

3

Methods of
Sterilization

5

Cutting
Contamination

9

Considerations
in Sterile
Manufacturing

11

Cleaning and
Decontamination

11

Regulatory Issues

11

Handling
Hazardous
Materials

13

What's Next?

STERILE MANUFACTURING OF SEMI-SOLIDS AND LIQUIDS



The role of sterility is a simple one--it is to protect people against infection and contamination, which is a particular issue when sterile products are used in seriously ill people whose immune systems are already compromised. Because of the risk of infection, sterility is particularly important for injectables and eye products, and the primary challenge related to their manufacturing and packaging.

"The key underlying principle behind sterile manufacturing is to produce contamination-free products and maintain their sterility until they are securely packaged and protected against contamination, thereby reducing the risk for patients," says John Erdner, VP of sales and marketing, IMA Life North America, distributors of aseptic processing solutions.

Gene Ciolfi, Vice President & General Manager Lakewood Site Operations, DPT Laboratories, added: "When we are manufacturing any product that is described as sterile, we have a legal and regulatory responsibility to make sure that it is."

However, sterile manufacturing of semi-solids and liquids is a complex process, requiring sterile (or sterilizable) ingredients and a sterile manufacturing environment. The aim of sterile processing is to reduce and prevent contamination, with the most common source of contamination being the people involved in the manufacturing process. Therefore, the most important principle in sterile processing is keeping operators and product as separated as possible, as well as reducing operator intervention to a minimum.

There are choices that need to be made at every step of processing, which may depend on the product and its ingredients and formulation, or on the facilities available:

- What method of sterilization?
- What approach to processing--aseptic techniques, restricted access barrier systems (RABS) or isolators?
- What level of automation?
- How can the formulation be optimized for sterility?
- Should small and large volumes be processed differently?
- Which regulatory requirements are the most important to follow?
- How should hazardous materials be handled?
- How is the industry going to change and how can we prepare for the future?

Vital steps and approaches in sterile manufacturing include employee training, process qualification and validation, processes and protocols for cleaning and decontamination, and methods to protect sterility and reduce contamination during processing. ●

BROUGHT TO YOU BY:



Methods of Sterilization

Sterile semi-solids and liquids can either be made in a sterile environment using sterile ingredients, or can be made in a clean environment and then sterilized once they are completed (terminal sterilization).

“Terminal sterilization is the most economical process, and the one that regulatory authorities prefer, because it gives higher levels of assurance,” says Charles Shaw, scientific advisor at DPT Laboratories.

The choice of method of sterilization will depend on the product, and those semi solids and liquids that cannot withstand terminal sterilization, including injectables, infusions, vaccines and protein- or peptide-based products, or whose packaging will be damaged in the terminal sterilization process, will have to be manufactured and packaged in a sterile environment using aseptic processing techniques (1).

Semi solid and liquid products and ingredients can be sterilized using filtration, heat, ethylene oxide gas or gamma radiation. The stability and solubility of the API will determine how it is sterilized and manufactured, for example, and the level of sterility required may vary from product to product.

- Filtration is used for liquids that are sensitive to heat or irradiation. Microfiltration uses a filter with 0.2 µm pores to remove bacteria and fungi; nanofiltration uses a filter with 20 -50 nm pores to remove viruses, and smaller pores mean lower filtration rates.

- Heat sterilization can be used for equipment and heat-stable liquids and semi-solids. This process will inactivate bacteria, fungi and viruses, but will degrade protein-based drugs.
 - Ethylene oxide gas is a powerful antioxidant, and can be used to sterilize solid materials that are sensitive to heat or irradiation. However, it is highly flammable and toxic for the operators.
 - Gamma radiation is an effective sterilizing method but has limited ability to penetrate formulations containing water.
- The use of any method of sterilization will need to be validated, to ensure that the process doesn't



“There are differences in the primary components, but the basic rules of sterile manufacturing and processing remain the same.”

Gene Ciolfi, Vice President & General Manager Lakewood Site Operations, DPT Laboratories

add anything and is only removing or inactivating contaminating microorganisms, with no impact on the product's safety or efficacy.

Handling semi-solids and liquids

Semi-solids and liquids do have to be handled differently from solid products, both in the process of sterilization and in the techniques of packaging. Liquids are generally sterilized using filtration, with

the sterile product then held in a presterilized storage tank. The oil and aqueous phase of an emulsion can be sterilized separately and then combined in a presterilized tank.

Ointments or gels can be too viscous to filter, but petrolatum (petroleum jelly) and other ointment and gel bases can become thin enough to filter when heated. The ointment or gel is then sent to a presterilized tank where it is cooled and mixed with the sterilized API (active pharmaceutical ingredient) using a sterile glove box. The API is introduced using isolator technology over the hatch, and the isolator environment is sterilized before opening the hatch. The whole process is

qualified through a media fill (see ‘Designing and qualifying the process’).

Generally, liquid manufacturing and sterilization is a one-stage process, whereas semi-solids will require a number of stages. Increasing the number of stages increases the cost and complexity, as each step will need to be validated, and may increase the need for human intervention

and the risk of contamination.

Types of packaging also differ for liquids and semi-solids--gels and ointments are likely to be packaged in tubes, whereas liquids will mostly likely be filled into a vial or a prefilled syringe.

“There are differences in the primary components, but the basic rules of sterile manufacturing and processing remain the same,” said Ciolfi. ●

COUNT ON USSM



FROM GELS AND CREAMS TO OINTMENTS AND AEROSOLS

FROM NON-STERILE TO STERILE

FROM CONCEPT TO COMMERCIALIZATION

FROM VIRTUAL TO LARGE PHARMA



Work with the leaders at bringing semi-solids and liquids to life.

www.dptlabs.com



COUNT ON USSM

Cutting Contamination



Sterile processing and manufacturing needs to remove or prevent contamination, and the most common source of contamination is from people, because of the microbial fauna naturally colonizing the body, including the hair, skin, mouth, and nose.

"A fully gowned operator may release as many as 10,000 colony forming units [CFUs] per hour using controlled and defined movements, with certain movements exacerbating the situation as his or her clothing essentially pumps air, and therefore microbes, through the openings," says Erdner.

The fundamentals of sterile processing are based on keeping operator intervention to a minimum, by separating or removing people from the aseptic environment (1). Other necessary steps include increasing automation, training employees, qualifying the processes, reducing contamination

during processing, and ensuring that material and personnel transfer does not violate the integrity of the system.

"You can fix machines and processes, but it is harder to fix human failings, so the best thing is to simply take the operator out of the equation through isolation and automation, reducing variability," says Jim Agalloco of Agalloco & Associates, a provider of technical services to the pharmaceutical and biotechnology industries. "It is only

possible to have a good product if the materials, controls, and people are right."

Keeping operator intervention to a minimum

Systems such as restricted access barrier systems (RABS) and isolators reduce the contact that operators have with the sterile products (1).

"It is easy to sterilize the packaging and the environment--it is the people that are the problem; any way that will keep people away from the products will improve the process," says Shaw.

RABS setups use the following 'Quality by Design' characteristics (2; 3) :

- A rigid wall or enclosure separating the workers from the sterile processing area
- A one-way airflow from the clean area (ISO 5/class 100 standard)
 - Passive RABS uses a laminar flow from the cleanroom

venting system; active RABS has its own HEPA filter and laminar air flow drawing air from the cleanroom and exhausting it back; closed RABS (cRABS) is a sealed system that can be operated under pressure and the air is circulated within the enclosure

- Sterilization-in-place (SIP) for parts contacting liquids and semi-solids, with the transfer of autoclavable parts aseptically
- A transfer system for consumables and other equipment
- Automation for the filling operations, or glove ports or half suits for operators who are involved with the process
- High level disinfection of all non-product contact surfaces
- The system should be in a room that is ISO 7/class 10,000 minimum
- The access doors should be lockable and/or alarmed
- Controlling contamination during any processes that involve an open door intervention through disinfection, positive airflow, and maintaining ISO 5/class 100 standards around

the area of the door using a unidirectional laminar airflow.

As an example, IMA Life North America has installed a RABS system for DPT Laboratories. "This system is not completely sealed but is contained within solid walls, and the pressure can be increased in the enclosure," says Erdner.

An isolator is a sealed system that completely segregates the worker from the sterile processing space. The equipment can be designed to separate different zones within the isolator and create pressure gradients. The air within both the isolators and RABS only travels in one direction (3). RABS and isolators use glove ports, for example in filling areas and stoppering and capping areas, to allow human interaction while minimizing the risk of contamination. RABS may be simpler to operate, lower cost and more flexible than isolators, but are not sealed systems, so there are some areas that are vulnerable to contamination (1).

Increasing automation

Manual processes increase variability, so introducing as much

automation as possible makes the process easier to validate and more reproducible.

"Every manual step is an opportunity for contamination, and the best scenario would be vials in at one end, product out at the other, without human intervention," says Erdner.

Automated systems do also reduce the number of people that need to be involved, again reducing the contamination risks as well as the operational costs.

Employee training

To reduce variability for the steps that still require operators, training is a vital part of the process.

"Operator's variability is a weak point in the process," says Agalloco. "Everyone has good and bad days, and the aim should be to make the process so robust and so reproducible that people can succeed even on their worst day."

Training needs to be robust and detailed, and include how to gown or suit-up and enter the cleanroom, how to operate the system, processing, and filling using aseptic techniques if manual

steps are required, and how to clean the system. Employees will need to qualify at each step.

"One of our training focuses is on the behavior in the cleanroom, making sure that people use aseptic technique, such as not leaning over open vials. Better training reduces the variability, and qualifies both the people and the process," says Ciolfi.

Designing and qualifying the process

Sterile processing needs to have standard operating protocols (SOPs) in place, including risk mitigation approaches and checks and balances for every step. However, to put SOPs in place, the facility design has to be optimum --as Shaw says, it is important to design in quality rather than bolt it on. It's then possible to create the best and most effective processes and procedures.

Once the system and the SOPs are in place, the effectiveness of the sterility assurance controls can be checked using a 'media fill'. These are samples of microbiological culture growth medium that go through the manufacturing process following the usual procedures, ensuring that they contact the same surfaces that the product ingredients will during manufacturing. The media is then incubated for 14 days, and the presence of microbial growth will indicate any contamination in the system. Regulatory authorities may also require a media feasibility study to confirm that the media will still support growth after processing. Media fills are typically run twice a year.

"The role of these media fills is to confirm and validate the sterility of the process. A successful media



fill means a qualified sterile manufacturing process,” says Ciolfi.

If a media fill shows up evidence of contamination, then the whole process has to be examined to find the probable root cause.

“If the root cause is found, then the issue will be easy to fix,” says Ciolfi. “However, if it can’t be found, then it is a case of going right back to the beginning, setting the process up all over again and revalidating it.”

However, the necessity for the media fills and the media feasibility studies adds to the burden of the development side of product manufacturing, particularly for small companies, and it’s possible that, now that sterile manufacturing is so automated, their necessity is becoming more limited.

“The costs of sterile manufacturing have fallen and the effectiveness has increased,” says Agalloco. “Now, most facilities are so good that the microbiological testing process is almost ‘ceremonial’, and only the very worst plants will fail. Some monitoring processes can even increase the risk of contamination. However, media fills are likely to remain in place as it will always be needed by the weakest companies, and regulators are unlikely to be happy with no testing.”

The products will also need to be tested for the stability of the active ingredient before and after processing.

Protecting sterility during material and personnel transfer

As mentioned before, sterile manufacturing systems will generally use cascading airflows to maintain sterility, with the highest (positive) air pressure in the cleanest area,

reducing the risk of environmental contaminants and particles moving from ‘dirty’ to ‘clean’ areas, and the lowest pressure areas acting as ‘airsinks’. Workers entering the system will usually go through multiple gowning or suiting steps and pass through a number of cleanrooms or airlocks that become increasingly hygienic.

“The large pressure cascade gives greater assurance that the products are not contaminated with particles or pathogens,” says Erdner.

Generally, anything that has to come into the sterile environment is enclosed in multiple bags or wrappings, with layers removed in increasingly clean environments separated by airlocks (4). Techniques include trapping the packaging in the airlock door, so that the item is transferred into the cleaner area and the packaging remains in the ‘dirty’ area. Any damage to the wrapping can cause problems.

“It is vital to think about what is needed and how it gets into the sterile system, from a piece of paper or a pen to a clock,” says Agalloco. “However, getting things out of the system is not as hard as getting them in.”

This process is effectively reversed when items are removed from the system, and the sterility is maintained by the positive airflow from ‘clean’ to ‘dirty’.

Reducing contamination during processing

Packaging components for semi-solids and liquids, such as vials or syringes, can be supplied already sterile and double-bagged, or manually washed and then sterilized as part of the process. Tech-

niques will vary according to the material—for example, vials can be decontaminated by heating to high temperatures in a depyrogenation tunnel, and plastic can be sterilized using gamma radiation. It is important to maintain the sterility of the vial between depyrogenation and filling, and reducing the distance that any sterile components or ingredients have to travel cuts the risk of contamination.

Increasing integration, keeping the processes within one piece of equipment or integrated system, will also reduce the risk of contamination by

reducing the need for transfers from one piece of equipment to the next.

“The sterile manufacturing process should be as completely integrated as possible,” says Ciolfi.

This doesn’t necessarily mean buying a fully-integrated system from the get-go; systems such as those from IMA can be created from modules that can be added on as required.

Increasing the efficiency of the system is also important, because any major intervention, such as blockages, repairs, or removing damaged vials, will generally

require stopping the production line. This will expose other vials to potential microbial contamination, and may mean throwing contaminated vials, or even, occasionally, an entire batch.

In a sealed system, if the production line has to be stopped and the system opened up, the batch may have to be thrown away. Shaw says: “This kind of wastage can be built into the costs. Any sterility failures can shut plants down for months, so it is worthwhile writing off one single batch,” says Shaw.

There are a number of approach-

es to increasing efficiency and reducing breakdowns, and IMA’s approach is to make the whole process a little gentler.

“The line for smaller batch sizes runs at a slower speed of 120vpm, which provides the opportunity for us to design the component-handling parts with a little wider tolerances. The entire system is more ‘forgiving’ of component variability increasing the overall efficiency. We believe that running slower can sometimes result in increased net production,” says Erdner.

Contamination doesn’t just involve pathogens—fragments of stoppers or broken glass can also contaminate the finished product, creating a hazard for patients. As the rubber stoppers that seal vials move they generate particles, in what is known as the ‘eraser’ effect, and these can be transferred into the vial during stoppering and sealing.

“One way to avoid this,” explains Erdner, “is to ensure that the stopper sorting and pick up is positioned below the neck of the vial and there is minimal component movement above the vial during placement of the stopper. In the capping process, we synchronize the rotation of the cap and vial, as well as limit the amount of rotation to 460° to minimize particulate generation. Particle count in this area will remain under 100 per cubic foot of air. A continuous vertical force is maintained and monitored to ensure consistent sealing results.”

Once the products are filled and sealed, then the sterile part of the process is completed, but any labeling and secondary packaging must not affect the integrity. ●



Considerations in Sterile Manufacturing

There are a number of considerations that must be taken in sterile manufacturing, from the volumes to be handled through the dosing accuracy in the vials or syringes, to the costs. Optimizing formulations for sterility is perhaps one of the key considerations.

Optimizing formulation for sterility

Sterility requirements may constrain the formulation of a finished drug, and so drug developers need to keep the sterile manufacturing process in mind during the development process, even before formulation and API manufacturing. Collaboration as early as possible between formulation teams and microbiologists or sterile manufacturing personnel can help develop robust, safe, and easily sterilizable formulations, by advising on how to protect against contamination, or how to remove and destroy any such contaminants (5).

“Developers should think about the sterile manufacturing process for the market at the end of phase I--by phase III it is too late and the product is defined,” says Agalloco.

It’s important to begin the formulation process by understanding what characteristics and factors will support microbial growth, and use this information to help select the ingredients that are the safest and easiest to sterilize. It’s key that both excipients and APIs come from reputable sources with good quality testing processes and clear sup-

ply chains, and that they are thoroughly audited and checked before use (5).

To reduce the number of ingredients to be sterilized, and the steps required in the process, formulations should be kept as simple as possible, using basic carriers for the API such as water or petrolatum where possible, depending on the route of administration. Other ingredients that may be needed could include a buffer, antioxidant, and chelator. Simple adjustments to formulations can improve the chance of inhibiting microbiological growth, such as adjusting the pH (5), though it’s vital to ensure that this doesn’t affect the finished products safety, efficacy, or pharmacokinetics.

It’s also important to be aware of particle size for any products that will be sterilized through filtration, to ensure that the API (and therefore the end product’s efficacy) is not removed in the process. Any ingredients should also be easily controlled and standardized--for example, natural ingredients are more likely to come from sources that could be contaminated, and are harder to sterilize or standardize.

“Natural materials should be avoided in formulations where possible, for example using synthetic thickeners rather than xanthan gum, as these are easier to control,” says Shaw.

Handling small and large volumes

Sterile manufacturers will have to handle both small and large volumes, and a flexible system is needed to cope with the variability needed for manufacturing smaller

volumes, such as those for very small markets or for clinical trials, and large volumes for sterile products for the major markets.

Larger volumes will generally be more-cost effective, as there will be fewer set-up and clean-down costs, and systems designed for larger volumes are likely to be faster and have more automation. However, machines designed for smaller volumes can add flexibility to a manufacturer’s repertoire.

“Large volumes increase the length of the run, meaning that sterility has to be maintained over a longer period, and perhaps over a number of shift changes. The best way to maintain sterility in this situation may be to break the process down into days or even individual

shifts, and clean the room each day or each shift,” says Shaw.

Changing sizes of packaging is a major intervention, and changes such as these, and shift changes, also have to be simulated during media fills.

Reducing the velocity that vials go through the system can paradoxically increase the overall production result. Some systems, such as IMA’s, are designed to run at around 60-70 vials a minute, for example, but have just a 20 minute change-over process, compared with several hours for some faster machines.

Dosing accuracy

In common with other prescription drugs, some sterile-manufactured drugs may have to be measured

and dosed very precisely. The quantities of drug per vial or syringe can be measured very accurately using a number of different techniques (4), including:

- rotary dosing pumps
- peristaltic pumps
- positive displacement pumps
- time-pressure filling systems
- mass flow meters
- check-weighing.

“Statistical or 100% check-weighing allows manufacturers to ensure that they keep the process within the target range by automatically making adjustments to the fill volume if necessary,” says Erdner. “The optimum solution for reliability would be 100% weighing and filling, and this is important for high-cost or high-potency products.”

Historically, many filling machines only offer one of these filling methods. As different methods suit different products, being able to change the filling system from batch to batch improves flexibility.

“Making a system interchangeable is an advantage for companies dealing with different types of liquids and semi-solids, such as viscous gels and ointments, or alcohol- or water-based liquids,” says Erdner.

Maintaining sterility during use

An additional issue in sterile processing and packaging is designing in ways that products can remain as sterile as possible during use, particularly for multi-use products. Many sterile products also include preservatives, because multiuse products are only sterile until the first use. After this, the preservatives keep the product free of contamination. The delivery device can also help to maintain sterility--for example, preservatives in eye drops and nasal sprays can cause problems, so the delivery systems can have a sterilizing filter built in, so that as product is used and air is drawn in to replace it, the filter prevents contamination. This allows these products to be preservative-free.

Considering costs

Sterile manufacturing does add to manufacturing and packaging costs, as it requires additional stages and more controls, so manufacturers will need to balance cost with safety and sterility standards.

“Sterile products are generally branded prescription products, so they are less cost-sensitive than over the counter or generic products,” says Shaw. ●



Cleaning and Decontamination

Cleanrooms for sterile manufacturing are created to strict criteria laid down by regulatory bodies, ensuring that they are as 'cleanable' as possible. Examples of design to facilitate this include the use of smooth and nonporous materials for the walls, floors, and any other surfaces; the use of curves rather than straight edges and corners to make cleaning easier; avoiding windows and ledges where possible; and making sure that areas such as shelves, light fixtures and door handles are designed to be easy to clean. The equipment should be made of stainless steel wherever possible, and HEPA filters keep the air clean.

"It is important to keep natural products such as wood or card out of the system, as it is not cleanable, and it can carry spores and microbes," says Shaw. "For this reason, secondary packaging needs to be kept

well away from the sterile areas."

The process for cleaning and sanitizing the facility, which uses disinfectants and sporicidal agents as well as sterile water, has to be scrupulous and detailed, right to the smallest details, such as cleaning behind the clock.

"The best trained and most capable people actually have to be the facility cleaners and sanitizers," says Agalloco, "but this can be a weak link as it is often outsourced. Ideally there need to be random inspections and reviews of this part of the process."

Isolators generally have automated cleaning procedures, whereas other systems have to be opened and cleaned. If parts of the system have to be removed and cleaned by hand, they should be wrapped after washing and then autoclaved before being reintroduced into the system. ●



Regulatory Issues

Regulators want reliability, safety, and certainty from the sterile manufacturing process, and they enforce this through regulations and guidelines. The rules are similar between the U.S. and Europe, but most manufacturers tend to gravitate towards the most stringent ones, as these will cover all potential issues.

"There are two key different regulatory systems, the European rules as described in Annex 1 (5) and the U.S. rules (6)," says Agalloco.

loco. "The EU regulations are more definitive, and the U.S. ones are more flexible and less well defined. This means that

the EU guidelines can be too restrictive for some people, but may help manufacturers new to this area, and the U.S. guidelines may not provide enough guidance for people. However, the regulations are still evolving."

An example of the differences in is vial sealing--the European and U.S. regulations require the crimping of the vial under different standards of cleanliness.

"Now the U.S. has joined the Pharmaceutical Inspection Con-

vention and Pharmaceutical Inspection Co-operation Scheme [PIC/S], there is likely to be more cooperation between the U.S. and Europe," says Agalloco.

There are subtle differences between requirements for sterile manufacturing for clinical trials and for the market.

"The requirements for commercial use are more stringent than those for clinical trial use--typically there is more process validation for marketed products--but it is all still being given to people, so it really should all go through the same processes," says Ciolfi. ●

"The requirements for commercial use are more stringent than those for clinical trial use--typically there is more process validation for marketed products--but it is all still being given to people, so it really should all go through the same processes."

Gene Ciolfi, Vice President & General Manager Lakewood Site Operations, DPT Laboratories

Handling Hazardous Materials

Creating sterile versions of hazardous materials that could be toxic to the operators, such as very high potency anticancer drugs or radiolabelled therapeutics and diagnostics, can cause issues.

"There is a double challenge in hazardous sterile manufacturing, with an aim to protect both the patient from contamination and the worker from exposure," says Agalloco.

Generally, sterile products are prepared under positive pressure to prevent environmental contaminations entering the preparation area, and potentially hazardous agents are prepared under negative pressure to prevent them reaching the environment.

"The dilemma is whether to

use positive or negative pressure in the isolator, and there is no single answer," says Agalloco.

To get around this, specialist companies often handle sterile hazardous products, with operators wearing full-face respirators and full body suits, using disposable equipment where possible, or working with completely sealed isolators or cRABS.

"We would generally use the same basic process for hazardous and non-hazardous materials, but would ensure that members of staff are protected, for example they would be monitored for radionuclide exposure, and a working group would look at opportunities to improve their safety," says Ciolfi. ●



What's Next?

Like all sectors of the biopharma industry, sterile processing is evolving all the time

"There are a lot of shifts within the industry at the moment," says Agalloco. "Larger companies are moving to isolation technologies, with the product inside and workers outside, with an aim to increase the separation between the two. However, smaller companies may struggle with this.

These moves are likely to be supported by regulatory authorities.

"The FDA and EMEA are pushing towards the use of isolators, with grade A or class 100 standards inside the system. This can have cost issues, but the isolators can be operated in cleanrooms that are as low as class C or class D, which will reduce operational costs," says Erdner.

Despite this, there will still be cost implications in these changes, as Ciolfi adds: "This could be costly and challenging for some companies, especially smaller ones,

as they will need to install new equipment and implement additional training for all their staff."

There are changes in packaging that will have an impact on the filling and sealing stage of sterile manufacturing—for example more injectable products are being packaged in disposable syringes and novel delivery systems such as microneedles are in development. Manufacturers are also tending towards using plastic rather than glass, as it is cheaper to manufacture, shipping costs are lower because it is lighter, and plastic is less likely to break or chip during filling, sealing, and shipping, reducing the risk to patients and cutting the likelihood of having to stop the line during processing. Changes in the process itself could additionally improve efficiency and lower costs.

"There is a trend towards using disposables, from filters right through to fill needles, which will reduce cleaning and assembly errors," says Agalloco.

Looking to other industries could drive changes in sterile manufacturing.

"We can learn a lot from the huge scale clean and sterile manufacturing in the food, electronics, and even the automobile industry. These industries have focused on process simplification, whereas the biopharma industry's approach has tended towards optimizing technologies. The electronics industry, with its adoption of Six Sigma, should be taken as an example."

Agalloco concluded: "The technology is there but manufacturing perhaps doesn't get the emphasis and investment it needs—investment can get focused on marketing and R&D." ●



Bibliography

1. **Mayberry, Jonnatha.** Creating Safe Pharmaceuticals, Aseptically. *PharmPro*. January 11, 2012.
2. **Agalloco, James P and Akers, James E.** RABS and Advanced Aseptic Processing. *Pharmaceutical Technology*. 2006, Vol. 30, Supplement, Aseptic processing, pp. 20-24.
3. **Lysfjord, Jack.** ISPE Definition: Restricted Access Barrier Systems (RABS) for Aseptic Processing. *Pharmaceutical Engineering*. November/December 2005, Vol. 25, 6.
4. **Rothbauer, Jürgen, Schäfer, Jürgen and Beyer, Sonja.** From Clean Rooms to RABS and Isolators — Design Criteria for Barrier Technologies. *Process Worldwide*. October 8, 2011.
5. **Akers, Michael J, Strother, Curtis S and Wald, Mark R.** Sterile Formulation. [book auth.] Henry C Vogel and Celeste L Todaro. *Fermentation and Biochemical Engineering Handbook: Principles, Process Design, and Equipment*. s.l. : William Andrew, 1996, pp. 616-634.
6. **Singer, Donald C.** A Strategy for Developing Robust Pharmaceutical Microbiological Control. *American Pharmaceutical review*. August 27, 2012.
7. **Poslovski, Matthias.** *Pharmaceutical filling systems – an overview*. PharmaTech.com.
8. **European Commission Enterprise and Industry Directorate-General.** *The Rules Governing Medicinal Products in the European Union*. [ed.] EudraLex. Brussels : s.n., 2008. Vol. Volume 4: EU Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use (Annex 1: Manufacture of Sterile Medicinal Products [corrected version]).
9. **U.S. Department of Health and Human Services Food and Drug Administration.** *Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice*. Rockville : s.n., 2004.
10. **Friedman, Barry A.** FDA Increases Vigilance on Aseptic Processing Facilities. *Bio/Pharmaceutical Outsourcing Report*. November 2011, Vol. 16, 11.