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Nitrogen Dioxide Sterilisation: The CEO's View

In March 2013, US developer of nitrogen dioxide (NO_2) sterilisation equipment Noxilizer acquired Japan-based Saian Corporation. Both companies have been involved in developing nitrogen dioxide as a sterilisation solution for pharmaceutical, biotech and medical device companies, as well as hospitals. The strategic acquisition is intended to strengthen the global effort to promote acceptance and growth of nitrogen dioxide sterilisation as a powerful and less-expensive alternative to current sterilisation methods. Sam Anson spoke to Noxilizer's president and CEO Lawrence Bruder to find out more about the company's growth trajectory and some of the challenges which come with being a new small player in a vast market.

SA: Can you provide some background on Noxilizer?
LB: Founded in 2004, Noxilizer pioneered the development of nitrogen dioxide as a sterilant. We are focused on two large markets: life science manufacturing and hospitals. Today, Noxilizer is at the commercial stage, already servicing a number of pharmaceutical, biotech and medical device companies. We offer customers contract sterilisation services and sell sterilisation units to companies interested in bringing sterilisation in-house. Noxilizer is based in Baltimore, Maryland, USA, with an office in Japan.

SA: What attracted you to join the company?
LB: In a professional career, there are very few opportunities to bring a new technology to market, not to mention a technology that addresses real unmet market needs. Noxilizer has a safe, proven technology, all the key patents issued for major markets including the United States, Europe, Canada, Australia, and India and a very strong team. From my experience, all the key elements were in place for our success.

SA: NO_2 sterilisation is new and not well recognised yet. How do you plan to overcome that?
LB: The short answer is by focusing on customer needs. From my conversations with customers, there is a clear market need for a truly room temperature sterilisation process and all the benefits that delivers. Medical device, pharmaceutical and biotechnology companies are developing new drugs and devices that can't be sterilised using the existing sterilisation methods. While no sterilisation method can do everything, at Noxilizer, we are very focused on the unique benefits nitrogen dioxide sterilisation delivers.

SA: Tell me about the technology.
LB: NO_2 sterilisation is a room temperature process, leaves no cytotoxic residuals, can scale to larger units, operates with or without a vacuum, and is safe to bring in-house. For many applications, it is a superior sterilisation method. Not to mention, there is a real financial advantage. If a company uses contract sterilisation today, their product is typically out of their control for 2-4 weeks. At a minimum, they are paying for transportation and inventory carrying costs. And, they are limited in their ability to respond to their customer needs. The typical Noxilizer sterilisation cycle is about two hours (including aeration). It does not take long to do the cost/benefit analysis to understand the benefits of bringing nitrogen dioxide sterilisation in-house. This is the message we take to the key industry meetings: Medical Design & Manufacturing (MD&M, USA), Parenteral Drug Association (PDA), and the ISPE (International Society for Pharmaceutical Engineering). We have been invited to present at these meetings and have had a number of articles published in the USA and Europe. The word is getting out. Companies are enthusiastic, and are now coming to us.

SA: NO_2 sterilisation is a new player in a well-established market and Noxilizer is a very small company with big competition, how can you compete?
LB: Well, that is always the challenge as the new player in an established market. But, that challenge is part of the fun. Noxilizer's early success has come from identifying companies who are "early adopters" to new technology or have a sterilisation challenge with an existing or new product. By partnering with those types of companies, demonstrating success with NO_2 sterilisation, alongside the financial advantages of NO_2, we have been successful in selling the RTS 360 Industrial NO_2 Steriliser. In addition, we have a number of contract sterilisation customers in the United States and Europe that we serve from our new facility in Baltimore.

SA: What type of products is Noxilizer sterilising and how were they sterilised in the past?
LB: We have focused on the types of products that are not really compatible with ethylene oxide (EO), gamma radiation or hydrogen dioxide, like prefilled syringes and other drug delivery devices, as well as bioresorbable implants. These are ideally suited for room temperature nitrogen dioxide and they are growing markets. NO_2 sterilisation compares favourably to traditional methods for a wide range of products.

While a company may be using EO, gamma or hydrogen peroxide today, the results are not satisfactory. With EO, there are concerns about a range of issues, including contamination of the drug, temperature, vacuum, long aeration times and the high hurdles to bring sterilisation in-house. With gamma, changes in the mechanical properties of the implant are troublesome, or simply unacceptable. The capital investment required makes it impossible to bring this method in house. And finally, hydrogen peroxide also operates at a somewhat elevated temperature, requires a vacuum, and is not scalable. This becomes a big challenge as product volumes increase. In addition, Advanced Sterilization Products (ASP, a J&J company) has announced that they are exiting the life science market.

There will always be a place for all these sterilisation methods. Today at Noxilizer, we are focused on the products that will realise benefit from the nitrogen dioxide sterilisation process.

SA: In February, Noxilizer acquired SAIAN Corporation in Japan. What attracted you to SAIAN?
LB: SAIAN was founded shortly after Noxilizer. They were also working with nitrogen dioxide for use in life science and hospital markets; however, the SAIAN team took a very different approach to sterilisation. I saw the opportunity to combine the expertise in NO_2 and leverage both companies' products to form a stronger organisation versus the competition in the established market. That has already paid off. The company in Japan has been renamed to Noxilizer Japan KK.

SA: Can you speak a bit about their technology and how you plan to leverage it?
LB: The acquisition of SAIAN Corporation immediately brought us an expanded product line. In fact, we have already collaborated on a joint development project with a well-known pharmaceutical equipment manufacturer. The unit is complete and testing will begin in September.

We view much of the SAIAN technology as our next generation offering that includes: onboard sterilant generation, recycling and abatement capabilities. This approach offers real promise for our customers in the next 3-5 years.

SA: What are your plans for Asian markets and how does the acquisition complement these plans?
LB: Now that Noxilizer has a facility in Japan, we have a base of operations as the gateway to other Asian markets. Today, Noxilizer Japan KK is focused on product development. We have plans to add commercial staff next year.

SA: What about other areas outside the USA—Europe for instance? What are your plans there?
LB: We are on schedule to submit the CE package this year for the RTS 360 Industrial NO_2 Sterilizer. That will allow us to sell the unit in

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Europe. I have already identified a commercial leader who will oversee European operations. Noxilizer recognises the need to move into Europe and Asia to support our current US customers. Pharmaceutical, biotech and medical device companies have global manufacturing locations and they want to use the same manufacturing and sterilisation processes around the world.

CEO Spotlight: *Lawrence Bruder President and CEO, brings over 25 years of leadership and operational experience in large and small life science companies, including Becton Dickinson, Applied Biosystems, Leica, Olympus, and Guava Technologies. Most recently he was President and CEO of venture-backed Guava Technologies, which was sold to Millipore Biosciences in 2009. Most of his experience prior to Guava was at Becton Dickinson, where he held a number of significant positions over a 10-year period. His responsibilities in both companies included the clinical and regulatory aspects of 510(k) submittals to the FDA for medical devices, significant commercial interaction with pharmaceutical companies, and high-level business development transactional activity; all of these being a critical part of Noxilizer's needs. Mr Bruder holds a BS from Rochester Institute of Technology and Master of Management in Marketing & Economics from the Kellogg Graduate School at Northwestern University.*

Product Information: *Noxilizer provides medical device manufacturers with contract sterilisation services based on nitrogen dioxide (NO_2) technology. The company also sells the RTS 360 Industrial NO_2 Sterilizer (pictured) to customers interested in bringing sterilisation in house. Its proprietary, room-temperature NO_2-based sterilisation solution compares favorably with traditional sterilisation methods using EO, gamma irradiation and hydrogen peroxide in terms of safety and processing cycle length. The standard cycle lasts 60-90 minutes and features immediate release. NO_2 sterilisation maintains material properties, requires no additional aeration, leaves no cytotoxic residuals, and is highly-compatible with a wide range of products including bioresorbable implants, prefilled syringes, vials and drug-device combination products. NO_2 sterilisation is a safer, simpler, more economical alternative.*

Considerations for Parametric Release Sterilisation

by **Bill Young**, Vice President Global SteriPro Services, Sterigenics, and **Peter Strain**, Vice President Technology EMEAA, Sterigenics.

Over the past two decades, the growth in popularity of single-use, pre-packaged medical devices has been followed by the increased industrial use of traditional terminal sterilisation methods such as ethylene oxide (EO), electron beam, and gamma irradiation. The growth in specific procedural and surgical needs has created a number of sterilisation challenges for these methods. This is due predominantly to the inclusion of drugs and greater diversity in product designs, material types and packaging applications. The relative suitability of EO to a broad range of materials, coupled with the flexibility of sterilisation process, has meant that EO has often emerged as the sterilisation method of choice.

The effort to reduce overall EO sterilisation process time has provided a strong incentive to develop and optimise large-scale EO sterilisation technology while also continuing to deliver the required product sterility assurance levels.

On the surface it is not uncommon for medical manufacturers to focus on the total process time which includes the processing time, aeration or degassing time and the product quarantine time which may coincide with the microbiological incubation period.

Historically, a typical timeline for an industrial EO sterilisation process includes the following phases and times:

- Preconditioning—18 to 24 hours (1 day);
- Chamber Processes—8 to 14 hours (0.5 day);
- Product Aeration—24 to 168 hours (1 to 7 days); and
- Microbiological Testing—72 to 168 hours (3 to 7 days).

Industrial and contract sterilisers have responded to the demand for improved processing time in a number of ways. Those clients who have been able to optimise their EO sterilisation process may be able to reduce the amount of EO necessary to provide the required 10^{-6} sterility assurance level and as a consequence end up with a shorter product aeration period (ie 24 -72 hours). Routine sterilised loads which are under quarantine pending successful microbiological results may be excellent candidates for using parametric release in place of biological indicators.

The standard ISO11135-1:2007, *Ethylene Oxide—Requirements for Development, Validation and Routine Control of a Sterilisation Process for Medical Devices*, in conjunction with ISO11135-2:2008, which provides guidelines on the application of the former, identifies either one of two acceptable methods for routine release of EO sterilised loads.

1. Microbiological based (biological indicators). This method requires that the sterilisation process is audited to show compliance with the validated specification and is supplemented with biological indicator test results. The biological indicators are commonly placed in a 'worst-case' process challenge device, placed on the sterilisation load before process, removed after processing and endpoint sterility-tested for 3-7 days.

2. Parametric release of a load is based on a documented confirmation that the process parameters delivered during the process within the validated specification only—this routine release method does not include the use of biological indicators, but does require the measurement of additional process parameters, that is to say humidity and ethylene oxide concentration within the steriliser.

Benefits for manufacturers arising from these initiatives include a faster response to market and a reduction in work-in-progress materials. For those clients with relatively short aeration or degassing hold times, the implementation of parametric release (ie product is sterile) has been extremely advantageous given that the load is not held pending the microbiological incubation time. Speed to market for the product is then dependent on aeration time and conditions that are validated to ensure compliance with ISO10993, Part 7.

ISO11135-1:2007 requires direct measurement of humidity and EO concentration from the chamber throughout the applicable phases during routine cycles. To meet this requirement, Sterigenics uses relative humidity (RH) data loggers and installed humidity/EO infra red (IR) spectrometer units for measuring concentration directly from the chamber.

Sterigenics recommends a two-step process to establish the parametric release parameters once the validation has been completed. The initial step is to perform a run and record study to confirm the process capability in which the loads are released via the standard or conventional (biological indicator) approach while recording the key parameters necessary for parametric release. Once a suitable sample size of runs has been completed—as determined by the variation of the product types and load materials—the humidity and EO concentration data are analysed to identify a suitable set of parametric tolerances. Generally, Sterigenics suggests that the EO parameter is calculated by evaluating the average concentration throughout the EO gas dwell in order to meet the ISO11135 requirements. Prior to implementation of these tolerances, Sterigenics recommends that manufacturers perform a fractional cycle in which the EO concentration is set at or below the tentative parameters and demonstrate the ability of the minimal EO concentration as capable of delivering adequate lethality to products.

In conclusion, rapid response to market has driven the implementation of parametric release for ethylene oxide sterilisation, and has resulted in its acceptance by regulators and application in all geographies across the world.