The technology alternatives open to medical device manufacturers when considering sterilization of their products are diverse. This guide from Synergy Health will provide insight into the principal sterilization methodologies and some considerations from product design and materials performance perspectives.
Introduction

Historically the trends in sterilization approaches for medical devices have been quite clear. Sterile medical devices have progressed from re-useable equipment manufactured from rubber, glass and metal through to single use items manufactured from a wide range of both natural and synthetic polymeric materials. Sophistication has increased tremendously as products have developed from essentially inert delivery and protective systems to complex multifunctional implantable devices, and devices with measuring functions employing combinations of biological systems and electronics. As devices have developed so has the use of sterilization systems and technologies employed to render these devices sterile. In the days of glass and rubber, sterilization was typically by moist heat, with steam at 121°C or 134°C based on the predominant hospital sterilization techniques of the time. As polymers derived from oil became freely available they enabled the development of ‘single use’ devices. However their inability to tolerate the conditions associated with steam sterilization resulted in the growth of Ethylene Oxide sterilization technology and moist heat processes declined. During the final quarter of the 20th century radiation sterilization technologies took an increasing proportion of market share. This development was driven by a number of factors:

• Increasing concerns over the safety of Ethylene Oxide, both to patients and to operators.
• Environmental pressures to eliminate CFCs that were used as inerting agents and diluents.
• Pressures towards inventory reduction and JIT manufacturing methods that were facilitated by the faster turn-round enabled by radiation sterilization.
• Increased availability of radiation compatible grades of those base polymers affected by radiation sterilization processes.

There continue to be powerful arguments for the use of Ethylene Oxide; for example manufacturers may have considerable investment in ‘in-house’ plants and their product design process may be inextricably linked to the Ethylene Oxide sterilization process. Conversion of established products from Ethylene Oxide to radiation sterilization methods may have significant revenue implications in terms of re-engineering, product qualification and ongoing sterilization costs. Furthermore there is always a risk associated with change, and the benefits of change have to be appreciably greater than the unanticipated hazards that may be associated with making those changes.

Management of the Ethylene Oxide sterilization process has also improved considerably with practices such as exhaust gas management, via treatment or capture, to improve environmental performance. The amount of time to product release is improving with the advent of rapid BI (Biological Indicator) systems and the application of parametric release (and its acceptance by regulators). Novel cycles have been developed to treat products with unusual, restrictive, physical requirements. These and other developments have enabled the technology to address many of the issues it faced. As a result the relationship between the sterilization technologies has reached a balance.

It is generally reported that in global volume terms around 45 - 50% of sterile medical devices are sterilized using radiation and around 50 - 55% by Ethylene Oxide and these numbers seem to have remained stable for the last 15 years or so. However there have been developments within these technology areas. In the field of radiation technologies the advent of reliable high energy electron beam systems has resulted in a significant growth in the proportion of radiation sterilized medical devices being processed via electron beams (typically reported as 7 – 10% of the global total). Most recently the availability of very high powered electron beam installations capable of generating X-rays on a reliable commercial scale has seen the emergence of X-ray sterilization as practical alternative. There is currently one X-ray commercial facility available.

Whilst steam (moist heat) sterilization processes are employed for medical device sterilization, the volume is very low and it tends to be associated with older ‘low tech’ products.

Some of the pressures that sterilization providers and their technologies will face in the future which will force further development include:

• Increasing sophistication of medical devices as measuring functions, pharmaceuticals and biologics are combined in novel products.
• Increasing demands to tailor sterilization service to the unique requirements of devices, including wide variation in dose requirements, smaller batch sizes and unique patient configurations.
• Increasing environmental concerns whether it be over the use and effects of Ethylene Oxide on operators and patients, the cost, safety and handling of radioactive isotope, or the costs associated with electricity supply for electron beam and X-ray plants.

This guide aims to provide some general background to these sterilization technologies and in particular to provide some insight into their relative strengths and weaknesses in their interaction with materials used in the manufacture of medical devices. It is hoped that it will provide information for new product designers to select sterilization methods on the basis of relevant knowledge, rather than copying what
was done previously, and also to avoid some of the pitfalls that are encountered as result of considering sterilization as an afterthought to the product design process.

**Background to sterilization technologies**

In order to understand the implications of choosing a particular sterilization process it is valuable to have some insight into the mechanisms and characteristics of these processes. This can be relevant from not only a product performance point of view, but also to the longer term economic consequences of sterilization decisions that might be taken by a device manufacturer.

**Radiation sterilization**

Historically sterilization by radiation has been achieved by two similar but distinct technologies, namely Gamma irradiation and Electron Beam irradiation, but recently X-ray has become a practical third radiation based option. All radiation sterilization processes typically treat product in its final sealed packaging and usually packaged in its shelf and shipper cartons. However for a number of reasons electron beam plants may choose to treat products individually or in smaller shelf packs rather than final cartons, the reasons and benefits of this approach for this technology are explained further on.

**Gamma irradiation**

Gamma irradiation involves the exposure of products to gamma radiation generated by the decay of the radioisotope cobalt-60 in a specially designed irradiation cell. A variety of gamma irradiator designs ranging from small flexible trial irradiators through to high volume, high efficiency industrial systems can be viewed on the Nordion Sterilization Technologies website. This high energy radiation is powerful enough to destroy biological systems, but not sufficiently energetic to interact with nuclei and induce radioactivity in the materials being processed. Because it is electromagnetic radiation at short wavelength, its penetration capability is high and because it is emitted by the decay of an isotope, its energy is fixed.

As gamma rays penetrate the product, energy from photons of gamma radiation is transferred to electrons in the target material molecules resulting in ionisation. This process yields highly active electrons and highly reactive free radicals. It is primarily the activities of these species that are responsible for the polymer modification and sterilization capabilities of gamma radiation. In the context of sterilization it is generally accepted that these species induce damage and breaks in the DNA double helix, preventing replication or expression and hence sterilization, as well as damaging other sub-cellular metabolic systems.

In the context of interaction with materials the deposition of energy will result in a shower of energetic electrons within the polymer which may be either free or remain bound. The highly reactive ejected electrons can ultimately generate highly reactive free radicals. Alternatively the parent cation may undergo spontaneous decomposition or become involved in a variety of subsequent reactions. This transfer of energy from gamma photons to generate excited electrons and excited free radicals and molecules is known as the Compton effect. Whether and which of these effects takes place will depend on the energy of the radiation, as well as constituents and configuration of the target molecules.

Note that we talk about ‘absorbed dose’ when referring to the amount of radiation energy absorbed by a product. Absorbed dose is measured in ‘gray’ (Gy) and a typical sterilization dose is 25 kGy. Units are defined at the end of this document and are the same for all the radiation technologies discussed.

![Gamma absorption](diagram.png)

![Electron beam absorption](diagram.png)

*Fig. 1 Schematic representation of dose distribution through a target package for gamma and electron beam double sided irradiation processes*
Electron beam irradiation

Electron beam irradiation involves exposure of product to a high energy (typically 5 – 10 MeV) beam of accelerated electrons. Accelerated electrons are generated via a variety of approaches but all require the same principal components of an electron source, an acceleration energy (can be RF power or DC potential difference), a highly evacuated beam tube, typically closed with a thin foil window in a scan horn through which the beam is emitted.

Electron accelerators can best be described by analogy with a television tube. A heated filament forms the electron gun, a high voltage placed across this filament draws electrons away from the filament and accelerates them down an evacuated tube. The beam is focused by electromagnets and finally passes through an oscillating magnetic field which ‘scans’ it back and forth (analogous to the horizontal scan of a TV tube), so that it emerges from the scan horn through a thin metallic window, usually made from titanium, in a fan-shaped configuration. Products then pass through this curtain of electrons to receive the required dose of irradiation.

These accelerated electrons will penetrate the product and its constituent materials and by direct interaction with the electrons within it, will generate a similar electron shower and similar reactions to those noted above for gamma radiation. Consequently similar free radicals and activated species will be formed and similar reactions will occur. There are two fundamental differences between the two processes. Firstly, because it is particulate in nature, the degree of penetration of product by electrons is much lower than by gamma radiation; secondly, the time required to achieve a given absorbed dose is much shorter with electron beam irradiation (seconds or minutes) than with gamma (typically a few hours). As a result of the latter characteristic the temperature rise associated with electron beam irradiation may be greater than for gamma and the degree of oxidation reactions that take place within the product is generally considered to be less than for gamma. However as a result of the poorer penetration characteristics of beam compared to gamma it is likely that the maximum to minimum dose ratio experienced by beamed product will be greater than for the equivalent gamma treatment. Clearly this becomes important in qualifying products and materials through the process. A simplistic representation of the relationship between absorbed dose and the depth of an irradiated package for both electron beam and gamma irradiated products are shown in Fig 1.

X ray irradiation

For X-ray processes, X-rays are generated by targeting a beam of accelerated electrons onto a metal target (typically tantalum). X-rays will be generated at approximately the same energy as that of the incident electrons. The X-ray radiation generated has equivalent properties to gamma radiation and consequently the comments above for gamma will apply equally to X-rays. The benefits of X-ray systems lie in the fact that they combine the ability to deliver highly penetrating radiation but do not require the use of radioactive isotopes which continually decay whether used or not (like electron beam plants they also avoid the complications of transporting and holding large quantities of radioactive material). The current generation of X-ray plants generate X-rays at slightly higher energies than Gamma radiation generated by cobalt-60 decay, which offers some improvement in minimum to maximum dose ratios. The obvious question is that of the equivalence of the effects of X-ray irradiation and gamma irradiation on materials. Demonstration of this equivalence has been reported for polyethylene (PE), polypropylene (PP), plasticised PVC (pPVC), polystyrene (PS) and acrylonitrile-butadiene-styrene (ABS). However X-ray systems do require a large electricity supply and the efficiency of energy conversion from electricity into electron beams and then into X-rays is poor. Presently the design of commercial X-ray irradiation plants is focused on batch operation mode, whereas both gamma and electron beam irradiators are usually designed to operate as continuous processes, although electron beam plants are frequently operated in a batch process mode.

Ethylene Oxide sterilization

Ethylene Oxide sterilization involves exposure of products in their final packaging to an atmosphere containing Ethylene Oxide gas at defined, controlled concentration, humidity and temperatures. Since Ethylene Oxide is explosive when mixed with air the process takes place under vacuum and significant attention is given to ensuring safe cycle conditions. Minimum conditions to achieve lethality are generally reckoned to be an Ethylene Oxide concentration of 4-500mg/l, a minimum temperature of 40°C and a relative

![Ethylene Oxide cycle](image)

Fig 2 Typical Ethylene Oxide cycle illustrating pressure changes with time.
humidity of approximately 50 - 60%. Moisture content is critical, resistance of micro-organisms to Ethylene Oxide increases significantly as the moisture level falls. Thorough and uniform penetration of heat, moisture and Ethylene Oxide into the product load (typically ranging from 1 – 2 pallets to 30 full pallets in industrial processes) is critical. As a result the Ethylene Oxide process cycle within the sterilization chamber is lengthy, typically several hours, plus equivalently lengthy preconditioning and degassing phases. So the total process time could be 36 hours or longer. The sterilization cycle will involve a number of vacuum and pressure cycles to remove air and introduce humidity and Ethylene Oxide, a ‘dwell’ period under Ethylene Oxide, and then a further series of vacuum and pressure cycles to remove Ethylene Oxide and replace the chamber atmosphere with air. A typical Ethylene Oxide cycle is illustrated in Fig 2. Ethylene Oxide achieves its microbicidal effect via its role as an alkylating agent, attaching an alkyl group to DNA and other functional moieties within the cell to prevent its replication.
Structure and characteristics of polymers with reference to sterilization

Polymers are comprised of long chains of atoms with a predominantly carbon to carbon backbone (silicone polymers have a silicon - oxygen backbone). The strength within a chain can approach that of metals, whereas the strength between chains is generally fairly weak. Polymers can be primarily aliphatic, that is predominantly straight chained, such as polyethylene, or substantially aromatic, that is ring structures, such as polyimide. They are classified as thermoplastic of either amorphous or crystalline structure, and thermoset, cross-linked structures.

Ethylene Oxide tolerance of polymers

The stability of materials used in medical device manufacture and their exposure to Ethylene Oxide has been comprehensively documented. By and large the consensus view is that most materials are stable through single or double sterilization cycles. However after multiple cycles (6 or more) effects on some polymers can be seen, for example styrene polymers exhibited crazing and evidence of stress cracking. This observation has been confirmed for a range of styrene based polymers (PS, HIPS, GPPS, SAN, ASR) whilst HDPE and PE have been shown to exhibit a reduction in tensile strength after repeated Ethylene Oxide sterilization. ABS, PC, RTPU, PVC, nylon and acrylic are not significantly affected. Likewise PET and PETG have been reported to be unaffected by Ethylene Oxide sterilization. There is evidence however of Ethylene Oxide interacting with some biological materials such as heparin and albumin to decrease their efficacy in a clinical environment.

The key interaction of Ethylene Oxide with polymers is the absorption by the polymer of Ethylene Oxide and the persistent presence of residues of Ethylene Oxide and its reactants with moisture, ethylene glycol and 2-chlorethanol (ethylene chlorhydrin). The amount of these compounds that remain within a medical device will be a function of the materials and the degassing processes associated with the sterilization cycles. Solubility in and subsequent desorption of Ethylene Oxide from polymers is highly variable, and can vary between grades of the same polymer. For example solubility in PVC is ‘high’ but desorption from plasticised PVC is much faster than from non-plasticised polymer.

The requirements that medical devices must meet for levels of residual Ethylene Oxide and its by products are defined in ISO 10993 Biological evaluation of medical devices, Part 7 Ethylene Oxide sterilization residuals. These are categorised by the nature of the device, its intended method of use and the consequent challenge to the patient.

Basic radiation chemistry of polymers

Probably the most common impression that people have about radiation sterilization is that gamma radiation might damage their products. This impression dates back to the early days of Gamma sterilization when major problems were encountered with discolouration and hardening of PVCs and embrittlement of polypropylene. These problems however should be consigned to the history books. The vast majority of polymers in use in the medical device industry – with a few notable exceptions – are radiation stable to doses well above the typical sterilizing dose. Where polymers were marginal in their performance, for the majority of materials, radiation stabilised grades are now readily available. Where performance of a polymer remains marginal, successful use in a radiation sterilization environment will require an appreciation of the fundamentals of radiation chemistry, in particular an appreciation of radiation yields (G values), of free radicals and their scavengers, of oxygen effects, thermal effects and moisture effects.

A brief review of the radiation chemistry of the materials most commonly encountered in medical device manufacture will enable a reasoned understanding of the effects of radiation on polymers. Gamma, electron beam and X-ray will have an effect on all polymers to some extent, resulting in potential changes to their physical properties. The radiation dose required to induce marked changes in polymer properties can range from as little as 1 kGy for PTFE to greater than 10 kGy for polystyrene. This is a vast range and more than encompasses that value required to successfully sterilize a product for medical use, where typically a dose of 25 – 50 kGy would be employed. The question of the absorbed dose required to achieve an adequate level of sterility assurance
is addressed later on, but historically the generally accepted sterilization is a minimum of 25 kGy, although there are many examples of lower doses (c15 kGy) and higher (c40 kGy) doses being required.

The free radicals and ion species produced within a polymer by the incident radiation can suffer a variety of fates. They can exist independently for a limited time and induce changes within a polymer matrix. They can either instantly effect chemical change or can be substantially trapped in the polymer structure. They can recombine and be effectively neutralised or they may lay dormant for subsequent attack. Note however that in an aqueous environment the life of these moieties is very short. Irradiation of aqueous solutions gives rise to many types of radical, these include the hydrated electron (eaq-), the hydrogen atom (H), the hydroxyl radical (OH), the perhydroxyl radical (O2-, HO2, and H2O2+), the superoxide anion (O2-), singlet oxygen (1O2) and hydrogen peroxide (H2O2). It is generally recognised that all of these species are very short lived with half lives in some cases of a fraction of a second. This is in contrast to the activities of free radicals in polymeric and crystalline environments. The absence of water in these environments results in the trapping of free radicals, and their slow release over time is a well recognised phenomenon. The ultimate result of their activity is a modification of molecular weight, either a decrease as a result of chain scission or an increase as a result of cross-linking. Both of these mechanisms will occur in most polymers but one will usually predominate. Polymers with largely unsubstituted carbon to carbon aliphatic backbones exhibit predominantly cross-linking (e.g. polyethylene), whilst chain scission will prevail of a quaternary substituted carbon atom (e.g. polysobutylene).

In different application fields the ability of radiation to induce cross-linking is widely employed to enhance the properties of materials in a variety of applications. Improving the performance of cable insulations and the development of radiation cured carbon fibre composites for vehicle use are two typical examples.

Other manifestations of the irradiation process include discoloration, due to the formation of polyene sequences which absorb in the visible spectrum, the generation of gasses and the release of latent stress crazing. Phenolic antioxidants are frequently incorporated into polymers and are often the cause of discolouration. The problem can be overcome by using alternative chemicals and increasing the level of antioxidants can often help to improve radiation stability.

In general aliphatic polymers have less radiation resistance than those polymers exhibiting an aromatic character. The resistance of the latter is attributed to the conjugate double bond system dissipating much of the absorbed energy by resonance. From these generalisations the stabilities of some of the common polymers used in medical device manufacture can begin to be understood. At typical sterilizing doses high energy radiation has little effect on the majority of polymers used in medical device manufacture (Fig 3). Where polymers were marginal in their performance, in many cases radiation stabilised grades have been developed. In these situations the polymer formulation has been substantially modified to overcome undesirable characteristics such as loss of strength, un-aesthetic colour change or odour generation. For that group of polymers that still remain incompatible with radiation sterilization (acetal, PTFE, butyl rubber) alternative polymers are generally available.

General guidance on selecting polymers for radiation sterilization and the effects of radiation on some common polymers can be found in AAMI TIR 17 2008. A further useful general reference guide to understanding the stability of various polymers through the common sterilization processes can be found in The Effect of Sterilization Methods on Plastics and Elastomers, 2nd edition.

**Radiation chemistry of some common polymers**

The notes below summarise aspects of the radiation chemistry of some of the most commonly used polymers in medical device manufacture. Where stabilised grades are referred to, polymer stabilisation is achieved essentially by the addition of a material to the base polymer which either quenches the excited molecular states, scavenges the free radicals that may be formed, or is preferentially oxidised.

**Polyethylene(PE)**

Polyethylene predominantly undergoes cross-linking on irradiation and for all practical purposes can be considered stable to irradiation in both bulk and film forms. LDPE is considered to be the most radiation tolerant of the PE grades. Thick sections may exhibit slight yellowing and lower density preparations generally exhibit greater stability than high density variants. An enormous amount of research has been undertaken on polyethylene formulations used in high load implanted environments such as knee and hip prostheses. To adequately evaluate this application a thorough literature search should be undertaken.

**Polypropylene(PP)**

Polypropylene has major usage as a medical polymer and undergoes both cross-linking and chain scission resulting in significant loss of physical properties. It is intermediate between polyethylene, which predominantly cross-links and polysobutylene which exhibits almost total chain scission. A more rapid rate of free radical reaction in an oxygen rich environment compared to polyethylene is attributed to the greater amorphous content in polypropylene. The free
radicals trapped in the crystalline regions of polypropylene may exhibit delayed release which gives the base polymer its classic long term ageing problem. Unless stabilised, polypropylene will become brittle on irradiation; this effect is obvious in thin films immediately after irradiation, but may take several months to appear in thicker sections. Stabilised polypropylene formulations are now readily available from several suppliers which overcome the problems of embrittlement and the loss of physical properties at typical sterilization doses. Information on how stabilisation is achieved is usually considered proprietary and not released. Some of the methods available include the following: the use of combinations of alkylated phenols and derivatives of thiophosphate and phosphites; polypropylene copolymers with polyethylene and the incorporation of mobilising additives such as polyethylene wax, atactic polypropylene and hydrocarbon oils (further discussion on stabilisers for polypropylenes can be found in references 16, 17, 19).

Poly (ethylene terephthalate) PET
PET and PETG are reported to have high levels of radiation resistance although some yellowing may occur which will fade to an extent over time. The benzene ring in these materials is reported to be responsible for their stability.

Polyvinyl chloride (PVC)
Both rigid and flexible grades of PVC undergo several types of reaction on irradiation including cross-linking, chain scission, hydrogen chloride gas formulation, oxidation and discoloration attributed to free radical reaction. At sterilization doses both odour and colour change can be significant although mechanical properties are only marginally affected. Colour change occurs when at least seven unsaturated conjugated double bonds exist in sequence. Once again a wide range of suppliers of radiation stabilised grades are available, but even amongst these some stiffening of plasticised tube can be experienced. The mechanisms of stabilisation are complex but essentially requires substitution of a stable ester group for an unstable chlorine atom to quench the excited state. Multimetal stearates which benefit from synergistic interaction are commonly used stabilisers, along with non-phthalate type plasticisers.

Hydrogen chloride generation can cause problems when PVC is used in close juxtaposition to carbon steel or stainless steel, when visible corrosion may occur.

Polycarbonate
The mechanical properties of the base polymer are unaffected at sterilizing doses, however even at these relatively low radiation doses there may be an increase in the number of yellow bodies resulting from the formation of free radicals and other charged species. Colour compensation techniques such as the addition of blue or purple pigments to mask the colour change; or the addition of polymeric stabilisers to quench the polycarbonate derived radicals are now used by resin suppliers offering stabilised grades. These alterations only achieve cosmetic benefits; unmodified polycarbonate is used extensively in radiation sterilized products. Discolouration often fades with time. At a more detailed level it has been demonstrated in polycarbonate films that at typical sterilization doses (25 – 50 kGy) cross-linking reactions predominate within the polymer, but as dosage increases up to 250 kGy chain scission and degradation predominate.

Polysulphone
The mechanical properties of polysulphones are unaffected at sterilization doses, though there may be some low level increases in yellow colour formation which can be masked by pigments.

Styrenes
The styrenes as a family, polystyrene, acrylonitrile butadiene styrene (ABS), polystyrene acrylonitrile (SAN), are generally unaffected by irradiation as far as their physical properties are concerned. Some colour change may be induced, but in many cases (e.g. SAN) radiation induced colour will disappear on standing.

Quaternary carbon type structures
A linear polymer which has the alpha carbon atom devoid of a hydrogen atom, i.e. a quaternary atom, will often be readily degraded by radiation, preferentially by chain scission. This can apply even with a polymer that includes aromatic elements. Therefore the performance of polymers within this group is difficult to predict, it will vary depending on the detail of material formulations and additives. Therefore evaluation of the polymer in its final moulded or extruded form is essential. Polymers that fall into this category include polymethylmethacrylate, polysisobutylene, polycyanoacrylates and polyvinylidene chloride.

PTFE and other fluoropolymers
Polytetrafluoroethylene (PTFE) will not usually withstand the radiation sterilization process. Indeed irradiation is regularly used to degrade the formed polymer for inclusion into materials such as printing inks, where it acts as a lubricant. PTFE undergoes chain scission even if the carbon – fluorine bond is the point at which radiation energy is absorbed, internal non-radiative processes will transfer the energy to the weaker carbon – carbon bond and result in main chain cleavage. Attempts at stabilisation of this
polymer for general applications do not appear to have been successful. Although it has been claimed that in an unstressed environment, e.g. when supported by an inert polymer it may prove satisfactory, it has been reported that electron beam processes may be used for the sterilization of PTFE coated guide wires. Generally however PTFE is probably best avoided and alternative polymers with similar properties such as the polyurethanes should be employed. Alternative fluoropolymers such as polychlorotrifluoroethylene (PCTFE) polyvinyl fluoride (PVF), polyvinylidene fluoride (PVDF) and the copolymer fluorinate ethylene propylene (FEP) show greater radiation resistance than PTFE and are reported to perform satisfactorily at 25 – 100 kGy. However the performance at radiation sterilization doses may still be considered marginal under some circumstances and evaluation should be extremely thorough. Attractive alternative polymers are materials such as aliphatic polyurethanes, which by varying the proportion of hard and soft segment polymers can be made to mimic the stiffness of PTFE and elasticity of silicone. Additionally they can be insert moulded or bonded by conventional methods. They have excellent long term implant properties and cannot hydrolyse to methylene diamine, a potential process exhibited by aromatic polyester and polyether urethanes, which have been considered as alternatives to PTFE.

Acetal

Acetal becomes very brittle on irradiation, particularly where thin sections are present. There appear to be no stabilised grades available. This polymer should be avoided and alternatives such as polycarbonate or radiation stabilised polypropylene employed.

Elastomers

Most natural rubber (latex) formulations will tolerate radiation processing up to doses of 50 – 100 kGy before significant loss of physical performance characteristics is incurred. Areas of stress within an item may show failure at lower doses. Nitrile and neoprene rubbers are similarly stable. Butyl rubber is likely to show appreciable softening and may shed particulates at relatively low doses of radiation. The urethanes as a group show excellent stability.

Cellulosics

Cellulose and its commonly encountered esters: cellulose acetate, cellulose propionate and cellulose butyrate will tolerate radiation sterilization doses. However after multiple sterilizations reaching cumulative doses of 75 – 100 kGy loss of physical characteristics becomes noticeable. Cellulose is less tolerant than its esters.

From a practical viewpoint cardboard cartons become brittle and lose strength after 3 – 4 irradiation cycles and cellulose wadding may show reduced absorbancy at 25 – 50 kGy and become friable at 50 – 100 kGy.

Acrylics

Acrylics will generally show some colour change on irradiation, indeed historically one of the uses of polymethylmethacrylate was as a dosimeter, its colour change being proportional to absorbed dose. The cyanacrylates seem to be a widely variable group of compounds in their radiation tolerance. Some are tolerant to 50 – 70 kGy, whilst others lose their physical strength at well below sterilization dose levels.

Silicones

Fully polymerised silicone (the silicone rubbers), are tolerant of radiation doses well above those required for sterilization. However the fluid silicone coatings, used as lubricants, may show increased levels of polymerisation as a result of radiation sterilization which may affect their performance.

Textiles and fibres

Textiles and fibres such as polyester, acrylic, wool, viscose, rayon, silk and cellulose film will usually withstand the doses encountered during radiation sterilization and may well tolerate repeat sterilization. Fine fibres of nylon and cotton however should be treated with caution. The majority of synthetic combinations used for gown and drape manufacture are compatible with radiation sterilization, though in some instances the binding agents and other additives employed may give rise to odour generation. Careful selection of materials or in some cases the use of odour masking compounds can overcome this problem. Fabrics containing polypropylene elements are unlikely to withstand irradiation unless stabilised formulations are used.

Glasses

Glass varieties will generally withstand extremely high doses of radiation, though discolouration may occur to varying extents. Much of this colour change is reversible if held at elevated temperatures. In general terms borosilicate (e.g. Class I neutral borosilicate glass) will discolour and soda glass (Class II sulphate treated and Class III untreated) will not. Addition of cerium will help prevent discolouration and grades of glass treated in this fashion are readily available.

Thermosets

The thermoset compounds most likely to be encountered in medical device manufacture are the phenolics, polysters
and polyurethanes. Epoxies with chemical cure systems are often included in this category. All generally show excellent resistance to irradiation.

Nylons
Nylons (polyamide) and polyimide show good tolerance to radiation in thick sections, however thin sections e.g. hinge applications or packaging films may show reduced resistance.

Adhesives
Adhesives and cements will generally mirror the radiation tolerance of the plastics on which they are based. Structural adhesives such as epoxy and phenolic resins and styrenes have excellent resistance. Vinyl type adhesives such as polyvinyl acetate should be evaluated carefully. Oxidative breakdown of pressure sensitive adhesives may render them unstable, though in many instances these problems can be overcome. Polyisobutylene adhesive has been reported to undergo chain scission in thin films and may require stabilisation\textsuperscript{27}. Experience has shown that in some systems, particularly hot melt adhesives, increased cross-linking as a result of irradiation may increase seal strength.

Inks
It is difficult to generalise about the radiation stability of inks, but practical experience tells us that it is rare to encounter problems with irradiation stability of most commonly used printing inks at typical sterilization doses. Some loss of colour intensity as a result of oxidation may be encountered with some formulations.
Packaging materials and packaging considerations

Packaging can often be a contentious issue, often of little relevance to the customer, frequently the focus of all marketing attention, and potentially a significant source of cost. The comparison between the impact of radiation sterilization and Ethylene Oxide sterilization technologies can be obvious in some circumstances and more subtle in others.

Clearly radiation with its powers of penetration avoids the need to vent packages to allow the ingress and egress of air and sterilant gases, and also avoids subjecting the package to thermal and pressure cycles associated with Ethylene Oxide sterilization. This offers some flexibility in choice of packaging material and may facilitate the use of lower cost packaging options and alternative product presentation. Conversely whilst many of the materials reviewed above are encountered as packaging materials many of the comments above will apply and can result in constraints.

The fact that different forming methods are employed and that these polymers typically are presented as thin films, often with areas of high stress, may result in altered (reduced) tolerances to radiation. For instance polyamide in thick sections is generally satisfactory after irradiation; in thin film form the reduction in physical properties may become unacceptable. Thin sections generally become more susceptible to oxidative attack during irradiation compared to bulk polymer, partly due to the high surface area to volume ratio. Nevertheless there is a wide range of packaging material available to those looking towards radiation sterilization.

Paper – polyethylene and paper - polypropylene pouch systems are satisfactory providing radiation stabilised varieties of polypropylene are employed. Medical grade papers will show some loss of tensile strength at normal sterilization doses, this may become problematic on repeat sterilization. Grid lacquer adhesive systems may discolour and that these polymers typically are presented as thin films, often with areas of high stress, may result in altered (reduced) tolerances to radiation. For instance polyamide in thick sections is generally satisfactory after irradiation; in thin film form the reduction in physical properties may become unacceptable. Thin sections generally become more susceptible to oxidative attack during irradiation compared to bulk polymer, partly due to the high surface area to volume ratio. Nevertheless there is a wide range of packaging material available to those looking towards radiation sterilization.

The stability of paper to radiation has been widely investigated and the treatment of books to eliminate mould and insect contamination is well established. However the formulation of paper is highly variable and the specific effects on the material in question should be established by trials since the deterioration of its physical strength is a widely recognised consequence. Stability to 15 kGy has been reported in specific trials in this field.

Laminates such as polyethylene/polyamide, polyethylene/polypropylene and polypropylene/polyvinylidene chloride will generally tolerate radiation sterilization well provided radiation stabilised grades of polypropylenes are used, although some loss of physical properties should be expected. Laminates of PVC will discolor unless radiation stabilised grades of PVC are used. Polyethylene films show high levels of stability, both in terms of colour and physical performance. An evaluation of the tolerance of PET/PP laminate from the food industry tested at electron beam doses up to 45 kGy has shown an improvement in some properties (elongation at break) and minimal effects on tensile strength and penetration resistance whilst sealing properties showed considerable deterioration. In the same study multilayer PET/LDPE/EVOH/LDPE laminate showed what was described as moderate to severe deterioration of its mechanical properties.

The rigid polymers PET, PETG and polystyrene frequently found in packaging applications are all radiation and Ethylene Oxide stable and will tolerate radiation to several times the levels encountered in sterilization.

Research on the packaging of food for irradiation indicated no increases in migratable fractions and no deterioration in gas barrier performance for a range of materials tested, albeit at relatively low (10 – 15 kGy) doses.

One of the benefits of the Ethylene Oxide cycle is its relative inertness in terms of reactivity with packaging materials which consequently avoids any issues associated with induced changes and allows almost any material to be considered as a component of packaging systems. The breathable element can vary from a small patch to 50% of the package. This element must enable the transmission of air, Ethylene Oxide gas and humidity, and sophisticated specifications for packaging materials suitable for use in Ethylene Oxide environments to be established. However the combination of temperature pressure cycles and high humidity can leave some packaging presentations looking the worse for wear. The design of Ethylene Oxide cycles is important from both packaging and product perspectives. The pressure changes involved can exert forces on both product and package which need to be considered and in some instances can result in unacceptable damage. In particular the combination of elevated temperature and pressure change can challenge some sealing systems.

Processing implications

It is apparent from all of the above comments that radiation sterilization will have some effects on the physical characteristics of all polymers. Whilst Ethylene Oxide sterilization is largely chemically inert there can be consequences of the extended period at elevated temperatures. It is important therefore to ensure that the components being subjected to all sterilization methods retain their maximum performance capabilities after manufacture. Consequently attention must be given to all stages of the manufacturing process, i.e. compounding, extrusion, and injection moulding through to assembly, to
minimise the accumulation of unwanted side effects. The heat history of a polymer can affect its ultimate properties and efforts should be made to avoid excessive levels (e.g. excessive heating promotes the discolouration of PVC). The use of regrind material should be discouraged. In-built stresses from the forming process of moulded and extruded articles will be relieved with time. These stresses can sensitise the component polymer to degradation by radiation and warping by elevated temperature processes such as Ethylene Oxide sterilization.

Whilst these comments are aimed initially at manufacturing processes prior to a radiation sterilization process, they could be considered ‘good manufacturing practice’ and applicable to component manufacture ahead of any sterilization process. The distortion and deformation of components following an Ethylene Oxide cycle can often be attributed to the relief of internal stress within a component as a result of a relatively long period at mildly elevated temperatures, and can be minimised by ensuring a sound manufacturing history.

A polymer has an internal stress level which it can withstand indefinitely under defined conditions. If, during the forming process this level is exceeded then creep or stretching or breaking of bonds will occur with time. It is this phenomenon, a consequence of poor mould design and/or inadequate processing conditions, which is responsible for the only too common failure of medical device components e.g.:

- Split protectors, distorted luer connectors and tubing joints
- Cracked stopcocks and Y sites
- Brittle bottle spikes
- Distorted burette chambers
- Splits and tears in membranes

These faults are to an extent time dependent and depending upon the levels of internal stress, may become apparent soon after processing, e.g. at component inspection, or later on during the manufacturing process, typically after sterilization but occasionally in the worst instance, in the ‘in use’ environment. Both Ethylene Oxide and radiation sterilization methodologies can crystallise these events; the visible effects tend to be the results of Ethylene Oxide processes whilst the impact or radiation processes is often not visible (other than colour change) but manifested in performance changes.

The performance of polymers in a given situation can be optimised by ensuring that basic design considerations are recognised. For instance thin films and thin sections are generally more radiation sensitive than thicker sections. Film forming techniques used in the manufacture of packaging materials differ from those of bulk polymers and their structures may therefore behave differently with irradiation. A useful review of the common forms of component failure, their reasons, and the relevance of sterilization methods which essentially reinforces the comments above can be found in an interesting case study by Stubstad.

**Physical validation (performance qualification)**

‘Performance qualification’ has a particular meaning in the context of the standards that are applicable to Ethylene Oxide and radiation sterilization. In both cases there is a requirement that that the capability of the product after the sterilization process is assessed to ensure that it has not been compromised by the process. The tests and procedures employed are by and large similar regardless of the sterilization process (other than specific consequences of the process such as Ethylene Oxide residual assessment). The most common processing and design errors and failure modes of common medical device components are well documented. A range of simple tests based on assessment of visible changes, tensile strength, and flexural strength (embrittlement) is usually sufficient to answer most questions on product security.

These tests need to be developed with two aims in mind. Namely to quantify the effects of the sterilization process on the physical characteristics of the component and to demonstrate the acceptability of the sterilized component in an ‘in use’ situation. Obviously where particular parameters are of key concern to product performance these must be monitored. Attention should also be given to thin film coatings, particularly where these are fluid coatings such as silicones on needles or catheter blades. It should go without saying that these protocols need to be documented, reviewed and appropriately approved. Similarly they should also include regular communication with marketing departments to ensure that the finished items meet with marketing approval.

In the final analysis all products require performance to be verified after sterilization. Test protocols must be developed from an understanding of the necessary performance requirements, the capabilities of the materials employed and the impact of the sterilization process on these properties. However, as noted earlier, effects of sterilization, particularly radiation sterilization, may continue to develop over a period of time, assessment of shelf life therefore needs to be considered. The use of accelerated ageing studies at elevated temperatures has a role to play in evaluating the effects of sterilization. Commonly used amorphous materials will usually complete molecular stress relaxation within a few hours. Crystalline polymers may develop their structures over weeks and ageing to 60°C for 24 hours may be useful to rapidly bring them to their shelf life condition. Similarly, elevated temperatures of e.g.,
40°C for weeks or months should be considered to drive all reactions, particularly in irradiated materials, to completion. Approaches and guidance on the use of accelerated ageing can be found in an explanation of the rationale behind AAMI TIR 17 - 199734 and for packaging materials in ASTM F1980 – 0735. In addition extreme sterilization conditions such as elevated radiation dosage or elevated temperatures and Ethylene Oxide concentrations can also be used to establish safety margins. Results from all of these studies should always be verified by evaluation of ‘normal’ retention samples. Shelf life evaluation of irradiated products have been widely addressed and an example of a quasi theoretical approach, which allows a prediction of shelf life effects to be made and may be useful36. The availability of real-time aged processed materials makes the development of alternative shelf life predictions possible37, 38. These predictions are material dependent and need to be conducted on a ‘material by material’ basis, the device behaviour is then based on an understanding of component behaviour and how components interact.

Once design is optimised and the product validated, the remaining activities follow the normal ‘fitness for use’ procedures such as safety clearance, product liability and clinical evaluation.

**Material substitution**

Where problems are encountered with the tolerance of materials to radiation sterilization essentially two options are available. One can either consider radiation stabilised grades of the material in question or one can consider employing alternative polymers.

When employing stabilised grades, one should encounter no significant changes in the characteristics of the polymer such as its RF weldability or stress crack resistance etc. Historically these grades have carried a price premium but with increasing availability as a result of increased interest by polymer manufacturers, this premium has to a large extent disappeared.

When considering alternative polymers, apart from the performance of material after irradiation sterilization several other factors will need to be considered. Polymer costs may vary considerably, for instance polycarbonate may be three or four times as expensive as a rigid PVC. Similarly processing characteristics will vary, and the modification or manufacture of new tooling may be necessary.

Solvent bondability, RF and ultrasonic welding characteristics and stress resistance should also be considered. However conversion to alternative polymers may also offer opportunities; improvements to design may be available, increased moulding efficiency may be achieved and improved component performance by result.

**Radiation sterilization dose**

The absorbed dose required to achieve sterilization is potentially variable. The traditional minimum absorbed dose to achieve sterilization of 25 kGy whilst still widely employed is now being superseded by doses set according to product bioburden in accordance with the current ISO standard for radiation sterilization ISO 11137 part 2. Doses as low as 12 – 14 kGy may be justifiably employed when bioburden is extremely low. These doses are predicated on achieving sterility assurance levels of 10⁶, however alternative sterility assurance levels of i.e. 10⁻³ may be justifiable based on the application of the device concerned. Clearly these concepts offer significant opportunity to device manufacturers experiencing problems with performance of polymers. It must be acknowledged that whilst technically feasible, practical examples to date are few.

The availability of stabilised polymers and the potential flexibility in sterilization dose should enable many of the problems of material compatibility to be addressed. However from a radiation plant operator’s perspective gamma plants are generally not very flexible. They are at their most efficient when operating to deliver an absorbed dose to large volumes of consistent product. They are at their least efficient when dealing with small quantities of product requiring widely differing doses and of widely differing product densities. The likely changes in medical device manufacturers’ requirements as they take advantage of product specific dose setting approaches will generate new demands on commercial gamma radiation plant operators. In contrast however, the current generation of electron beam plants by the nature of their operation and control systems are able to give specific doses on a product–by–product basis as they pass through the machine.

In the context of product design it must be remembered that not only must the minimum dose required to achieve sterilization be recognised, but that there will always be a range of dose above this figure experienced by products being subjected to a given irradiation cycle (see Fig 1). This is a characteristic of product presentation, density, and plant design. For gamma plants processing medical devices the maximum to minimum dose ratio will typically be in the order of 1.2:1.75. The implications of this mean that for a required minimum dose of 25 kGy a maximum of 30 – 43 kGy could be experienced. In practice the key parameter determining dose spread will be product density.

When considering electron beam processing even wider dose ranges may need to be contemplated. Product design and presentation, particularly orientation during processing, can have a major influence on maximum to minimum dose range. In practice ratios of 3:1 have been encountered – yielding maximum doses of 60 – 80 kGy. With adequate
thought given to product packaging and presentation this ratio can be controlled to around 1.5 – 1.7:1. In optimised environments where effectively the unit pack is processed the ratio can be even lower. Note however that determining the location of maximum dose and accurately quantifying dose distribution in electron beamed product is a complex and sophisticated activity.

Clearly the potential differences of these magnitudes need to be recognised when assessing product performance after radiation sterilization, no matter which technology is employed. The designer should therefore take as a starting point a minimum sterilization dose based on the dose setting studies described in ISO 11137 and a maximum dose derived from an understanding of the radiation plant on which the product will be processed. To this range the requirement for a safety margin should be considered and also the possible requirement for re-sterilization. Out of this process a maximum dose against which a product should be qualified can be determined.

**The validation of sterilization**

The two international standards referenced above provide guidance on the development, validation and routine control of sterilization processes under discussion. ISO 11137 sterilization of health care products – radiation in parts 1,2 and 3 outlines the requirements as they apply to gamma, electron beam and X-ray sterilization processes, whilst in parts 1 and 2 of ISO 11135 sterilization of healthcare products – Ethylene Oxide, outlines the requirements and guidance applicable to Ethylene Oxide sterilization systems.

ISO 11137 for radiation sterilization offers no guidance on the requirements to validate product performance, or on the interaction of materials and radiation, (AAMI TIR 17 1997 does address this area and provides a simple look-up table similar to that in Fig 3 to obtain a preliminary insight). It does require that a maximum acceptable dose for the product is determined and that evidence is obtained to demonstrate that the product will meet acceptance criteria throughout its specified shelf life. This ISO standard does provide detailed guidance on the establishment of sterilization dose; it offers a number of approaches based on establishing the radiation resistance of bioburden as it occurs on the product, or based on establishing the relationship of the radiation resistance of the bioburden to that of a reference microbial population. The microbiology involved is sophisticated and extensive but it does offer ways in which a meaningful sterilization dose can be established, upon which a subsequent product performance qualification programme can be based.

ISO 11135 for Ethylene Oxide sterilization does not address the effects of Ethylene Oxide on the wide variety of materials used in medical device manufacture, but it does require an assessment of the effects of Ethylene Oxide on the finished product. In general terms it requires that products meet defined requirements for safety, quality and performance following the application of a defined sterilization process. In particular it refers to the requirements for biological safety and Ethylene Oxide residuals that can be found in ISO 10993. The standard offers two approaches to qualifying the Ethylene Oxide sterilization cycle (methods A and B). Method B is generally considered to be the most frequently used and is essentially an overkill approach that results in delivery of a 12 log reduction in the population of a control biological indicator made from bacterial spores. It is from this cycle that evaluation of post sterilization product performance and Ethylene Oxide residual levels, should be determined.

**Units**

The SI unit for absorbed dose or the energy dissipated per mass of material is the gray (Gy).

- One gray = 1 joule per kilogram
- The historic unit of absorbed dose, the rad, is related to the Gy as follows:
  - 1 Gy = 100 rads
  - 25 kGy = 2.5 Mrads

The energy of accelerated electrons is expressed in electron volts (eV). This is the energy required to accelerate electrons through a potential of 1 volt.

- 1 eV = 1.602 x10-19 joules (1.602 x 10-12 ergs)
- 1 MeV = 1.602 x10-13 joules (1.602 x 10-6 ergs)

(1 joule = 1 x 107 ergs)

The unit of radioactivity used to describe a gamma plant is normally the curie (Ci), however the correct SI unit is the bequerel (Bq).

- 1 Curie = 3.7 x 1010 becquerels
- 1 becquerel = 1 atomic disintegration per second
- 1 MegaCurie (MCi) = 106 Curies = 3.7 x 1016 becquerels
Glossary

- **Phenolic**
  A resin (plant secretion) which possesses the ability to become permanently hard and rigid when heated.

- **Photons**
  An elementary particle; one that is not comprised of other particles.

- **Polymer**
  A group of natural or synthetic molecules.

- **Stearates**
  A salt (or ester) produced from stearic acid.

- **Thermosetting**
  The process of hardening polymers through the introduction of heat.

- **Oxidation**
  The combining of oxygen with other compounds and elements.

- **Qualification**
  The process of checking the performance of electrical equipment.

- **Alkylating**
  The process of breaking down DNA.

- **Cation**
  This is a positively charged ion.

- **Chain scission**
  The process of breaking a molecular bond by a chemical reaction.

- **Cross-linking**
  The process of joining together polymers to become stronger and therefore more resistant to degradation.

- **Electrons**
  Negatively charged particles which always come in pairs.

- **Ester**
  A chemical compound produced by the reaction of acid and alcohol without the presence of water.

- **Epoxies**
  Thermosetting polymers formed from the reaction of resin with a hardened compound.

- **Free radicals**
  Are molecules with at least one unpaired electron which causes the molecule to be highly unstable and therefore reactive.

- **Ion**
  A molecule which contains electrons which are not equal to the number of protons. This results in the molecule having a positive or negative charge.

- **Ionisation**
  Any type of radiation with sufficient energy to remove electrons from their orbit in atoms or molecules. This form of energy is sufficient to destroy molecular bonds without disrupting atomic structure.

- **Isotopes**
  A variable of an atom with the same chemical element but contains a different number of neutrons.

- **MeV**
  Refers to a unit of measurement of energy - a million electron volts.

- **Oxidation**
  The combining of oxygen with other compounds and elements.

- **Qualification**
  The process of checking the performance of electrical equipment.
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