

THE USE OF IONISING RADIATION IN THE MANUFACTURE OF MEDICINAL PRODUCTS

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Additional Notes	This note for guidance deals with the use of ionising radiation in the manufacture of medicinal products. It should be read in conjunction with Volume IV of “The Rules Governing Medicinal Products in the European Union”, particularly the annex on ionising radiation.

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THE USE OF IONISING RADIATION IN THE MANUFACTURE OF MEDICINAL PRODUCTS

1. INTRODUCTION

This note for guidance is intended for applicants wishing to use ionising radiation in the manufacture of medicinal products. Irradiation may be used for microbial decontamination, sterilisation or other treatments. Different materials or products may be irradiated: starting materials, packaging materials, intermediate products, bulk products and finished products.

Information should be given in sufficient detail to enable the competent authority to evaluate whether or not the manufacturing subprocess is effective and the product is safe for the patient.

Manufacturers using ionising radiation in the manufacture of medicinal products should refer to the Guide to Good Manufacturing Practice (Volume IV of “*The Rules Governing Medicinal Products in the European Union*”) and in particular to the annex on ionising radiation used in the manufacture of medicinal products and, where relevant, to the annex on manufacture of sterile medicinal products.

2. ADMINISTRATIVE DATA

- a) The name and description of the product (including its packaging material) to be irradiated should be given. Its shape, size and composition (type and quantity of substances) should be described in detail. Furthermore, it should be made clear whether starting materials, packaging materials, intermediate products, bulk products or the finished product are irradiated. Sizes of production batches and of irradiation batches should be defined. In the case of a continuous process, a batch comprises all the units processed in a given period of time.
- b) The purpose of the irradiation should be stated. Both the minimum dose to achieve this purpose and the maximum permissible dose should be stated.
- c) In addition to the names and addresses of all manufacturers involved in the manufacture of the product, the name and address of the irradiation plant should be given, making clear which operations are to be conducted at which site.
- d) A copy of the authorisation referred to in Directive 75/319/EEC as amended and covering the irradiation plant should be attached to the application.

3. MANUFACTURING PROCESS

Irradiation of a medicinal product is part of its manufacturing process and the description of that part of processing should be sufficiently detailed. The application should include the following information:

3.1 Description of the irradiation plant

- a) Type (radionuclide source, electron generator) and builder of the plant;
- b) working mode (batch- or continuous mode);
- c) authorised and actual activity of the radionuclide in the radiation source (GBq), or the maximum and minimum electron energy (MeV) of the generator as appropriate;
- d) concise description of the plant including drawings, showing clearly the course of the product within the plant, the position and geometry of the irradiation source and the conveyor system including the source pass mechanism.

3.2 Description of the irradiation process

- a) a description of the material to be irradiated should be given, including limits (if any) on bioburden and any process aimed to limit or control the bioburden. Action to be taken when particular bioburden limits are exceeded should be stated;
- b) the number and positions of the irradiation containers in relation to the position of the source during the whole dwelling time, and the method of moving them through the chamber, should be described;
- c) the material and dimensions of the irradiation container should be described;
- d) the maximum total irradiation time and the maximum dwelling time of the product in the irradiation chamber should be stated;
- e) results of dose mapping studies using a “dummy product” are required;
- f) the loading pattern of the product must be stated for each irradiation container. If the load consists of mixed products, the composition of the load must be described including their stated position in the irradiation container. The mean density of the load and the acceptable maximum density should be given. A modification of the loading pattern may be acceptable provided a new dose mapping is performed, showing that the stated minimum and maximum doses are not exceeded;
- g) when the loading pattern of the product within the irradiation container has been defined, dose mapping should be performed with a sufficient number of appropriate dosimeters to show the distribution of the absorbed dose within the loaded irradiation container and to show the places of minimum and maximum doses. This dose mapping should be carried out for a representative number of irradiation containers to determine the variability of the absorbed dose in the load of one container and the differences between several containers.

Note: Separate dose mapping exercises should be carried out for each product or distinct category of products and each pathway to be used for processing products.

- h) a written standard operating procedure should be established including the following minimum items:
 - the loading pattern of product(s) within the irradiation container;
 - the type, number and location of routine dosimeters within one irradiation batch or within a stated period of time in the case of a continuous process;

- any adjustments to be applied to the routine dosimeter measurements to convert them into the absorbed dose at both minimum and maximum positions;
- the stated minimum and maximum absorbed dose including experimentally determined errors of dosimeters;
- whether or not repeated treatment is acceptable; for the product concerned, the circumstances in which such repeated treatment is allowed, and the number of occasions on which it is allowed for a particular batch;
- in the case of electron beam irradiators electron energy, average beam current, beam width and conveyor speed should be stated with acceptable limits.

Note: The stated minimum dose is that required for the intended purpose, the stated maximum dose is limited by unacceptable changes induced by irradiation in the product and/or the packaging, or imposed by official restrictions.

A minimum absorbed dose of 25 kGy may be regarded as adequate for the purpose of sterilising pharmaceutical components or products which have a low initial bioburden and no radioresistant spores. Other doses may be used provided that a biological validation has been performed.

4. VALIDATION OF THE IRRADIATION PROCEDURE

4.1 Validation with regard to the irradiation procedure and dose

- a) with electron irradiation, if the maximum electron energy exceeds 10 MeV, it should be demonstrated that no radionuclides develop in the product;
- b) information derived from experimental investigations into the acceptable variation in the loading pattern should be given;
- c) information should be included on the errors due to the type of dosimeters used and on the influence of their position;
- d) information on the relationship between the absorbed doses in the extreme positions within the load and the positions of routine dosimeters should be given.

4.2 Validation with regard to the purpose of irradiation (see section 2.b)

For reduction of bioburden and/or sterilisation:

- a) Where appropriate, information on the bioburden of the product before irradiation should be given with data from several batches to show the usual bioburden levels and types of organisms usually present;
- b) data on the reduction of bioburden during the irradiation with different doses, including the minimum dose, should be given for at least 2 batches;
- c) an inactivation curve derived from the above data should be submitted. If the test specimen itself has a low bioburden, it should be artificially contaminated with $> 10^7$ cfu/single unit preferably with a microorganism originally occurring in the product and with a minimum D-Value of 3 kGy;

- d) the bioburden limit on the product prior to irradiation should be based on data derived from a) – c).

In other cases, experimental results should show that the purpose of irradiation has been achieved.

4.3 Validation with regard to the quality of the product

- a) Information should be given about any qualitative and quantitative changes in the product, including its packaging, as a result of irradiation;

Note: Methods used for quantitative determinations should be validated in accordance with the note for guidance *Validation of Analytical Procedures: Methodology*.

- b) Information should be given about the formation of radiolysis products or other degradation or interaction products. Whenever possible, the radiolysis products should be identified;
- c) the results of the studies carried out with high doses of radiation to determine the maximum dose should be given;
- d) as assessment of the significance of any observed changes should be included;
- e) information should be given about the effect of irradiation on the stability of the product and therefore stability studies should be performed on products which have received the maximum absorbed dose.

Note: The relevance of any changes in the product induced by irradiation as regards quality of the product as well as health and safety of the patient should be discussed. The toxicological risks caused by products of irradiation (see section 3.3.b) should be evaluated. Safety of the irradiated product for the patient should be discussed in the expert report.

GLOSSARY

Absorbed Dose

The quantity of radiation energy imparted per unit mass of material. The unit of absorbed dose is the Gray (Gy) where 1 Gray is equivalent to absorption of 1 Joule per kilogram (J.kg⁻¹).

Batch

A defined quantity of starting material, packaging material or product processed in one process or series of processes so that it could be expected to be homogeneous.

Note: To complete certain stages of manufacture, it may be necessary to divide a batch into a number of subbatches, which are later brought together to form a final homogeneous batch. In the case of continuous manufacture, the batch must correspond to a defined fraction of the production, characterised by its intended homogeneity.

For control of the finished product, the following definition has been given in Directive 75/318/EEC as amended: 'For the control of the finished product, a batch of a proprietary medicinal product comprises all the units of a pharmaceutical form which are made from the same initial mass of material and have undergone a single series of manufacturing operations or a single sterilisation operation or, in the case of a continuous production process, all the units manufactured in a given period of time'.

Bioburden

The total number of all viable aerobic bacteria, yeasts and moulds expressed as colony forming units (cfu) per unit or gram of product.

Bulk Product

Any product which has completed all processing stages up to, but not including, final packaging.

Dose Mapping

An exercise conducted within the irradiation equipment to determine the distribution of absorbed dose throughout a load of product or simulated product of specified density ("dummy product") arranged in the irradiation container in a defined configuration.

Dosimeter

A device or system having a reproducible measurable response to radiation, which can be used to measure the absorbed dose in a given material.

Dummy Product

Homogeneous material of known density for filling the irradiation container for the purpose of carrying out dose distribution experiments with ionising radiation.

Finished Product

A medicinal product which has undergone all stages of production including packaging.

Intermediate Product

Partly processed material which must undergo further manufacturing steps before it becomes a bulk product.

Irradiation Container

The outermost container in which the products are irradiated.

Packaging Material

Any material employed in the packaging of a product, excluding any outer packaging used for transportation or shipment. Packaging materials are referred to as primary or secondary according to whether or not they are intended to be in direct contact with the product.

Starting Material

Any substance used in the production of a product, but excluding packaging materials.