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Nitrogen Dioxide Sterilisation: The CEO’s View

In March 2013, US developer of nitrogen dioxide (NO₂) 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: NO₂ 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: NO₂ 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: NO₂ 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 exiting or new product. By partnering with those types of companies, demonstrating success with NO₂ sterilisation, alongside the financial advantages of NO₂, we have been successful in selling the RTS 360 Industrial NO₂ 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. NO₂ 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 NO₂ 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 NO₂ Sterilizer. That will allow us to sell the unit in

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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 flexiblity of sterilisation processes, 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);
- 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 (i.e. 24–72 hours). Routine sterilised loads which are released via the standard or conventional method require a 24–72 hour aeration period. Routine sterilised releases are validated to ensure compliance with ISO10993, Part 7.

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 to 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.