Minireview

Confirmation of the Sterility of Medical Devices and Changes in the Characteristics of Polymers upon Sterilization

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STERILITY

Medical devices may be sold and used in two different conditions in terms of their bioburden (that is, the number of viable microorganisms present on the device): sterile or nonsterile. If they are intended to be used in the sterile condition, the actual act of sterilization may be either performed by the manufacturer or by the user (though the latter is commonly the case only for reusable devices and instruments, such as surgical instruments at a health care facility). If the manufacturer has sterilized the instruments, then this is specified in the Device Master File (and in product related literature), along with the means for having achieved a suitable degree of sterilization and specification of a program to assure proper performance of the process.

The sterility assurance level (SAL) is the statistical probability that a device is not sterile even after going through an established sterilization process. Residual microorganisms are usually measured as colony forming units (CFUs), with the amount of sterilization required to reduce the number of CFUs by an order of magnitude for a specific device being termed the D_{10} (the sterilization period or radiation dose or period to produce a tenfold reduction in bioburden). D_{10} here is both a concentration (or, for radiation, a power level) and the time interval the device (or material) is exposed to that dose (Prince and Rubino, 1984).

Sterility tests

The following procedures are applicable for determining whether a pharmacopeial article purporting to

be sterile complies with the requirements set forth in the individual monograph with respect to the test for sterility. In view of the possibility that positive results may be due to faulty aseptic techniques or environmental contamination during testing, provisions are included under the interpretation of sterility test results for two stages of testing.

Alternative procedures may be employed to demonstrate that an article is sterile, provided the results obtained are equivalent or greater reliability. When a difference appears or dispute occurs, evidence of microbial contamination must be confirmed by the validated procedure. The result so obtained is conclusive of the failure of the article to meet the requirements of the test. Similarly, failure to demonstrate microbial contamination by the validated procedure is evidence that the article meets the requirements of the test.

The following considerations apply to sterilized devices manufactured in lots, each consisting of a number of units. Special considerations apply to sterile devices manufactured in small lots or in individual units where the destructive nature of the sterility test renders such conventional sterility tests impracticable. For these articles, validated modifications to the sterility tests must be made.

For articles of such size and shape as to permit complete immersion in not more than 1000 ml of culture medium, test the intact article, using the validated media, and incubate for a validated incubation period.

For devices having hollow tubes, such as transfusion or infusion assemblies, or where the size of an item makes immersion impracticable and where only the fluid pathway must be sterile, flush each lumen of 20 units with a sufficient quantity of fluid thioglycollate medium and each lumen of the same 20 units with a sufficient quantity of soybean-casein digest (SCD) medium to yield a recovery of not less than 15 ml of

each medium. Then, incubate not less than 100 ml of each of the two media as directed under the validated procedure. For devices in which the lumen is so small that the fluid thioglycollate medium will not pass through, substitute an alternative thioglycollate medium for fluid thioglycollate medium, but incubate the validated medium anaerobically.

Where the entire intact article, because of its size and shape, cannot be tested for sterility by immersion in not more than 1000 ml of culture medium, expose that part of the article most difficult to sterilize and test that part, or where possible, remove two or more parts each from the innermost part of the article. Aseptically transfer these article parts to the specified number of vessels of validated media in a volume of not more than 1000 ml and incubate for the validated incubation period.

Where the presence of the test specimen in the medium interferes with the test because of bacteriostatic or fungistatic action, rinse the article thoroughly with a minimal amount of rinse fluid. Recover the rinse fluid, and test as directed for devices under validated test procedures using membrane filtration.

Sterile empty or prefilled syringes

Sterility testing of prefilled syringes is performed by employing the same techniques used in testing sterile products in vials or ampuls. The direct transfer technique may be employed if the bacteriostasis and fungistasis determination has indicated no adverse activity under the test conditions. Where appropriate, the membrane filtration procedure may be employed. For prefilled syringes containing a sterile needle, flush the contained produce through the lumen. For syringes packaged with a separate needle, aseptically attach the needle, and expel the product into the validated media.

Special attention should be paid toward demonstrating that the outer area of the attached needle (that part which will enter the patient's tissues) is sterile. For empty sterile syringes, take up sterile medium or diluent into the barrel through the needle if attached, or, if not attached, through a sterile needle attached for the purpose of the test, and then express the contents into the validated media.

Devices that are purported to contain sterile pathways may be tested for sterility by the membrane filtration technique as follows. Aseptically pass a sufficient volume of test fluid through each of not less than 20 devices so that not less than 100 ml is recovered from each device. Collect the fluids in aseptic containers, and filter the entire volume collected through membrane filter funnel(s).

Where the devices are large and lot sizes are small,

test a validated number of units.

INTERPRETATION OF STERILITY TEST RESULTS

At the prescribed intervals during and at the conclusion of the incubation period, examine the contents of all of the vessels for evidence of microbial growth, such as the development of turbidity and/or surface growth. If no growth is observed, the article tested meets the requirements of the test for sterility.

When microbial growth is found, but a review of the sterility testing facility of the monitoring, materials used, testing procedure, and negative controls indicates that inadequate or faulty aseptic technique was used in the test itself, the first stage should be declared invalid and may be repeated.

If microbial growth is observed and there is no evidence invalidating the first stage of the test, proceed to the second stage.

The minimal number of specimens selected should be double the number tested in the first stage. The minimal volumes tested from each specimen and the media and incubation periods are the same as those indicated for the first stage. If no microbial growth is found, the article tested meets the requirements of the test for sterility. If, however, it can be demonstrated that the second stage was invalid because of faulty or inadequate aseptic technique in the performance of the test, the second stage may be repeated. Sterility testing can be used as part of a quality assurance program for a production lot or batch or as one of the quality control criteria for release of such a lot or batch.

STERILIZATION

There are three major means employed for sterilizing medical instruments (Nair, 1995), each of which has advantages and drawbacks.

Heat sterilization

Heat (steam) is effective and inexpensive but can only be used for medical devices of a relatively small volume and materials, which are not degraded or deformed by it. Accordingly, it is typically useful only for smaller metal devices and cannot always be successfully applied to plastics and such. It is most commonly used for reusable steel instruments and glassware.

Steam sterilization by autoclaving has traditionally been the most widely used method for medical instruments. Today, prevacuum, high-temperature steam sterilization is considered to be the safest and most practical means of sterilizing the majority of surgical instruments, surgical dressings, fluids, fabrics, and

other absorbent materials. The process should be used with caution while sterilizing polymers and composites as both heat and steam can drastically alter their properties. The main deleterious effect from steam sterilization of polymeric materials occurs when hydrolysis of the polymer takes place leading to undesirable contaminants. Under prolonged steam autoclaving, a few ppb of 4,4'-methylene dianiline (MDA) or less has been detected (Shintani, 1989, 1991, 1992 and 1995) in the aqueous extract of methyl diisocyanate (MDI)-based polyurethane which was attributed to the hydrolysis of the polymer. Researchers observed the release of contaminating substances, whose structure was not elucidated, when polyvinyl chloride (PVC)-containing aqueous suspensions were autoclaved (Habermann and Waitzova, 1985). Repeated autoclaving of PVC intended for biomedical applications was found to increase the mechanical properties of PVC of both covered and uncovered PVC samples. The change in the mechanical properties was attributed to the rearrangements in the PVC macromolecular chains giving rise to branches of varied lengths. Repeated autoclaving of uncovered PVC samples for 150 minutes was seen to induce higher leaching of the plasticizer such as phthalate esters (Shintani, 1985 and 2000).

Seemingly stable polymers can also undergo changes in the surface morphology, especially if the glass transition temperature of the polymer is exceeded during autoclaving. This may cause changes in biocompatibility or blood contacting properties of the material. Oligomers or other inadvertent contaminants introduced subsequent to steam sterilization may have significant effect on the biocompatibility and the performance of the polymers. A scanning electron microscopy (SEM) study of different types of arterial prostheses made from Dacron found that all the prostheses were coated with a layer of oligomers on autoclaving. The Cooley knitted Dacron grafts show the maximal amount of oligomer crystals, which was progressively increased with each subsequent successive resterilization procedure. This coating of oligomers also resulted in increased hemolysis. Berger and Sauvage (1981) also noted late fiber deterioration in 493 Dacron arterial prostheses, which had been implanted for 3-15 years. One of the contributing factors to this deterioration was believed to be autoclaving.

Commercial poly(ethyleneterephthalate) (PET) is known to contain cyclic and linear oligomers as natural impurities, which are formed as a byproduct during polymerization and texturing (Shintani, 2000). Cyclic trimer is a major oligomer component, and the content of cyclic trimer is actually a criterion for the quality of PET. The study of the effect of steam sterilization on

PET has shown that oligomers and, in particular, the cyclic trimer increases on PET with repeated autoclaving. Studies (Nair, 1995) of the PET materials indicated increased values of heat of fusion and percent crystallinity, which suggested reorganization of the amorphous phase. Generation of new crystalline regions was ruled out as there was no increase in the intensity of the infrared peak of 973 cm^{-1} which indicates crystallinity. Chain scission of amorphous regions, resulting in the formation of new amorphous regions, was, therefore, believed to be the reason for the increased values of crystallinity. The changes in the molecular weights of Mn (number average of molecular weight) and Mw (weight average of molecular weight) suggested that though degradation would take place when autoclaving for 15 min, subsequent sterilization of 30 min results in solid-state polymerization or cyclization reactions. These cyclization reactions were responsible for the formation of fresh cyclic trimer molecules which could migrate to the surface. As moisture and air enhance oxidation and hydrolysis reactions, subsequent autoclaving for 60 min would result in more degradation of amorphous regions. The increased temperature could also facilitate the easy migration of the cyclic trimer to the surface.

Chemical sterilization

Chemical sterilants include ethylene oxide, glutaraldehyde, and formaldehyde. These can all be used for most devices that do not have any readily chemically reactive (degradable) components. Ethylene oxide (ETO) is the most widely used, but is a mutagen and carcinogen, and is neurotoxic and causes hypersensitivity responses in some individuals (Golberg, 1986).

Ethylene oxide is an effective bactericide active at temperatures as low as 60°C . As ethylene oxide can easily diffuse into materials to be sterilized, it is possible to sterilize heat- or moisture-sensitive materials even through sealed plastic wrapping. One of the disadvantages of this method for polymeric materials is that they retain varying amounts of ethylene oxide (Shintani, 1979 and 1981). Residual ethylene oxide in sterilized plastic tubing has been reported to cause hemolysis of blood in heart-lung surgery (Golberg, 1986). Adverse hemolytic reactions were also caused when blood was exposed to plastics that retained significant quantities of residual ethylene oxide (Golberg, 1986). Ethylene oxide also possesses toxic properties and is a strong alkylating agent (Golberg, 1986; Shintani, 1998). As the ethylene oxide consists of two carbon atoms and an oxygen atom linked together in an unstable three-membered ring, it can react with various functional groups (Shintani, 1998). These functional groups are the sulfhydryl, amino,

carboxyl, and hydroxyl groups of proteins and nucleic acids. The lethal effect of the ethylene oxide arises from its alkylating effect on these susceptible molecules. However, due to the reactivity of the gas with such functional groups, this type of sterilization should only be carried out at room temperature with materials such as polyurethanes, polyesters, and other polymers with potentially reactive groups. Several of the composite polymeric materials used these days, such as albuminated Dacron grafts or heparinized grafts, are liable to lose the beneficial effect extended by the albumin coating or heparin coating by subjecting these materials to ethylene oxide sterilization. Ethylene oxide sterilization of heparinized polymers reduces their nonthrombogenic properties (Bruck, 1971), while Guidoin et al. (1985) reported that ethylene oxide sterilized albuminated polyester grafts were associated with a slower rate of healing when implanted in comparison to a similar graft sterilized by irradiation. Though retention of residual ethylene oxide is believed to be the cause for this slower rate of healing, it is likely that the alkylating action of ethylene oxide could denature the albuminated surface forming products that delay the healing process.

Most manufacturers of ethylene oxide sterilizer equipment routinely recommend at least five and preferably 14 days of aeration for ethylene oxide sterilized plastic tubing (Shintani, 1982). However, the time for aeration is dependent on the material sterilized (Shintani, 1982). Highly porous materials such as cellulose, paper, and natural rubber show very high values of ethylene oxide solubility and low diffusion coefficients (Shintani, 1979 and 1982). A study (Vink and Pleijsier, 1986) of residual ethylene oxide content in different polymers revealed that for a number of hydrophilic materials, the residual content was well above the levels which are currently considered to be safe even after aeration for 14 days. For a reliable determination of aeration times after ethylene oxide sterilization of medical devices, the type of the material from which the device is made and, in particular, its thickness as well as chemical characteristics should be considered.

Another point worth noting on the subject of deaeration is the procedure for estimation of residual ethylene oxide after sterilization. In a project involving the interlaboratory comparisons of the procedures for the estimation of ethylene oxide, it was observed (Marlow et al. 1987) that the average estimated total coefficient ranged from 8 to 22% even when following the same standard procedure of residual ethylene oxide estimation, emphasizing the need for standard and reliable procedures for estimating the residual ethylene oxide content. The concern with all of the chemical sterilants is residuals left on and (permeated) in

devices. If any chemical sterilants are used, residual levels must be determined and kept below (or brought below by allowing the devices to vent) certain established limits.

Radiation sterilization

An alternative to ethylene oxide or steam heat sterilization is the use of ionizing radiation to sterilize medical devices. The advantages of radiation sterilization are high efficiency, negligible thermal effect, and the fact that articles may be packaged and sealed prior to sterilization. The disadvantages are that some plastics are degraded (Shintani, 2000), and certain drugs become less active due to radioinduced chemical changes. Additionally, if a ^{60}Co source is used, the sterilization time is long.

Irradiation of high polymers results in either cross-linking or degradation depending on the chemical nature of the system. Though the accepted dose for radiation sterilization is 25 kGy, it is known that certain species require up to 60 KGy for complete destruction. This must be validated to define the sterilization dose setting. The effects of irradiation of increased doses or multiple sterilization treatments are assumed to be cumulative. Polymers which tend to cross-link show a steady increase in their molecular weights with increasing doses and with the formation of branches until a three-dimensional network is formed, while polymers that undergo degradation exhibit chain scission, the molecular weight steadily decreases with increasing radiation doses and mechanical properties of the system simultaneously undergo changes (Shintani, 1990, 1991 and 1995). These properties include tensile strength, elastic modulus, shear strength, elongation, and occasionally, color changes (Shintani, 1990, 1991 and 1995).

Though cross-linking and chain scission processes may occur simultaneously, usually one or the other predominates. In the case of vinyl polymers, if the carbon atoms of the main chain carry at least one hydrogen atom, the polymer tends to cross-link, whereas if the carbon atoms are fully substituted, the polymer tends to degrade. There is a correlation between cross-linking tendency and the heat of polymerization, showing that polymers which exhibits a high heat of polymerization (above approximately 16 kcal/mole) cross-link, while polymers that exhibit a low heat of polymerization (less than 16 kcal/mole) degrade. Irradiation of polymers can also result in gas evolution double bond formation, and the production of trapped free radicals. The presence of impurities can accelerate the degradation process with the possibility of producing irritants or other undesirable products. Free radicals produced in polymers by irradiation in air convert to peroxidic radicals. Additionally, the irradiation

process may result in discoloration of polymeric products.

While general effects of irradiation on polymeric materials have been extensively studied (Chapiro, 1962), relatively small changes in physicochemical, mechanical, and biological properties may be tolerable in the short term, whereas similar changes may lead to catastrophic failures in long-term application. Besides, seemingly unchanged materials may also suffer some minor damages which affect their biological and mechanical performance. In one case, the stability of cellulosic polymers was recognized up to 200 kGy, however in another case, the regenerated cellulose membranes were not always maintained characteristics with radiation sterilization. Rose et al. (1984) have observed that the wear of polyethylene exposed to γ irradiation increased with dosage and contact stress, becoming measurable in many cases only after a critical dose or stress was exceeded. The most significant effect noted was the pressure dependence of the wear rate. The increase in wear rate appeared to be a combination of chain scission and oxidation suggesting that the radiation should be carried out in an inert atmosphere.

Study of the effects of aging of γ radiation-sterilized isotactic polypropylene revealed that though both cross-linking and degradation occur simultaneously during irradiation and postirradiation, branching takes place during aging (Shintani, 1990, 1991 and 1995). A dose of 25 KGy was sufficient to introduce changes in crystallinity. These changes were attributed to the semicrystalline nature of the polymer and were observed to be different for the covered and uncovered samples. Additionally, the transitions between short- and long-range order and short- and long-duration stiffness in both covered and uncovered samples were affected by the formation of branches in the backbone of the polymer. A higher degree of branching was observed in covered samples resulting in greater long-duration stiffness in the transition between short- and long-duration stiffness. The higher degree of branching in the covered samples was attributed to the high diffusion of energized oxygen into the polymer matrix when compared to the uncovered samples.

PET, used extensively in biomedical applications, has been believed to withstand radiation sterilization without significant degradation. However, a study of PET fibers revealed that a single dose of 25 KGy was sufficient to induce chemical changes, which were reflected in the changes of crystallinity and breaking load of the fibers (Shintani, 2000). These changes were attributed to the degradation of PET in the amorphous regions and the recombination of degraded aliphatic segments. Baquey et al. (1987) report on the

increased stability of Dacron or PET fabrics coated with albumin during irradiation, but the results of the investigation also indicate a leakage of albumin with irradiation. The amount of albumin released was found to be dependent upon the nature of fabric used. The migration of chicken embryonic cells was also observed to be decreased for the irradiated fabrics.

Another group of polymers used extensively in biomedical applications is the polyurethanes. The γ irradiation of polyurethane based on 4,4'-diphenyl methane diisocyanate (MDI) has been reported to produce the carcinogen of 4,4'-methylene dianiline (MDA) with simultaneous detection of polyurethane oligomers (Shinani, 1989, 1991, 1992, 1993, 1995 and 1996). The γ irradiation of poly (DL -lactide/glycolide)-type microspheres has been reported to result in decreased molecular weights with the degradation continuing on storage. An inadvertent effect is the change in the release pattern of the drug loaded in the microspheres. Higher molecular weight polyglycolide sutures which were initially more resistant to enzymatic degradation become more prone to enzymatic attack as a consequence of the altered physical and chemical structure obtained from γ irradiation. Melberg et al. (1988) also report that the irradiation of PVC catheters of an external insulin pump produced chemical transformation products and damaged the insulin solution.

Bacterial endotoxins were found to be unaffected by γ irradiation, and, hence, gloves and software sterilized by irradiation have been observed (Shumnes and Darby, 1984) to contain significant amounts of bacterial endotoxins. As another inadvertent effect, it was also observed that the endotoxin levels were increased when the bacterial counts were elevated, in some cases leading to contact dermatitis (Shumnes and Darby, 1984). The γ irradiation of intraocular lens, however, decreased the inflammatory reactions observed on implantation of ethylene oxide-sterilized lens. Ludwig et al. (1988) attributed this decreased response not only to less absorption of the toxic agent, but also to polymerization of any residual monomeric methylmethacrylate. The γ radiation or ultraviolet (UV) light are both used, with the former being very predominant on the industrial scale.

Radiation has significant advantages, but there is a significant capital investment involved, safety precautions must be vigorously enforced, and some polymers are degraded (though this usually translates only to being discolored) by the absorbed energy in a gamma field.

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