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Shrinking Big Pharma

Why building smaller manufacturing plants is the next big thing

By Meagan Parrish, Senior Editor

Bigger isn't always better. In fact, the growing trend in pharma is looking at ways to shrink the industry's plant-floor footprint down.

A few months ago, Amgen announced plans to build a new "next-generation" manufacturing facility in Rhode Island, which will be modeled on the company's highly innovative plant in Singapore. What makes it cutting edge? Its smaller size. According to Amgen, its Singapore facility occupies about one-fifth the size of a traditional pharma plant but maintains a comparable level of output. It was also built in half the time and at a fraction of the price of a conventional plant — a new measure of efficiency Amgen intends to replicate in the U.S.

In the last few years, other pharma companies have followed Amgen's lead and have been thinking outside of the big box when building or revamping their manufacturing spaces.

On the surface, the environmental and cost benefits are clear. In aseptic processing in particular, every square foot can be a major expense and the less floor space there is to keep free from contaminants, the more a company saves.

Rethinking the way space is used is also helping companies increase their level of flexibility — a new must as the industry shifts from manufacturing medicines on a mass scale to meeting the rising need of making small batches of personalized therapies.

Inside Amgen's next-generation biomanufacturing facility in Singapore.

But there could also be wider implications for companies looking for and successfully finding ways to make manufacturing more compact, flexible and mobile. And the industry is far from done scaling down.

"Our vision is that one day, we can manufacture medicine in a space as small as this stage," Arleen Paulino, vice president of site operations at Amgen's Singapore facility, said earlier this year during a keynote presentation at the PDA Annual Meeting in Orlando.

If successful, the ability to make medicine using less space could change the way it is distributed around the globe.

What is allowing pharma companies to squeeze into tighter spaces? And just how small could we go? Many in the pharma world are on a quest to find out.

GETTING MORE FROM CELLS

It's tempting to call the trend of going small "downsizing," but Maik Jornitz, the president of G-Con Manufacturing, has a more accurate term.

"We call it 'process intensification,'" he explains. "In the past, one gained milligrams per liter of the target protein from a cell expression system. But now, cell development improvements make higher expression rates up to five grams per liter possible. In conjunction with much higher cell densities, a better rate of protein

expression is achieved, which means bioreactor volumes can be lowered."

According to Paulino, improving cell development was a major stepping stone for Amgen's goal of reducing its footprint. Advances in cell development made in the last 10 years have allowed companies to grow cells faster and express proteins for medicines in a more efficient way.

"We didn't just want to have one-tenth of the scale and get one-tenth of the total product out," Paulino explains. "We wanted our output to match or be more than what we are currently doing at a larger scale."

These improved efficiencies mean that companies can now reduce the size of the bioreactors inside their facilities. Instead of stainless steel tanks built to hold 15,000 liters, companies can now use 2,000 liter tanks.

Thus, advances in equipment technology have also been critical for achieving the goal of reducing manufacturing space.

THE RISE OF SINGLE-USE

Single-use systems have been widely embraced by the industry thanks to the boost in efficiency and ease-of-use disposable parts provide. They can also be major money- and space-savers.

"The adoption of single-use process technologies not only enables faster production turn-around schedules, but also a major reduction in the utilities size. Single-use equipment avoids high water and energy consumptions, as cleaning processes and the need for copious amounts of water for injection are avoided, and steam sterilization is replaced by pre-sterilization of equipment," Jornitz says.

All told, Paulino says about 95 percent of the contact surfaces the products touch in Amgen's Singapore plant are single-use systems, including disposable plastic bags in its smaller bioreactors. Removing the clean-in-place processes also allowed Amgen to create an aseptic system that is more closed, which reduces contamination risks.

"When you're operating in a way where you're not opening your connection or your product flows to the environment and it's in a closed manner, it helps protect your products," Paulino says.

THE PAYOFF

Since Amgen began production at its Singapore plant in 2015, several other companies have realized the benefits of going small.

"We all learned from Amgen's Singapore site, as they pioneered a fully functional single-use, process intensified, small footprint facility. The design and accomplishment of this site encouraged our industry to think in a new paradigm," Jornitz says. "Having said this, there are now newer, innovative

solutions, which create turnkey facilities that I think are even more flexible and more rapidly deployable."

According to Jornitz, the trend isn't limited to biomanufacturing and several companies have been looking at ways to make oral solid dose production more efficient with continuous processing modes. But in an aseptic processing environment, the payoff is especially large, as robust containment is a must.

"In aseptic, simple is always better," Barry Starkman, a principal consultant with DPS Group, explains. "The regulatory burden is always high. And for manufacturing, it comes down to dollars per square foot — $1,200-$1,500 per square foot adds up fast."

One of the biggest cost factors in an aseptic environment is air flow — as an ISO 5 environment demands up to 480 air changes an hour. Naturally, if you're operating in a smaller space, you don't need to run a high air volume to reach the required air changes to maintain the same cleanroom classification, which saves energy costs.

SMALLER, FASTER

Even in facilities producing bigger batches of medicines, Starkman says many companies are starting to see the value in running multiple small machines instead of a single large production line.

"I once worked with a vial line that did about 700 vials per minute and it was a monstrosity," he recalls. "The reality was that it was so complicated, it probably would have been more efficient to run several smaller lines so that if one machine went down, the others continued to operate and we didn't lose as much output."

According to Jornitz, many of the companies who come to G-CON Manufacturing — which produces prefabricated cleanroom systems called PODs — are looking to shrink their footprint while quickly scaling up operations.

"Speed of deployment is essential, as capital investment decisions can be

Inside Amgen's next-generation biomanufacturing plant in Singapore.

delayed and manufacturing processes come online without the need of upfront inventory burdens," he says. "Since our cleanroom PODs can be predesigned and are prefabricated within our manufacturing environment, we are able to gain much higher man-hour productivities. This typically means we are able to deliver standard PODs in three months and a POD project in five to nine months."

The trend is intensifying as more companies work with personalized medicines to fight cancer and rare diseases. In fact, with thousands of gene therapies in clinical trials, that segment of the industry is now the second largest class of medicines being developed — second only to traditional new chemical entities.

"The largest number of inquiries we get at G-CON is on the cell gene therapy side, as the autonomous air handling of our PODs guarantees robust containment," Jornitz says.

REDUCING RISK

Containing the biomanufacturing process to a small space is not only good for the pharma company, it's safer for patients.

"In cell therapy, the received patient sample is a very small volume. A potential contamination would not only represent an economical risk, but a tremendous patient risk, as one may not gain another sample," Jornitz says. "This means robust containment is crucial."

At Amgen's Singapore plant, some of the benefits of a smaller space have come from the facility's unique "ballroom" design. Traditionally, the different parts of operation — from the cell culture phase through to purification — are done in separate rooms. But if you stand on one end of Amgen's Singapore facility, you can see all the way across the plant — from the bioreactors to purification.

"In a traditional plant, you can see a lot of long stainless steel pipping running through the wall into another room that could be three floors down from where you're at," Paulino explains. "So to get them really close together allows us to use single-use systems to shorten our flow pathway and optimize our yield."

The change has also given the company an advantage in how it manages workers. One benefit is that employees don't have to frequently un-gown and re-gown as they move into new rooms, which saves time and space. But the ballroom design has also shifted the way employees interact with the manufacturing process.

"Instead of having employees who only do cell culture or purification, etc., we now train and develop our staff to be much broader manufacturing operators," Paulino says. "Our

staff don't identify themselves by where they are. They think about themselves as manufacturing professionals and get opportunities to learn about different parts of operations."

THE TRADEOFF

Shrinking manufacturing isn't for everyone. Although many companies are looking at ways to reap the benefits of producing in a more compact space, there still has to be some cost/benefit analysis to make sure it's a good fit for your operations.

"The end game is that form has to follow function," Starkman cautions.

When working with companies to design their spaces, Starkman says they always consider the tradeoffs between stainless steel versus single-use, the cost of utilities, air monitoring and all the other cost factors of running a plant.

Despite the many advantages of single-use systems, they don't automatically translate into space savings.

In fact, Jerome Pionchon, an engineering expert with the bioreliance solutions organization at the Merck unit in Martillac, France, says that switching their plant to mostly single-use systems didn't translate into a significant space savings.

"When you use single-use systems, you don't need to use clean-in-place anymore, but you need to store the disposable parts and need more storage space. It's just a different way to manage the facility," Pionchon says.

Although Pionchon says that single-use doesn't automatically mean that a company can downsize its facility, it has improved efficiency at the Merck plant in Martillac.

"It makes sense to switch to single-use systems when you need a high level of flexibility," he says. "But if you're still producing at an identical scale…I'm not sure you're going to get a huge improvement in terms of footprint."

There are also challenges to thinking small.

At Amgen, Paulino says the company has had to transition its relationships with equipment suppliers to be more like partnerships.

"As we pushed these technologies we are learning about the robustness of them, and we've had to work closely with our suppliers and partner with them to continue building that robustness," she says. "Because we rely heavily on suppliers for single-use systems … we are working with them to increase the expectations so that we get zero defects and 'right the first time.'"

THE FUTURE LOOKS SMALLER

What's it going to take to shrink

biomanufacturing to the size of a stage — or even smaller? For Amgen, Paulino says that improving its current systems will help reduce its manufacturing footprint even more.

"We're going to need to advance the cellular growth and productivity to continue yielding higher growth and we're going to need to look at our purification processes to think about how we can increase the protein yield and reduce the buffer volumes," she says. "We also need to take advantage of small-scale equipment with better automation and advance that technology for use in a GMP setting."

According to Starkman, robotics could also play a role, especially as they become more intuitive and capable of handling multiple tasks. The more functionality we can get from a single robot, the less space manufacturers will need to operate them.

"In aseptic processing, robots could be used in materials handling, manipulating all the components, cleaning and environmental monitoring inside the isolator," he says. "I think that's the key to all this."

Advances in continuous biomanufacturing could also be a game-changer.

"There are people playing around on the bulk side with continuous cell culture and fermentation," Starkman says. "I've seen a continuous freeze drying process, and then filling. So, there are some really cutting-edge technologies that people are experimenting with."

"With continuous processing bioreactor volumes and downstream processing, footprints can be further reduced. Certainly, media and buffer volumes increase, but also the preparation technologies in this area are evolving," Jornitz echoes. "Quite a few biomanufacturers are pursuing continuous manufacturing, which can help them shrink that facility footprint even further.

"Major advances in the field of antibody boosters need to be accelerated. The hope is that in five to 10 years, designs of more mobile, rapidly deployable bioprocessing spaces are available to fight any potential pandemic threat," Jornitz continues.

That solution could prove to be especially needed as the threat of the next global health crisis looms. For example, in May of this year, the World Health Organization reported that Ebola is back and several cases have been confirmed in the Democratic Republic of Congo (the disease claimed more than 11,000 lives between 2014-2016 in West Africa). The fresh outbreak has already killed dozens and health officials are scrambling to contain it before the disease spreads again.

Currently, one of their chief weapons of defense is a new experimental vaccine

created by Merck, which has been approved for "compassionate use" in outbreaks even though it has not yet been formally given the green light by any regulatory body. But because the new cases are in very remote areas, maintaining the cold chain to transport thousands of vaccines where they're needed has been a concern. Mobile manufacturing could change that.

"My dream is that four trucks drive into a warehouse anywhere in the world," Jornitz says. "One truck is utilities, like chilled water, electricity etc. The other two trucks are cell-based drug substance processing spaces, and the last truck is for final dosage formulation and filling. With that you could produce vaccines wherever they are needed.

"I think there is the potential to make that dream happen," he continues. "There's so much tremendous technology out there — we just need the support of regulatory authorities to utilize it. Because what do we do? We work for the same person: the patient. All of us in the industry — from manufacturers to regulaters — need to strive to serve that patient better, and this can only be done in a collaborative manner."

Sizing Up the Benefits of Sterile Drug Manufacturing Techniques

A comparison of several sterile processing techniques

By Christian Dunne, ChargePoint Technology

Sterile manufacturing environments are open to many sources of potential contamination if not managed correctly: air filtration systems, materials transfer and, not to mention, operators — a fully gowned operator may create as many as 150,000 particles per minute, many of which are viable and are potential hazards during the manufacture of sterile drugs. The need to ensure the safe and sterile transfer of active pharmaceutical ingredients (APIs) and formulation ingredients during aseptic processing has driven the development of multiple techniques that can be employed in cleanroom environments to minimize the risks from contaminants.

APPROACHES TO ASEPTIC MANUFACTURING

Barrier technologies, such as isolators and RABs, are designed to provide micro-environments which have been seen to provide better levels of microbiological protection for a process than that of traditional open cleanroom environments. The aim is to separate the operator from the product and prevent harmful contamination spreading to critical operations in the drug production process.

Isolators

Isolators are an arrangement of physical barriers that provide an enclosed working space that is detached from the surrounding environment. This enables manipulation to be undertaken within the space from the outside the enclosure without compromising integrity.

These enclosures use a combination of techniques to provide and maintain the

clean environment such as positively pressurized chambers maintained through closed loop control of the chamber pressure. HEPA filtered air, supplied to the chamber in a laminar flow to ensure particulate generation is suppressed and removed efficiently and integrated bio decontamination systems, to provide a six-log reduction to the chamber surfaces.

Due to the high-performance requirements for these enclosures, integrated pressure decay tests have become the norm during start up and prior to any bio decontamination phase, with the leak of the chamber being a key factor in the classification of the device. See ISO14644 on leak rates for separative devices.

RABS

The RABS approach puts a physical barrier between operators and production areas, while still offering the flexibility to interact with the process outside a sealed enclosure. To allow a more limited barrier to be permissible, RABS must be set-up in high-class, generally ISO 7 cleanrooms.

There are two different types of RABS which are commonly used. The first are active RABs, which actively pull the air from outside the cleanroom environment,

High level RABS	Standard level RABS	Base level RABS,	Traditional open cleanroom	Combination solutions
Active configuration, sporadically gassed with CIP/SIP as required, gloved access and aseptic rapid transfer devices	Active configuration, manual sporicidal disinfection, CIP/SIP as required, gloved access and aseptic rapid transfer devices sited in grade B – ISO 7 cleanroom. Possible 'open door' controlled operator access in-process.	Passive configuration, manual sporicidal disinfection, CIP/SIP as required, gloved access and aseptic rapid transfer devices (as required) sited in grade B – ISO 7 cleanroom. Typically, no operator 'open door' access in-process.	ISO 7 with ISO 5 critical zones using simple flexible barriers (curtains) and generally open for access.	Example 'RABS & isolator' In some applications practical limitations lead to the need to combine RABS and isolator operational features together with integration into different zone background environments.

filtering and extracting it so it is completely isolated. The second type are standard passive RABS that utilize the cleanrooms (HVAC) system. Within these two formats, these are sub-categories which can be defined as follows:

RABs categories

RABS contribute distinct advantages by enabling operators to maintain a distance from the process, while allowing the enclosure to be opened if significant intervention is required.

Comparisons between isolators and RABS

In comparison to isolators, RABS can ensure faster start-up times and improve the ease of changeover. They can also bring increased operational flexibility and reduced validation expenditure. Although Isolators do offer the advantage of higher integrity chambers for a more robust closed solution.

Many pharmaceutical companies are finding that the use of aseptic SBV technology integrated to either the isolator or RABS for the transfer of material in or out of the enclosure compliments the sterility assurance required for the encloses.

SBV technology

The aseptic Spilt Butterfly Valve (SBV) provides a safe method of transferring product from one container, process vessel, Isolator or RABS to another while ensuring the sterility of the transfer is not compromised.

Fundamentally, the SBV consists of two halves, the active (Alpha) unit and the passive (Beta) unit. Each half consists of half of the 'butterfly' disc. The active unit is attached to the stationary process equipment such as a mixing vessel, while the passive unit is attached to the mobile container such as an intermediate bulk container (IBC) or flexible bag. When the two parts are brought together, the discs halves join to form a single disc, sealing any surfaces which may have been exposed to a compound during transfer. The two discs then operate as one disc and can be opened to allow transfer of product from one location to another.

The unique design of the aseptic SBV enables decontamination to take place in a closed environment. Once sealed, a gap is created between the discs and hydrogen peroxide gas is flushed through this enclosure to decontaminate the space. The process of validation is done in the same manner as that of an Isolator or RABS with the use of, chemical indicators to ensure full coverage of the enclosure is obtained and biological indicators to ensure a 6-log reduction has been achieved.

Adoption of aseptic SBV technology allows manufacturers to benefit from a closed handling method that not only achieves the required sterility assurance level (SAL) and reduces the requirement for manual intervention, but also offers the opportunity to reduce the resource associated with cleaning

and validating large areas. The method minimizes cleaning requirements and, consequently, downtime, while also increasing flow and yield from product transfers.

Processing time varies between 4-30 minutes depending on the gassing system utilized. This is extremely fast when compared to a conventional airlock or Isolator which could be in the region of four to six hours. SBV can also contribute considerable cost savings in comparison to traditional approaches, being as much as three to five times cheaper than alternative methods. The aseptic SBV also makes it possible to downgrade the surrounding cleanroom environment because of the integrity of the approach.

EACH TECHNOLOGY HAS ITS PLACE

The selection of an appropriate aseptic transfer technology will come down to a variety of factors, including the unique requirements and possibilities within a manufacturing facility, as well as the type of products being processed. Isolators are easier to decontaminate, monitor and offer a high degree of sterility assurance, while RABS provide both increased operational flexibility and speed of changeover which appeals to many manufacturers, particularly contract manufacturers that need to be able to adapt to different customer products and manufacturing processes. Aseptic SBV technology not only complements and works in harmony with these solutions, but in some applications, can replace them, reducing the reliance on cleanroom environments while offering increased sterility assurance and improved ergonomics. Barrier systems are vital to ensure product quality and operator protection, and each of these technologies has its place.

It is vital that a full evaluation of products and processes against the various systems takes place in an early project phase to ensure the right technology is selected.

Less Space for Waste

As single-use technology becomes mainstream, biopharma companies need a better way to handle waste

by Karen Langhauser, Chief Content Director

"Single-use devices have clearly reached mainstream acceptance in the industry," concluded BioPlan, after reviewing the results of their Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production.

According to BioPlan's survey, almost 90 percent of respondents continue to use one or more single-use device at some stage in bioproduction (R&D through commercial). The most common uses were in tubing, disposable filter cartridges, and connectors and clamps.[1]

This should come as no surprise to the industry, as these single-use technologies offer distinct advantages compared to traditional, fixed stainless steel systems in terms of cleaning and validation. This can lead to a positive environmental impact by reducing the use of resources such as water and energy. Single-use options can also reduce the time and investment required to get facilities and process lines up and running.

But these advantages must be balanced against new operational challenges, chief among them, waste management and disposal.

The adoption and growth of single-use technologies in biopharma manufacturing is significantly increasing the amount of plastic waste being generated. It's estimated that by 2025, biomanufacturers will be producing 112,000 tons per year of plastic waste, globally.[2]

MilliporeSigma recycles all plastic containing products used in biopharma manufacturing.

DISPOSAL OPTIONS

Biopharma facilities produce different categories of waste: non-hazardous, hazardous, regulated medical waste and biohazardous. EPA regulations define what is considered hazardous and the Department of Transportation regulates how waste is handled and transported.

The industry standard for years has involved landfilling or incineration, depending on the type of waste. Biohazardous and regulated medical waste disposal typically involves contracting with a company authorized to contain, transport and dispose of this waste. Biopharma companies perform robust risk assessments to determine the right disposal options. Not surprisingly, many companies err on the side of caution, even going as far as choosing to autoclave waste before allowing it to leave the facility or labelling waste as biohazardous whether it is biohazardous or not.

But the increase in single-use plastics waste is pushing biopharma companies to address the environmental impact of these currently utilized methods of disposal, and question whether there is a better option.

RECYCLING PLASTIC

While recycling seems like an easy solution, there are challenges that arise when it comes to recycling single-use technologies in biopharma. Most standard recycling programs cannot accept biohazardous or medical waste without it first being sterilized. Additionally, many single-use products

used in biopharma facilities are made from multiple plastics and materials — and standard recycling programs are not equipment to handle separating these materials.

Perhaps the biggest hesitation has to do with traceability. The traditional recycling infrastructure does not allow for traceability.

"It makes sense that biopharma customers are very concerned about losing track of where plastic waste goes once it leaves their facilities. Obviously, they want to make sure that their waste is properly disposed and that nothing happens that isn't supposed to in the process," says Jacqueline Ignacio, global manager, Customer Sustainability Solutions, MilliporeSigma.

Ignacio points out that human rights are also a concern, given that labor violations are not uncommon in facilities that process plastic waste abroad.

"If you are a company making products that better people's lives, it would be contradictory for your trash to be doing the opposite," says Ignacio.

FINDING A SOLUTION

MilliporeSigma estimates that a single biopharma site produces about 12.5 tons waste per month that is eligible for recycling. As a leading supplier of single-use biopharmaceutical products, including single-use bags, tubing, connectors and filters, MilliporeSigma recognizes the need to reduce the environmental impact of its products.

In 2015, MilliporeSigma launched an exclusive partnership with Triumvirate Environmental in order to enable bioprocess manufacturing customers to fully recycle plastic single-use and disposable products.

Triumvirate's innovative program can utilize the entire product in its recycling process, without requiring segregation or disassembly. Triumvirate can accept regulated medical and biohazardous waste, as well as non-hazardous waste such as hairnets, gloves and gowns. The waste is shredded and sterilized in one step, and turned into landscape timbers, construction materials and plastic shipping pallets at Triumvirate's Pennsylvania facility.

"Having biopharma waste processed in the same facility that is manufacturing the next product completely takes traceability issues out of the equation. Biopharma manufacturers know where their waste went and what it was transformed into," explains Ignacio.

MilliporeSigma and Triumvirate are currently working with 11 biopharma customers, including Johnson & Johnson's Janseen site in Malvern, PA. Johnson & Johnson's reports that through this program alone, 50 tons of single use technologies were recycled last year.

IT'S NOT WASTE, IT'S OPPORTUNITY

Despite an impressive start, single-use technology recycling is still in its infancy in the biopharma industry. The MilliporeSigma/Triumvirate partnership is the only one of its kind in the industry and is focused primarily on East Coast facilities. As global disposable plastic production continues to exceed the ability of waste management to keep up, recycling is becoming imperative.

"This is just the tip of the iceberg for recycling processes. There's a whole economy surrounding plastic recycling that we've only just started to tap into," says Ignacio.

What's it going to take to make this happen in pharma? For starters, collaboration between waste management, single-use suppliers and biopharma companies, yielding programs such as the one put in place by MilliporeSigma and Triumvirate.

"My hope is that this gets people looking at waste differently and realizing that it's not just single use. It can become another product, safely and affordably. Eventually people will start to look at waste not as waste, but as a feedstock for something more," concludes Ignacio.

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Maximum and Minimum Loads in Steam Sterilization

Establishing a cycle development strategy that fulfills regulatory requirements

By James Agalloco, Agalloco & Associates

Steam sterilization is a critical process in the manufacture of many pharmaceutical and medical device products. Because of its importance and wide usage it receives a great deal of attention from both practitioners and regulators. Despite this focus, there are aspects relating to load size that prove troublesome, and can cause difficulty during sterilization cycle development, and validation. Regulators will routinely query users on their means for validation of varying load sizes in both pre-approval and routing inspection. The regulatory expectation is that the user has validated fixed and invariable load patterns, and thus load sizes for all sterilization processes.[1,2] This is expected for both parts (porous) and terminal (non-porous) loads. While defined loads has been used by some firms, their use constrains operational flexibility and many industrial users have sought more flexible, and efficient means. Depending upon the details of the individual sterilization processes, their ability to defend their practices relating to load size variation may not be adequate.

It has been common practice to utilize maximum loads as “worst case” demonstrations of sterilization lethality and assume that smaller size loads will be appropriately sterilized. The assumption is that the larger size, number, and mass of the maximum load represents a worst case and challenges the sterilization process sufficiently during validation that the minimum load (and all intermediate size loads) can be considered acceptable by default. Depending upon the manner in which the sterilizer is controlled during the process, this may or may not be true. Varying

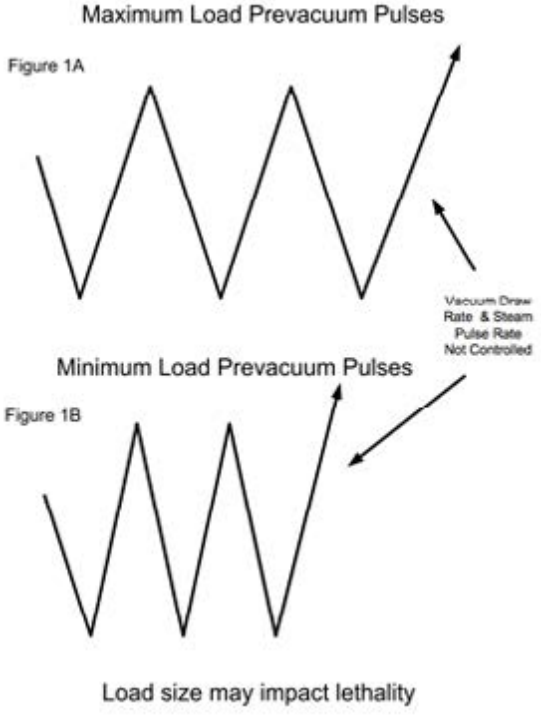
air removal, and/or differences in heating / cooling rate as is possible with varying load size, can result in process differences that can result in reduced cycle efficacy.

This article will address the effect of load size on both parts (porous load) and terminal sterilization processes. The specific means to address load size differ between the sterilization processes; however the general approach to follow is similar. Using the content provided herein, the practitioner can establish their sterilization processes for either porous or non-porous loads with confidence that they can meet regulatory expectations, while maximizing operational flexibility.

PARTS (POROUS) CYCLES

Agalloco1 sbThe maximum load should be studied initially in the validation effort. The maximum load can be an actual load, or one that is artificially created for the validation exercise. Depending upon the sterilizer usage there may be several different maximum loads. The maximum load(s) should be well documented as to component load item size, number and mass. The load items should have been previously evaluated to determine the 'slowest to heat' location when properly wrapped and oriented. This should be performed with temperature sensors introduced in a way that does not compromise the integrity of the wrapping materials. The maximum load(s) are then subjected to validation in replicate studies with thermocouples and biological indicators demonstrating that sufficient lethality has been delivered throughout the load.

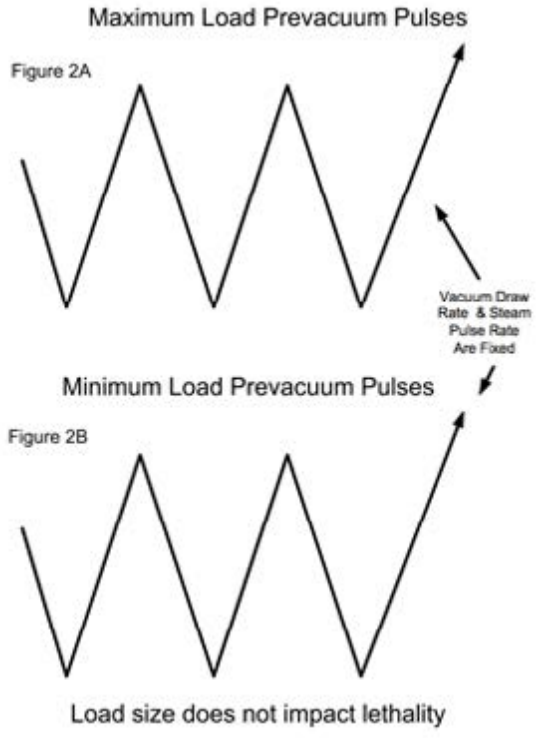
A major consideration with porous loads is that air must be efficiently removed from the load. As the maximum load typically has many wrapped items, the rate at which air can be removed can be influenced by the load size. Air present within wrapped items must diffuse through the wrapping, whereas air removal from outside the load has no restrictions and is rapidly removed (see Figure 1A). When a minimum load is processed, the amount of internal air is reduced and it is possible that air within the load items may not be adequately removed when the targeted vacuum level is attained (see Figure 1B). The presence of air retained within the load item can result



in the minimum load receiving less lethality than necessary for its reliable sterilization. The means to address this potential problem vary with the sterilizer control system and its sophistication. Note that in all of the scenarios the number of vacuum pulses would be the same and defined by what is necessary to meet any defined equilibration time requirements.

Agalloco2 sbSteam sterilizer with pressure set points, vacuum and steam injection rate control

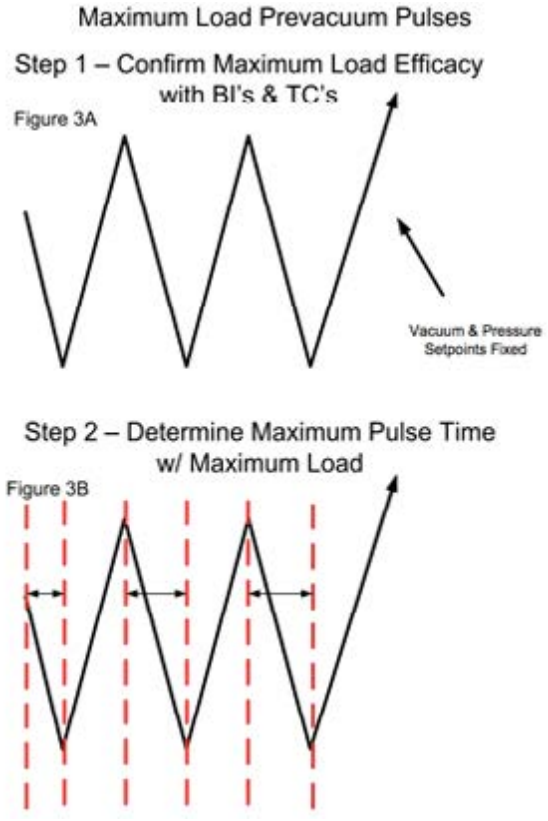
A sterilizer with this capability allows the rate of chamber pressure drawdown and steam injection rate during the vacuum pulses to be controlled. This is the optimal design, as controlled rates can be established such that the impact of load size is eliminated. Once confirmation of adequate air removal is established with the maximum load and verified with a minimum load the same vacuum draw down rate and steam injection rate are utilized used for all loads in the sterilizer regardless of size. The ramp rates should be set at no greater than 90% of the maximum possible for more reliable control. The pre-vacuum and steam pulse duration for the sterilizer will thus be reproducible allowing for complete air removal regardless of load size. The overall sterilization cycle times for all load sizes should be nearly identical (see Figures 2A and 2B). With this control approach, validation of the maximum load(s) would



support smaller loads comprised of similar items. To ease regulatory questions, a single challenge run for the minimum with thermocouples and biological indicators should be performed.

STERILIZER WITH PRESSURE SET POINTS AND VACUUM/ PRESSURE HOLD TIME CONTROL

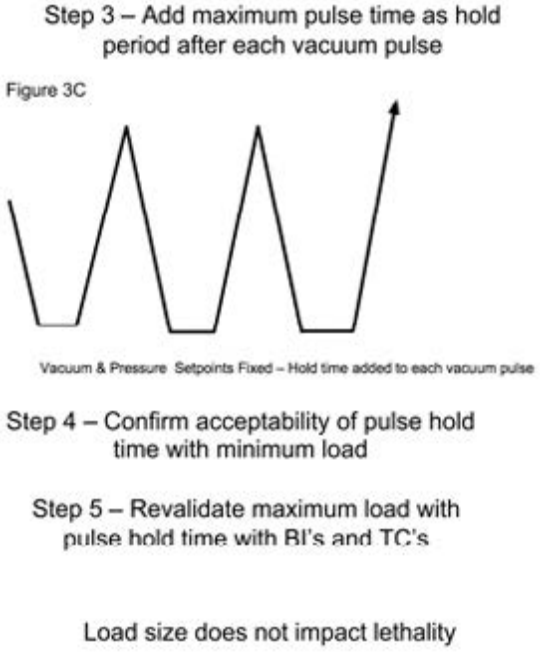
Agalloco3 sbWith this type of control, the vacuum drawdown time can vary with load size, with maximum loads typically requiring the longest time to attain the vacuum setpoint. The maximum load validation would be performed with no added hold period in each vacuum pulse and proven acceptable with physical and biological data (see Figures 3A and 3B). Next, the time required to draw the vacuum to setpoint



of the maximum load would be established as the hold time at full vacuum for each vacuum pulse (see Figure 3C). Even though the steam pressurization rate may be less important, a similar increment of hold time at the end of each steam injection is also used. This approach increases the full duration of the vacuum drawdown and steam pulses to that required for the maximum load, and assure that the minimum load has adequate time for air removal/steam penetration. The overall cycle time is extended only slightly because of the added hold times after each vacuum/steam pulse. The overall cycle times with this control scheme would be slightly longer than what is possible with vacuum/steam injection rate control. Nevertheless, even this less refined sterilizer control, validation of the maximum load(s) supports the sterilization of smaller loads comprised of similar items. A single run minimum load with thermocouples and biological indicators should be performed to confirm the process.

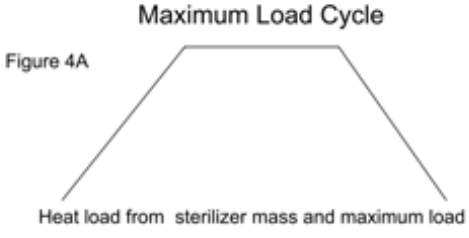
STERILIZER WITH VACUUM/ PRESSURE SET POINTS ONLY

Agalloco4 sbBecause neither the vacuum drawdown rate nor the vacuum hold time is controlled, this type of sterilizer control system is not amenable to the methods described above to assure adequate sterilization of minimum loads (see Figures 1A and 1B). Validation of this sterilizer design requires consideration of minimum and maximum loads in triplicate studies using thermocouples and biological indicators.

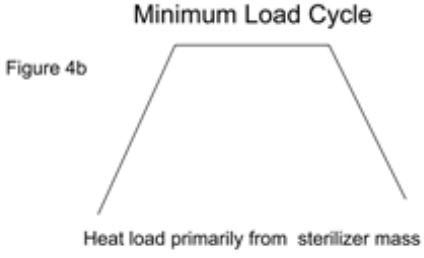


TERMINAL STERILIZATION CYCLES

The sterilization of liquid filled aqueous containers represents a more challenging situation in that not only is there a minimum lethality expectation; the materials in the load must also not be over-processed. The means to assure consistency across load size is often facilitated because terminal sterilizers are ordinarily equipped with more sophisticated control systems allowing for the regulation of heating and cooling rates. Before commencing the effort, the lethality required to sterilize the filled containers must be chosen from container mapping studies and information on the expected bioburden resistance and population. This calculation will typically include some added margin of safety to ease routine operation.



The additional mass of the filled containers results in slower heating and cooling than in the minimum load.



Replicate mapping studies with the maximum load are performed next to identify the minimum and maximum lethality locations (these are more commonly a region or zone than an individual container). During these studies the heating and cooling rates should be set at approximately 90% of the equipment's full capability (see Figure 4A). This value is selected to ensure controllability while not extending the overall cycle appreciably.

Agalloco5 sbThe critical concern in terminal sterilization is that the amount of heat to sterilize the filled containers varies with load size. The appropriate process dwell for the cycle must be established by adjusting for any lag time between the sterilization dwell control location (assumed to be somewhere in the chamber) and the 'slowest to heat' zone within the load. The lag time is greatest for the maximum load due to its greater mass but will vary based on load size (and to some extent upon the container size/ product heat capacity as well). Were the chamber heating / cooling rates allowed to vary freely for different load sizes, the dwell period, which is usually established from a probe outside the load, may start prematurely and sufficient lethality might not be delivered to smaller loads (see Figure 4B). A similar situation occurs during cooling of the load and has a similar effect.The smaller the load, the less affect it has on the overall heating of the chamber and, thus, on the initiation of the dwell period. However, it

should not be assumed that the parameters used for the maximum load are directly applicable to the minimum load. Both extremes should be confirmed, with the lag between chamber and load temperatures being determined experimentally. Because terminal sterilization processes must also consider the maximum conditions for their impact of product quality attributes, the comparative evaluation must consider high F0 locations as well. If the maximum and minimum lethality ranges are equivalent the control strategy is acceptable. Validation studies would then be performed for both maximum and minimum loads, in triplicate, using temperature probes and bioindicators. Confirmation of sterilization performance for intermediate load sizes would not be required as the extreme load sizes have been proven successful using an identical sterilization process.

CONCLUSION

The methods outlined should enable the practitioner to efficiently and confidently validate maximum and minimum loads undergoing steam sterilization with a fuller understanding of the control elements that will assure consistency of efficacy. The control suggestions indicated allow for greater flexibility in operation while maintaining the required lethality and product stability which are essential to regulatory compliance

REFERENCES

1. *FDA, Guideline - Guidance for Industry for the Submission of Documentation for Sterilization Process Validation in Applications for Human & Veterinary Drug Products, 1994.*
2. *EMA, Annex 1, Sterile Medicinal Products, 2008.*