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Radiation Sterilisation of Advanced Drug–Device Combination Products

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Sterilisation of drug-device combination products presents unique challenges and demands some new thinking. Issues such as dose setting and controlling free radicals for these ultraclean, high-cost products are discussed together with the future advancements required for their efficient terminal sterilisation.

Image: PhotoDisc

Unique factors

Pharmaceutical, biotech and medical device manufacturers, and radiation processing experts came together on 6 December 2006 in La Jolla, San Diego, California, USA, at a workshop sponsored by the international irradiation Association (iiA). The objective was to explore scientific advances, future technical challenges and practical aspects of the radiation sterilisation of advanced combination drug-device products. Combination products are comprised of more than one type of regulated article or component (device, drug or biologic) and typically have more than one identifiable mode of action or therapeutic benefit.

Manufactured under highly controlled conditions and in small quantities for just-in-time delivery, these products are likely to have an extremely low bioburden. Many require stringent temperature control and have extremely tight dose tolerance requirements. In the case of tissue allografts there is no such thing as a standard size, shape or material, and the small quantities and possible presence of viruses add complexity. These issues pose unique challenges for any sterilisation method.

Regulators, when comparing aseptic processing with terminal sterilisation, are saying that wherever possible terminal sterilisation is preferred. This is because it lowers the chance of error and the risk of a contaminated product causing infection or transmitting a disease to the patient.

During the workshop it became apparent that the successful irradiation and regulatory approval of these high value-added combination drug-device products requires fresh and creative thinking. There are several areas that require further attention and these are discussed below.

Lower sterilisation dose

Because the efficacy of drug or biologic molecules is likely to be dose-dependent, then every effort should be made to determine the lowest possible radiation dose that is required to make the products "safe for their intended use." The current dose setting guidelines of the International Organisation of Standardisation and the Association for the Advancement of Medical Instrumentation, although first-rate, have a number of limitations when they are applied to these types of products:

- They do not work well for "ultra, ultra" clean products, which will often be the case with drug components with a bioburden of less than 0.1 colony-forming unit per product unit.
- Dose setting using VD_{max} can allow a Dmin of 15 kGy, but if products have already been aseptically filled or are ultraclean, a dose in the order of 7 kGy may be all that is required.
- Current dose setting methods require the sacrifice of a large number of product samples for dose setting and/or verification dose testing; the high cost and small volume batch size of combination products may make this prohibitive.
- The definition of sample item proportion (SIP) and selecting the SIP needs to be re-examined because drugs can be in bulk powder form in relatively large packages and worth thousands of dollars/euro per gram.
- It is questionable whether the standard bioburden population and distribution now used in the current dose setting methods for medical

devices are applicable to drug (fluid) products.

■ The establishment of sterilising doses for medical devices using current dose-setting methodology takes into consideration product bioburden and its resistance to radiation, but is currently tied to an arbitrary sterility assurance level (SAL) of 10^{-6}.

Alanine, which is of reference standard quality and performs in a dose range of 0.02–200 kGy, may become the dosimeter of choice.

■ The medical device and pharmaceutical industries and their regulators may define sterility in different terms.

A collaborative approach effectively resulted in the development of the international standards ISO 11137, Parts 1, 2 and 3:2006, Sterilisation of Health Care Products, Radiation. To address the issues associated with combination drug-device products industry experts and various regulatory authorities will need to work together and reconsider the product SAL that is essential for patient safety, prescribed use of the product, evolving microbial challenges, and the benefits to health care and patients.

Dosimetry and modelling

Because it is incumbent on us to minimise the sterilisation dose, it is of increasing importance to select the dosimetry system that has the minimum inherent number of uncertainties or complications associated with its use. It should cover the broadest dose range and ideally experience no dose rate effect. Dosimetry for refrigerated products may need a temperature correction factor and be calibrated accordingly. Therefore alanine, which is of reference standard quality and performs in a dose range of 0.02–200 kGy, may become the dosimeter of choice for these drug-device combination products.

In the future, mathematical modelling will play a greater role in three fundamental areas: facility design, operation of radiation processing facilities, and predicting or assessing the dose distribution in products. Significant benefits are being realised as companies implement modelling to lower costs, reduce the amount of sacrificial product, better manage process and product complexity, enhance quality systems, and accelerate time to market for irradiated products.

Process control in facilities

Further analysis is required to determine in more detail how, and if, the current extensive infrastructure of large-scale radiation processing facilities can most effectively be used to process this class of products. Specifically, the important differences between traditional medical devices and these products may include:

■ temperature control, that is, irradiation in a frozen state
■ inert atmosphere
■ low sterilisation doses with tight dose uniformity ratio (DUR), which is the ratio of the maximum to minimum absorbed dose in the product, for example, DUR 1.3/1.0 may be required
■ small production batches of high value products amounting to, for example, a monetary value of US$500000 to US$1 million in a facility
■ just-in-time irradiation
■ additional irradiator controls to further eliminate the possibility of overdosing product
■ new strategies to effectively deal with process interruptions.

In some cases this is likely to require modifications of existing irradiators to accommodate the special requirements associated with the sterilisation of drug-device combination products. Critical for success is working with the irradiation service provider early in the product development process.

The longer-term outlook may include the integration of new radiation processing systems (cobalt-60 gamma facilities, electron beam or perhaps X-ray systems) into manufacturing lines. Selection of these specifically designed systems will need to take into account the fundamental differences between the radiation source (penetration and dose rate delivery), process optimisation and economics.

Radiation chemistry

Understanding radiation chemistry, the roles of reactive oxidative species and implications of the target theory are leading to new techniques for irradiating combination drug-device products. Irradiating the product →

Table I: Reasons why radiation processing has become the preferred method of sterilisation.

■ The inherent ability of gamma radiation to effectively penetrate large thicknesses of dense material, thus providing extreme flexibility in product and packaging design, which has resulted in the evolution of a wide range of essential medical devices
■ The fact that the gamma irradiation process itself has proven to be extremely reliable with only one process variable to be controlled during the sterilisation process, namely, product exposure time
■ Electron beam radiation is also a proven and rapid sterilisation method used for depositing energy into less-dense, thin and relatively homogeneous product, where beam-to-product orientation can be controlled or is not an important factor
■ The product does not become radioactive when exposed to gamma or electron beam and there are no sterilant residues left behind on the product
■ Finally the establishment of an international network of large scale contract irradiation facilities, each of which serves multiple companies, has made the process economically viable for small as well as large volume producers

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in the frozen state can optimise the direct effects of damaging the deoxyribonucleic acid (DNA) or ribonucleic acid of the microorganism, while at the same time minimising the ability of free radicals to recombine with the drug components. Another option is to irradiate the drug in a lyophilised or freeze-dried state. Additives, which act as scavengers, may also help alleviate degradation effects caused by the indirect action of free radicals. At the forefront of the research is the development of strategies that most effectively protect the product and not the microorganisms.

Materials and packaging

Many materials are available that are radiation compatible. However, it is important to consider the sterilisation method early in the design phase to avoid incorporating limiting materials such as natural polypropylene, acetals and polytetrafluoroethylene. It is advisable to use the existing compendia of information; to qualify several suppliers; and carefully assess the functional, biocompatibility and aesthetics properties of the material being employed. Sometimes changing current practices and a thorough understanding of the science and business requirements can present new opportunities.

For example, standard glass containers used by drug manufacturers typically discolour when exposed to radiation; this is an issue for marketing, but not for the regulatory authorities. Closed-vial technology is emerging, which uses irradiation to sterilise a plastic vial prior to aseptic filling with a drug. Cyclo-olefin copolymer is used in the manufacture of vials because of its high transparency, purity and barrier properties. By using this material, pharmaceutical manufacturers are realising major cost and investment savings because of the elimination of several steps, including washing and depyrogenation, which is required with glass vials, and reduced clean-room space. This new plastic vial minimises breakage and spillage and thereby reduces worker exposure to potent or cytotoxic drugs.

Regulations and harmonisation

In reflecting on possible changes to dose setting for drug-device combination products, it is incumbent on the industry to involve at the outset appropriate representatives from the regulatory authorities. The most appropriate Agency in the United States is the Office of Combination Products, formed by the Food and Drug Administration in December 2002 to regulate products comprised of two or more regulated components, that is, drug-device, biologic-device.[1] As stated by workshop participants, European and other regulatory requirements should also be considered because many of these products will be marketed on an international scale. In some cases outdated notions such as the requirement of a 25-kGy minimum dose for sterilisation still exist. This thinking is counterproductive to the development of combination products that are safe, effective and of the highest quality.

The future

In 2004, the drug-device combination products market was valued at an estimated US$5.9 billion.[2] Growing at a compound annual rate of 10%, by 2009 the global market for combination drug-device product is forecast to reach US$9.5 billion. Today, combination products range from drug-eluting stents for coronary blockages and sophisticated monoclonal antibodies combined with a chemotherapy agent for the treatment of cancer. Each combination product offers significant solutions to many of the problems found in health-care delivery and ultimately better patient care.

During the past 50 years radiation processing has become the preferred sterilisation method and is used to treat approximately 55% of all single-use medical devices worldwide. The reasons for this are well understood (see Table I).

Radiation processing potentially has a strong role to play in the terminal sterilisation of advanced combination drug-device and biological based products. Looking forward, advances in the following areas can be envisaged:

- lowering of the sterilisation dose to reflect intended use and product need
- increased use of more sophisticated dosimetry and modelling
- improved process control in existing facilities and the design of new systems
- more irradiation of product in the frozen state
- the development of additional free radical scavengers
- new radiation compatible materials and innovative packaging
- development of applicable international standards and regulatory harmonisation.

About iiA

At the International Meeting on Radiation Processing (IMRP) 2003 in Chicago, Illinois, USA, members of Aiii, the old Association d'International Industrial Irradiation, agreed that to continue to be effective the Association needed to be revitalised and strengthened. It was time for a change. Accordingly, an industry funded, permanently staffed and not-for-profit international irradiation Association (iiA) was incorporated in the United Kingdom. To date, it has made considerable progress in building a strong united global voice to effectively and efficiently deal with industry challenges and opportunities.

Members of iiA include the leading suppliers of isotope-based and machine-based radiation sources and equipment, multinational health-care companies and the providers of more than 90% of the world's contract irradiation sterilisation services. There are currently approximately 42 member companies from North and South America, Europe, Africa, Australia and Asia. An advisory council that includes the Chairpersons of a number of regional irradiation associations supports the eight-person Board of Directors, which has industry leaders from five countries. iiA has established nongovernmental organisation status with the International Atomic Energy Association. It is also becoming more involved in the organisation of International Meeting on Radiation Processing planned for September 2008 in London, UK. www.doubleia.org

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→ The diversity, flexibility and sophistication of radiation processing present valuable options as the convergence of technologies has driven and will continue to drive the development of increasingly complex, sterile health-care products.

The workshop was informative with respect to the current state-of-the-art, it outlined some of the issues that need to be addressed, and appeared to be enthusiastically received by the participants. The roundtable discussions were most appreciated and generated some insightful discussions.

Based on this positive response it is the intention of iiA in 2007 to sponsor additional, more indepth workshops that are expanded to include an examination of the regulatory issues associated with the radiation sterilisation of drug-device combination products. mdt

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