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Industrial Ethylene Oxide Sterilization of Medical Devices: What Hospitals Need to Know About Re-Sterilization of Single Use Devices.

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NASP, under a single roof, is a fully integrated medical device manufacturing facility. NASP clients are in themselves medical device manufacturers. Some may outsource a line of products to NASP while others may depend entirely on NASP to produce their product. As result, NASP is involved with every aspect of medical device manufacturing from the device design phase, to planning the assembly process, to the development and validation of packaging and sterilization processes, device evaluation after accelerated aging, and investigation of product complaints. Our business is exclusively dedicated to producing new single use devices and as a result, we have an extensive knowledge of the attributes of these devices and of what is involved in bringing a disposable device to market.

Preamble

This presentation will discuss in general terms the worldwide trend of resterilization of used single use devices (SUDs). The scope of this presentation is not to lend support to this practice, but rather to advise practitioners of the incredible health risks posed by reusing a single use device. From a medical device manufacturing point of view, we feel it is impossible for a healthcare practitioner to examine a used device and understand enough about it to safely design a reprocessing program whose probability of surviving

organism per item meets or exceeds the industry standard of one in a million. The financial savings in attempting to reuse a disposable instrument is overshadowed by the risk of losing infection control.

Origin of Single Use Devices

Before the 1970's, most medical devices were made of durable materials such as glass, stainless steel or rubber. These materials were deliberately selected during the design of the device because the device engineering foresaw the reuse of the device as a normal part of its life cycle. The US Food & Drug Administration attributes the advent of disposable medical devices (SUDs) to market demand (in response to infection control efforts and faster device availability), the development of new plastics, and the rising popularity of ethylene oxide sterilization.

Single use/disposable devices allowed healthcare providers to economically maintain a constant inventory of sterile devices, ready to use at a moment's notice. Since these devices were terminally sterilized by the manufacturer, infection control was an automatic quality attribute. Hospitals had less chance of transmitting a patient-to-patient infection and could reduce its labor costs since devices no longer had to be reprocessed in-house.

Reuse of Single Use Devices

Today, some thirty years after the rise of SUDs, hospitals in almost every country in the world, actively pursue the reuse of used SUDs. It appears that the main reason why hospitals will clean and resterilized a used SUD is economics and not patient benefit. However, some argue that reusing SUDs translates into better management of the financial resources of the hospital and this, in turn, is a patient benefit. In today's world, every country has an argument in favor of reusing single use devices. Industrialized countries may cite the rising cost of healthcare due to declining public heath and aging population, and the cost of managing medical waste. Underdeveloped countries cite over population and the lack of funds to purchase sufficient quantities of both simple and complex devices.

The practice of saving, cleaning, repackaging and resterilizing SUDs started to develop when healthcare practitioners saw the similarity between devices designated as 'single use' and the previous generation of reusable devices. An SUD cost less than its reusable counterpart did, but in many aspects looked and performed the same. Therefore reusing an SUD could significantly reduce costs in an industrialized nation. In developing nations, reprocessing used SUDs is often the only way of maintaining an adequate supply.

The issues of reprocessing SUDs are multifaceted. The healthcare workers that must handle and store the used devices are at risk for sharps injury and microbial contamination from pathogens. Then there are the risks to the patients. The program to clean, recondition, repackage and resterilized the devices cannot achieve maximum

effectiveness if it lacks the knowledge and experience that only the original manufacturer possesses. In addition, most importantly, the variability of the contamination of a batch of used SUDs, along with staff and financial constraints imposed on the healthcare practitioner, render impossible the true validation of these critical processes. Resterilization of SUDs, to a predictable assurance level, is unattainable.

A search on the Internet yields an abundance of information regarding the effects suffered by the improper reprocessing of used disposable devices. The Association for the Advancement of Medical Devices (AAMI) and European Confederation of Medical Device Manufacturers (EUCOMED)[1] have both addressed this concern. The US FDA has determined that any US entity that reprocesses a disposable device in essence becomes the legal manufacturer of the reprocessed device and as such, is subject to all current Good Manufacturing Procedures (cGMPs).

Review of Manufacturing an SUD

When an inventor approaches a contract manufacturer such as NASP, he often has only the engineering drawings for a new device. The "client" in this case may consist of a business entity (Corporation) and a small team of device, medical and financial experts. In other words, some medical device companies do not have any in-house manufacturing capability. They rely on a contract manufacturer such as NASP. Often we are the ones to develop validated processes on behalf of the client. The client provides us with all the details regarding the functioning of the device and, under the assumption that the device must perform one time after which it will be disposed, we develop the process and product specifications. Our selection of components is based on which materials will provide the required performance characteristics while maintinaing a low cost. Items such as tubing, connectors, blood bags, valves, syringes, filters and packaging are selected based on client listed performance specifications. Our experience in manufacturing a wide selection of Class 1, 2 and 3 devices is such that we know we can trust certain materials to bond together correctly and maintain all quality attributes throughout the packaging and sterilization processes. If the devices are stored correctly and the sterile barrier packaging is not compromised, our devices can withstand a five-year shelf life storage prior to use.

The devices manufactured by NASP are all assembled in a Class 100,000 clean room environment that is maintained according to a validated cleaning procedure. We follow all U.S. cGMPs, as well as internationally recognized standards for packaging[2] and sterilization[3]. From the moment we begin producing a new SUD, all these regulatory documents prescribe validation and testing to certify the necessary quality attributes. Depending on the use of the device, biocompatibility of all materials is certified. Biocompatibility is determined on finished devices to factor in eventual impact of the manufacturing/packaging/sterilization processes. After a suitable package design is established, validation of all sealing parameters takes place under a specific protocol. Shelf life studies are conducted on sample groups sealed at minimum and maximum settings. Ship test/distribution studies are also performed on samples to determine

whether the device and its packaging can maintain all critical properties when shipped under harsh conditions throughout the world.

By the time that NASP begins shipping a new SUD to market, volumes of data and experience exist attesting to the daily maintenance of total control over the manufacturing process, the origin and validity of all materials, and the exact assurance level achieved by each validated process. The only exceptional testing we perform is on one set of product samples that are sterilized through two consecutive processes. Since a sterilization process (irradiation or ethylene oxide) may fail due to mechanical malfunction or human error, having data on file supporting product functionality and package integrity following a second resterilization is crucial to maintaining a production schedule. Other than double sterilization compatibility, NASP does not venture into investigating how a finished device may react if ever used and then reprocessed. We can have years of manufacturing data for thousands of lots released to market, annual revalidations of the clean room cleaning process, packaging and sterilization processes, accelerated aging and ship test studies, and yet we are unable to even speculate on whether any of our devices can be safely resterilized and reused. Considering that nobody, not even the 'owner' of the device design, knows the materials and assembly process better than NASP, we consider any attempt to resterilized an SUD to be a speculative process that ignores the benefit of the patient. In order to reprocess a used SUD one must do the impossible – duplicate in a hospital the exact process output achieved by the original device manufacturer.

Pitfalls of Reusing Single Use Devices

In many countries, including the USA, an entire industry has formed around the profitability of retrieving used SUDs from hospitals, reprocessing them and selling them back to the hospitals at a reduced cost. So far, the US FDA has published guidance and regulatory requirements for these firms to follow. However, hospitals, clinics and private practitioners throughout the world have also begun the unregulated in-house practice of reconditioning and reusing SUDs. Whether this reprocessing is performed by expert scientists in an official attempt to safely reduce healthcare costs, or attempted by persons untrained in microbiology or device engineering, original manufacturers such as NASP feel that reprocessing can never be trusted and that any immediate cost savings is lost when we consider the long term adverse effects on public health. As I stated before, reuse of SUDs does not benefit the patient.

An article was published in the New York Times[4] in which the reuse of SUDs in China is attributed with causing Hepatitis B in 60% (over 600 million) of the Chinese population. In addition, it estimates that 150 million Chinese carry the often-fatal form of Hepatitis C. High rates of Hepatitis C have been found in Chinese children who were infected with used syringes that local doctors supposedly cleaned after each use. The article goes on to describe the phenomena of reprocessing used devices. Despite cleaning, soaking in disinfectants, and possibly even some form of sterilization process, the devices remain contaminated with viable pathogens that infect the next patient. This article reflects the extreme of the SUD reuse debate.

Going towards a more serious attempt of reprocessing used SUDs, i.e., hospitals in industrialized nations, much evidence points towards the same dangers that routinely occur. Articles point out the fact that some hospital administrators do not even know that the facility reuses SUDs.[5] Among the most common devices chosen for reprocessing and reuse are[6]:

Eye surgery items
Staplers
Suction devices
Laparoscopic products
Saw blades, drill bits and burrs
Cardiac and other catheters

For the reuse of these devices to even approach a level of acceptability, detailed procedures must be developed into processes whose output can be quantified (i.e., 10^{-6} SAL), verified, and documented. Such a program requires a staff with scientific expertise and knowledge of the manufacturing technique of the particular device.

Difficulty in Designing a Resterilization Process

First, one must know the original sterilization technology used. Medical devices designed for terminal sterilization by Gamma or Electron Beam irradiation methods, were never qualified for resterilization with ethylene oxide. The material compatibility is therefore unknown as are the final ethylene oxide and ethylene chlorohydrin residual levels. Adhesives and bonding agents may not be compatible with the heat and chemical effects that are present in ethylene oxide cycles.

Second, if a device has been designed and terminally sterilized with ethylene oxide, it does not imply compatibility with EO resterilization. When we build a device and validate a specific ethylene oxide process, we rate each evacuation and injection according to the physical tolerances of the device. Our experience in assisting the client in specifying the components and developing the assembly process allows us to fully understand the product sensitivity to vacuum depth and rate, injection rate, temperature and positive pressure. The data from our sterilization process development studies documents the product sensitivity to the selected EO gas concentration. The devices produced by NASP are almost all sterilized in-house by ethylene oxide. Our processes vary in as concentration from 500-750 mg/l and all operate at sub-atmospheric pressure. We first inject 100% ethylene oxide and then follow with a nitrogen addition. We have never tested or products with an ethylene oxide blend such as the EO/HCFC or EO/CO2 blends often used in hospitals. These blends, although non-flammable, require the process to go to a deep vacuum and then inject sterilant blend to a pressure that exceeds atmospheric pressure order to achieve a significant concentration. As a manufacturer, we have no data supporting the assumption that any of our devices can withstand neither the deep vacuum nor the higher pressure achieved in a hospital sterilizer.

The NASP Quality System requires each vendor to be qualified and each material purchased to be specified. We only purchase ethylene oxide gas that conforms to a certain specification for purity. Each lot of 100% EO gas is analyzed and certified before delivery. Ethylene oxide produced by different suppliers may have concentrations of different contaminants that react with the device and its biocompatibility. Such contaminants may even react chemically with some of the device surfaces. Unless you know the purity of the EO used to sterilize the device by the manufacturer, use of alternate gas suppliers may compromise the device and its performance. Not even NASP could change gas suppliers without a full chemical comparison of the two supplies and a documented conclusion that they are equal in effect.

A current NASP client is bringing to market a blood treatment system. The system uses an intravenous tube set and blood bag to remove a quantity of blood from the body, treat it, and re-transfuse it back into the patient. The initial biocompatibility study on this one device, following FDA G95-1 Guidelines / ISO 10993-1 Biocompatibility test Category: External Communicating Device, Circulating Blood.....Duration "B" required an investment of US$17,600 (biocompatibility, whole blood hemolysis, and long term hemolytic tests). If the design of this device is changed in any way: exposed to a new chemical (liquid disinfectant), if a different type of tubing is used (PVC vs. silicone), or if it is sterilized with a different technology, the biocompatibility must be reestablished.

Device Engineering Concerns

When we validate an EO sterilization process, we subject a set of samples to two consecutive sterilization processes. Then the samples are tested for packaging integrity and product functionality. This is to confirm that if necessary we can sterilize a batch of devices twice. The first processing may be interrupted due to power outages or mechanical failures. Our studies do not always generate data concerning resterilizing a device a third time. If a hospital has a device that is opened but not used, they do not have the qualification to reprocess the device in-house and use it again. In fact, as an industry consultant, I examined several cases in which a manufacturer determined that their devices no longer functioned properly after a third sterilization process. Many devices are coated in order to reduce device/blood interaction. While ethylene oxide is an excellent low temperature sterilant, it is a strong alkylating agent and does react with other chemicals. With repeated exposure to EO, device coatings and drug additives are broken down. Again, biocompatibility may change. Reprocessing often involves physically scrubbing the device in order to remove patient contamination. Scrubbing may score soft surfaces and allow microbes to embed - glues and bonding agents may be weakened - and connectors may loosen.

Engineering Changes to Device

Certain medical devices are so basic that they seem to be manufactured in the same way year after year. However even with the 'foundation' devices that never seem to change, NASP routinely receives client orders to change materials or component vendors, modify

assembly processes, use different components, etc…. This is never noted on the labeling. As part of our Design Control system, we perform and document all the necessary studies to prove that the change does not affect the performance of the device. Again, the hospital that purchases the device does not receive this information. Any system that the hospital believes can effectively clean and resterilized one of our devices has to be reevaluated. If he hospital is not aware of every single change in the device assembly process, they cannot perform such an evaluation. Reprocessors, unaware of these changes, cannot study and revalidate their cleaning/resterilization techniques to continue compatibility.

Opened in O.R. but not used

In the USA, the hospitals and the 'reprocessing' industry have identified medical devices that have been 'opened but not used' as a particularly easy class of devices to reprocess and reuse. The argument is that if the devices have never made contact with a patient, there are no pathogens. Once the unused device is placed back into a sterile barrier package and re-exposed to ethylene oxide, it can be reused.

To this we respond that since the hospital is not the manufacturer, they do not know how many times the new device was exposed to sterilization. Therefore, they do not know if the device can withstand another exposure. In addition, the device may have made contact with patient pathogens by contacting the infected gloves of the O.R. personnel. While I can document the NASP clean room and device bioburdens, the hospital may not have this same information about the O.R. during a given procedure. Unknown bioburden deposited on unused devices need identification before a sterilization process can be validated. Once opened, a device is 'used' whether or not it makes patient contact.

SUD Traceability is Lost with Packaging

One of the critical elements of the NASP Quality System is that it allows us to maintain full traceability of components, assembly processes, and devices. Our records are maintained for a minimum of five years. Our devices are manufactured for single use only. As long as the SUD claim is respected, the goal of traceability is maintained. At anytime, if a vendor notifies us of a defect in a part we purchased, or if we discover a defect in a manufacturing process, we can identify and quantify in a matter of minutes all the devices affected. Likewise, our clients can track the whereabouts of the batch(s) and begin to recall them. Provided the hospital used the devices once, and recorded the batch number from the device package label on the patient records, even the affected patients can be identified. All of this is possible because of the batch code (or lot number) printed on the primary package and the related device history record (DHR). Within the DHR for a given batch, we also record the vendor lot numbers for every component and material used as well as sterilization process data.

Since there is no batch code or other identifying mark on a device, once the used device is grouped with other used devices for reprocessing, all traceability is lost. While our current computerized system allows us to reconstruct the entire manufacturing process of

any new device produced at NASP, there is no way to reconstruct the past of a device once it has been removed from its labeled packaging. Hospitals cannot possibly pick up a used/reprocessed SUD and know exactly how many times the device has been used, nor the original manufacturing lot code. If NASP and the client need to recall devices from a particular batch, there is no way a hospital can examine a contained of used devices and pick out the exact ones that fall under the recall.

After a new SUD is used, the patient is billed for materials used in the procedure. If the used device is reprocessed and used a second time on the patient, that patient is billed probably for the same amount. Therefore, there is no patient benefit for being subjected to a used SUD. As the patient is being wheeled from the O.R, the used device is placed in a container and sent for reprocessing. If the patient develops a post-operative infection, there is no way to trace the exact lot of devices that were used. There is no way to determine if the infection was a result of the hospital environment, or if it was transmitted from another patient via an improperly reprocessed SUD. In many cases, it may not even be distinguished on the patient records or hospital invoice if a used SUD or new SUD was sent to the O.R. for the procedure. When an SUD is separated from its labeled packaging, traceability is lost and so many critical questions cannot be answered.

Conclusion

In any country, the sole source of used SUDs is the healthcare system: hospitals, clinics, and doctors. An SUD can only be reprocessed if the healthcare system allows it to happen. Reprocessing is either an internally organized activity, an agreed upon business with an external vendor collaborating with the healthcare system, or a black market activity whereby used devices are allowed to leave the healthcare facilities intact and are later collected by third parties interested in reprocessing them and reselling them back to the healthcare system.

Stated in this way, it is clear that the healthcare system of any country can stop the dangerous practice of reprocessing SUDs. All hospitals, clinics and doctors should be required to render a device unusable (i.e., crush, compacted, cut or heated to deformity) once the package has been opened and the procedure completed. If every SUD is denatured immediately following use, reprocessing cannot take place. Government regulatory agencies, in an effort to prevent reprocessing and the spread of infection that has afflicted this practice, can pass legislation prohibiting the commerce of used SUDs. Finally, firms providing liability insurance should require all healthcare providers to disclose whether they reuse SUDs or not. An audit of the healthcare provider, comparing the number of devices purchased to the number of devices invoiced to patients can confirm adherence to this practice.

Prohibiting the reuse of SUDs is sure to increase the level of infection control in every country. However, I am the first to admit that this is a difficult policy to embrace in the face of millions of people who need the medical procedures to survive.

To conclude, I will take advantage of this forum to share one idea for ending the need to reuse SUDs. Infection control begins by returning to the original purpose of the SUD – single use only. The benefit of SUDs is that many of them can be assembled from less expensive materials and sterilized easily with ethylene oxide gas. For large metropolitan areas, clean rooms and package sealing equipment can easily be set up to manufacture devices at costs inferior to the costs of importing finished devices. Government sponsored manufacturing facilities, relieved of the need to produce profit, can provide devices at cost to developing areas of their countries. For remote areas, both device assembly and ethylene oxide sterilization employ equipment that can be fabricated and installed on any scale. Clean rooms for device assembly, as well as ethylene oxide sterilization systems, can be assembled and mounted on truck trailers. Such a tandem of mobile units, equipped with a multimedia Quality System for training, can be delivered to the less populated areas of a country.

Trained personnel sent to manage a mobile assembly unit can serve a multifaceted mission with both short term and long term goals. They can provide sterile SUDs to the local hospitals and clinics. The same personnel can ensure that the used SUDs are disposed of. In addition, over the long term they can teach the new government policies and help local healthcare providers to develop, implement, and follow modern quality system policies aimed at stemming the spread of infection.

Government agencies, both national and international, need to concentrate financing on providing local device assembly and sterilization services that can be rapidly deployed and installed. A mobile unit as I have described, equipped with an ethylene oxide sterilization system, can then become the basis for a larger permanent device manufacturing facility. Most importantly, a sterilization education center can shape the local culture and harmonize all regions of the country around a universal quality policy whose scope is to protect public health.

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[1] EUCOMED Press Release, Brussels, 12 March, 2003
[2] ISO 11607, Second Edition 2003-02-15, "Packaging For Terminally Sterilized Medical Devices"
[3] ANSI/AAMI/ISO 11135-1994, Medical Devices – Validation & Routine Control of Ethylene Oxide Sterilization; EN 550-1994
[4] Rosenthal, E. "Doctors' Dirty Needles Spreading Disease in China", 20 August 2001, New York Times.
[5] Wilson Duff. Cardiac Catheter Reuse: Cutting Costs or Cutting Corners? Seattle Times. 31 October 1995.
[6] Kleinbeck, S. et al. Reprocessing and Reusing Surgical Products Labeled for Single Use: A Survey of Current Practices. Surgical Services Management 4, Number 1. January 1998. (pp. 21-24)