the required level of sterility, and that dose can be lower than 25 kGy, but it is also possible that higher doses are required. The sterilization dose is determined on the basis of microbiological documentation, and EN 552 indicates that the choice must be based on the information on the radiation resistance of the microorganisms naturally occurring on the medical device. EN 552 indicates the type of microbiological documentation that is considered acceptable. This may be either a measurement of the radiation resistance or it may be comparison with microorganisms with a known radiation resistance. The latter method is – with reference to ISO 11137 – referred to as Method 1, and it is briefly described here.

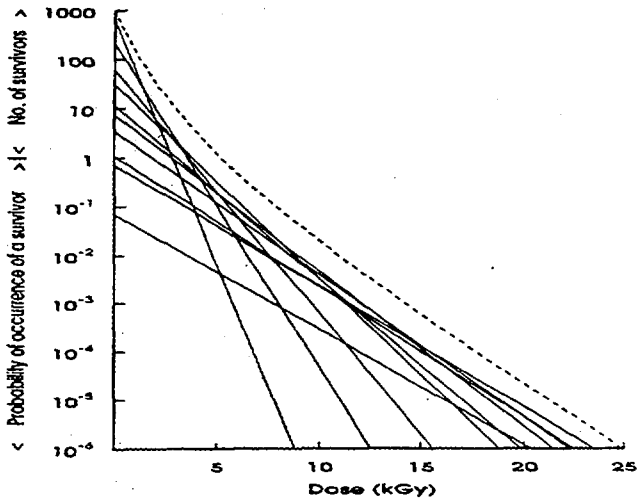

FIG. 3. The Standard Distribution of Resistances (SDR) is composed of several representative microorganisms having increasing radiation resistance. The dotted line is the combined SDR, that is used for prediction of the dose that will give SAL = 10^{-6}. In this example with an initial bioburden of N(0) = 1000, the dose for SAL = 10^{-2} is 11 kGy and the dose for SAL = 10^{-6} is 25 kGy. At lower initial bioburden values the sterilization dose will be reduced.

The main principle in Method 1 is that the radiation resistance of the microorganisms contaminating the product prior to sterilization – the bioburden – is compared with the population of microorganisms having a radiation resistance known as the Standard Distribution of Resistances (SDR). If the radiation resistance of the product bioburden is less than that of the SDR, then the SDR is used to select the dose that will produce an SAL of 10^{-6}

The procedure involves measurement of the product bioburden by testing 10 units from each of three different production batches. Based on the average of the three bioburden measurements a dose is found that will give a sterility assurance level of 10^{-2}, and 100 product units are irradiated to that small dose. These 100 units are tested for sterility, and if no more than 2 unsterile product units are found, the test is passed and the necessary dose for sterilization to SAL $\leq 10^{-6}$ is determined by extrapolation of the SDR. The SDR is represented as tables in ISO 11137. This dose is the required *minimum dose.*

Documentation that the microbiological status of the product is maintained must be produced by repeating the exercise about every three months. However, it has been suggested that under certain circumstances this frequency of verification may be reduced [7, 8].

4. DOSE MAPPING

Not all parts of a medical device will be irradiated to the same dose when it is exposed to electron or gamma radiation. Due to the local absorption and scatter of radiation a range of doses will be experienced, which for more complex product can be very difficult to predict, and which therefore have to be measured. This is done in a dose mapping exercise, where the doses in or on a medical

device are measured under actual processing conditions. This means that irradiation for the dose mapping as a rule shall be carried out at the facility, where the device is going to be sterilized, and the device shall be packaged in its final product package.

It is not possible to place dosimeters everywhere in the device, and choices have to made. Dosimeters shall be distributed throughout the device in a pattern, so that they are likely to measure the dose extremes. The information obtained during the dose mapping in facility qualification regarding maximum and minimum dose zones can be useful, and can provide guidance as to where to place the dosimeters for this exercise. Particular attention shall be given to inhomogeneous product distribution, orientation of the product relative to the direction of the radiation, voids, local differences in specific density, and interfaces. Previous experience may prove indispensable. The problems of defining the proper placement of dosimeters are most pronounced for electron irradiation, which because of a monoenergetic energy distribution and a well-defined direction of the electron beam is known to produce large dose gradients.

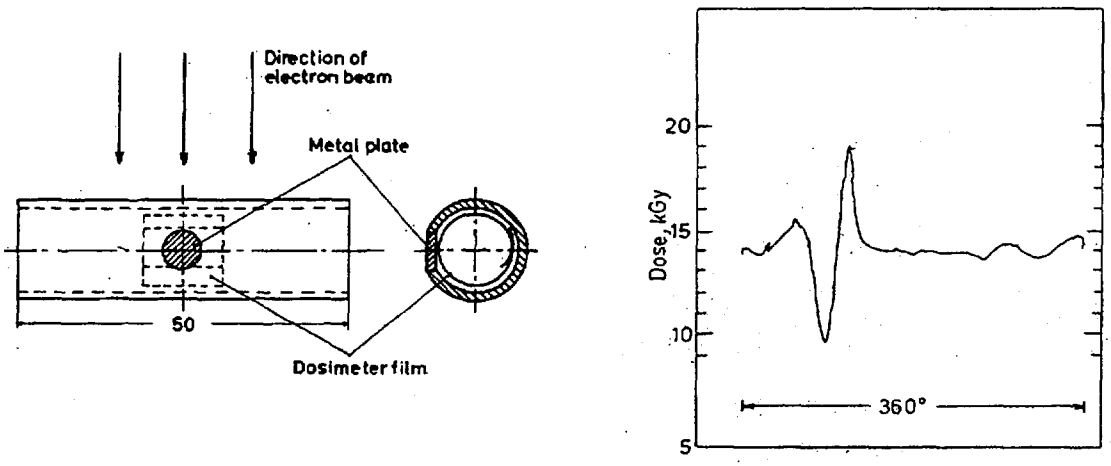

FIG. 4. The tube shown to the left was irradiated from one side with 10-MeV electrons. Dose distribution is shown to the right. 360^0 corresponds to a dosimeter length of 30 mm.

Another problem concerns the spatial resolution of the dosimeters. In particular for electron irradiation, dose gradients may occur within millimeters or even less, and the dosimeter system must be able to resolve and measure the doses at the location of these gradients, see Fig. 4.

The minimum and maximum doses and their locations are determined in this exercise, but the dose map should be carried out in more than one product box in order to determine the measurement uncertainty. A complete dose map may be carried out in – as a minimum – three product boxes, or repeated measurements (e.g. 10) of only the minimum and maximum doses can be made, if their locations have been well characterized in a one-box dose map.

Simultaneous with the measurements of the maximum and minimum doses, the parameters of the irradiation facility must be recorded and a reference dose must be measured. The reference dose is measured in a specific geometry outside the product (or often on the outside of the product box). It is a parameter that is used to monitor the output of the irradiation facility, and it is used for routine process control. A major outcome of the dose mapping exercise is to determine the relationship between the maximum and minimum doses and the reference dose.

For gamma radiation, ratios of D(max)/D(min) – the uniformity ratio – is often between 1.2 and 1.4, while this ratio is more likely to be between 1.5 and 2 for electron irradiation, and even higher

ratios are not uncommon. The allowable limit of the uniformity ratio is determined by minimum and maximum dose limits determined in Sections 2 and 3. If this limit is exceeded for the product being dose mapped, then redesign of the product or its packaging must be considered, or different irradiation parameters may be chosen that may fulfil the requirement.

A reference dose – and associated irradiation facility parameters – can now be chosen that will allow the measured minimum dose to be larger than the required minimum dose. During the normal radiation sterilization process the minimum (and maximum) dose cannot be measured, and therefore the parameters shall be chosen so that if measured, the minimum dose will be larger than the required minimum dose. Recognizing the statistical nature of dose measurement, the choice can be based upon the known measurement uncertainty, and to choose the measured minimum dose on average to be 2 standard deviations larger than the required value may seem a reasonable choice [9].

5. CONCLUSIONS

Radiation processing can be carried out within documented dose limits ensuring that products are produced with parameters that are in accordance with specifications. The procedures for providing the documentation are specific in some cases, in others not. For example the procedures for documenting the required minimum dose for sterilization are specific, but for measuring the minimum dose in a dose mapping exercise the procedures are not specific and choices will have to made. The basis for the choice must always be that no product may be irradiated outside specifications.

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