The medical device industry has undergone an impressive transformation over the last several years, resulting in new and innovative devices and solutions. As companies continue to innovate, they are finding that some of today’s most commonly used sterilization methods impose serious limitations in terms of efficacy, quality, or production processes of many of the newer device components (electronics), coatings (drug), or contents (drugs or biologics). Other novel approaches available on the market have the potential to overcome the constraints of legacy sterilization methods. This offers new opportunities for unimpeded innovation, increased efficacy, and a cost reduction in the overall production processes of many of the most promising medical device technologies.

Feeling The Heat: The Challenges Of Ethylene Oxide

Proper and thorough sterilization of medical devices is critical. As the rate of medical device innovation accelerates with novel designs, such as implantable electronic drug delivery and monitoring devices, drug-coated bioabsorbables, and biologics, today’s traditional sterilization methods are encountering major challenges. One of the most commonly used sterilization methods is exposure to ethylene oxide (EO) to kill microorganisms. Though other methods come with their own challenges, EO presents the greatest risk in terms of patient and worker safety and costs associated with risk mitigation requirements. Because of this, ISO 11135-1:2007 states, “It is important that patient safety is addressed by minimizing exposure to residual EO, ethylene chlorohydrin (ECH), and ethylene glycol (EG) during normal product use.”

ISO 10993-7:2008 further emphasizes, “It is important that the use of alternative materials and sterilization processes be considered during product design and development. EO is known to exhibit a number of biological effects. In the development of this part of ISO 10993, consideration was given to these effects, which include irritation, organ damage, mutagenicity and carcinogenicity in humans and animals, and reproductive effects in animals. Similar consideration was given to the harmful effects of ECH and EG.” It continues, “Moreover, when the choice for EO sterilization has been made, irrespective of the provisions of this part of ISO 10993, exposure to EO residues should be minimized.”
An FDA guidance issued in June 2016 encourages identification of sterilization residuals (e.g., ethylene oxide), and the agency has accepted EO residuals information based on the currently recognized version of ISO 10993-7. However, a commonly used rule of thumb in the medical device sterilization industry is “If it can be irradiated, it should be irradiated.” Gamma radiation, while good for dense, palletized materials, is moving out of favor due to geographic restrictions and cobalt 60 supply concerns. Improved technology and expanding capabilities for e-beam irradiation make it an appealing option; yet, it comes with a wide range of material compatibility issues, limitations on packaging configurations that enable thorough penetration of the e-beam, and generally poor geographical access.

The following three areas where EO presents its most serious challenges to medical device manufacturers:

1. Materials compatibility
   The innovation in today’s medical device industry is not limited to design. It also includes the use of new materials for medical device manufacturing, such as biosensors, bioborables, and electronics. These and others have the potential to improve usability and efficacy, and, in many cases, reduce the costs of manufacturing. Unfortunately, many promising newer materials are not able to withstand heat and humidity-inducing sterilization methods, such as EO. Also, any chemical reactions that might occur at higher temperatures and with humidity could create adverse chemical reactions that speed up degradation and corrosion of the device itself. In situations where a drug or biologic is present during sterilization, such as with prefilled syringes or drug-coated stents, the drug is at risk. Heat can affect the active pharmaceutical ingredient (API) or biologic and impact the stability or pH, which threatens its overall functionality. If sterilization isn’t considered early in the new product R&D process, where novel designs and materials are being considered, sterilization compatibility issues can add months or years to the new product launch timeline.

2. Patient and employee safety
   The limitations outlined in the ISO 10993-07 standard set guidelines on how much EO can be left on medical devices, which varies depending on the intended use of the device. There has been particular attention to this issue in France, where 85 percent of single-use sterile devices used in neonatal wards are sterilized using EO. Because of this, stricter regulations are in the ISO proposal process to further discourage the use of EO by requiring that manufacturers provide documentation of the rationale for choosing EO for sterilization (as opposed to an alternate method) and quantifying and limiting aggregate (multiple products) potential exposure to special patient populations, such as neonates. Due to the difficulty of making these calculations (with potentially multiple products by the manufacturer being used on a single patient), most would prefer a “risk versus benefits” approach. This enables the continued use of EO sterilization processes on critical life-saving devices for which there is no other commercially feasible sterilization method.

   The other side of this issue is the danger of EO to the health and safety of the employees in the manufacturing facility using it for sterilization. In 1994, the International Agency for Research on Cancer (IARC) reclassified EO as a Group 1 agent, which means it is carcinogenic to humans. This change prompted revision of ISO standards surrounding the use of EO. Recently, the Centers for Disease Control and Prevention (CDC) classified EO as a category 1B carcinogenic and mutagenic substance. OSHA has strict regulations around exposure to EO, which medical device manufacturers have to adhere to when using it in their facilities. For example, EO chambers must use blast-proof containment facilities, and employees are required to take extensive health and safety precautions. While protective measures are standard operating procedures whenever a process/material presents danger to employees, these precautions can become costly. Few manufacturers that do not already have experience with the risk and cost of on-site EO processing are willing to take on the regulatory and safety hurdles it brings.

3. Manufacturing efficiency
   While the sterilization process time itself varies greatly in accordance with the product being sterilized, every EO process requires pre-sterilization conditioning and post-processing aeration periods. This can add significant time to the overall process, ranging from several days to weeks. Because of the risks and costs associated with on-site EO sterilization, roughly 75 percent of medical devices are sent out to contract sterilization service companies. Depending on the location of the sterilization facility and the distribution logistics of the product itself, this can also add significant transportation time and inventory requirements that will impact the cost of goods sold (COGS). On-site EO operations bring the associated costs of required risk mitigation. Issues such as these are driving the sterilization industry and applicable regulators to adopt to the wider use and acceptance of other novel sterilization methods.
A Viable Alternative

Three categories of sterilization are recognized by the FDA:

- **Established Category A** — methods with a long history of safe and effective use as demonstrated through multiple sources of information such as ample literature, clearances of 510(k)s or approvals of premarket approval (PMA) applications, and satisfactory QS inspections. Examples of this category are dry heat and EO.

- **Established Category B** — “other established methods for which there are no FDA-recognized dedicated consensus standards, but for which published information on development, validation, and routine control is available.” Examples include hydrogen peroxide, ozone, and flexible bag systems.

- **Novel** — methods the "FDA has not reviewed and determined to be adequate to effectively sterilize the device for its intended use.” Examples of novel sterilization methods include high-intensity light/pulse light, microwave radiation, sound waves, ultraviolet light, and vaporized peracetic acid (VPA).

If a manufacturer wants to switch to one of these novel methods, the change requires the product and sterilization process to be resubmitted for 510(k) clearance. However, it is still possible these methods could provide safer, more cost-effective ways to sterilize. Where it makes the most sense to consider these alternative methods is if a company is designing a new product, going through changes that will need to be submitted for FDA 510(k) clearance anyway, or is planning new manufacturing processes/sites. In these cases, a novel method, such as VPA, can be a viable alternative that provides several benefits. For example, VPA can:

- **improve material compatibility and enable integration of less costly designs and materials by eliminating the use of heat for sterilization, which can damage newer, heat-sensitive materials, such as sensors and biologics.** Instead of using heat, a proprietary peracetic acid (PAA) biocide is injected directly into the on-site manufacturing process, reducing transportation and inventory costs associated with contract EO sterilization.

Additionally, while other newer sterilization methods, such as gas plasma and vaporized hydrogen peroxide (VHP), have proven efficacy and utility for various applications, they do not offer commercial feasibility in the industrial sterilization space in terms of their throughput capabilities.

The VPA process is noncarcinogenic, nonexplosive/flammable, requires no external ventilation, and breaks down to H₂O, CO₂, and O₃ within hours. With chamber capacities of up to eight pallets and short processing times, VPA is now a commercially feasible alternative that may help manufacturers further reduce the risk in the risk versus benefit decision tree. VPA can also be used as a valuable tool for bioburden reduction for preterm sterilization, eliminating pre-sterilization bioburden fluctuation, and allowing lower terminal sterilization exposure to whichever method is being used.

Overall, medical device manufacturers should consider novel sterilization methods as the industry continues to experience rapid growth of life-saving device designs.

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