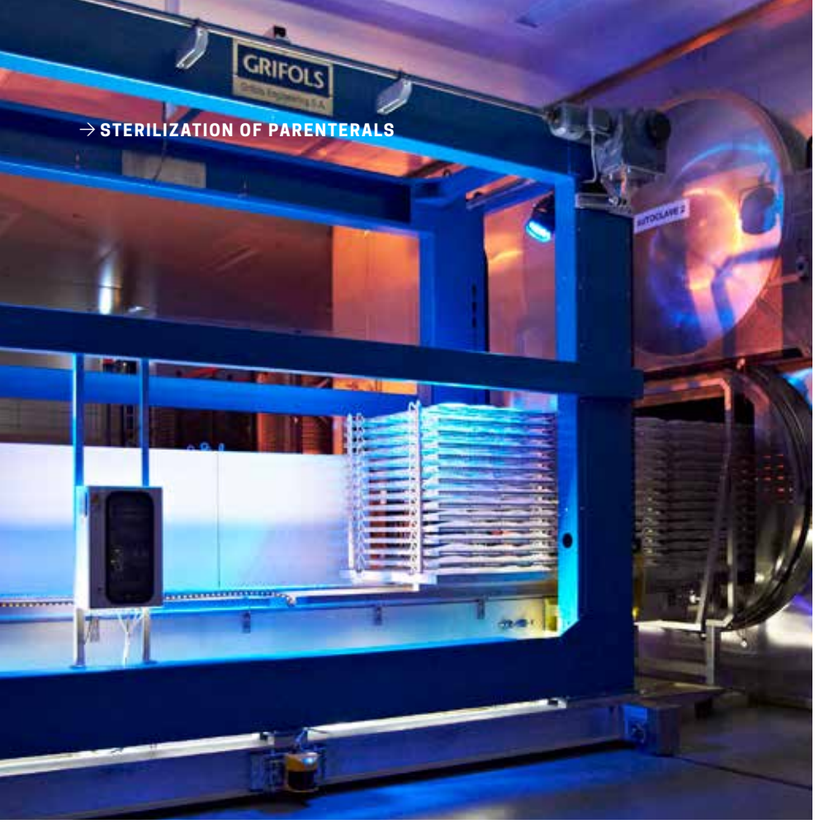

TERMINAL STERILIZATION FOR PARENTERAL DRUGS: FINDING THE RIGHT CDMO PARTNER

→ BY **LLUÍS TWOSE,** LABORATORIOS GRIFOLS

Parenteral products must undergo some form of sterilization, and terminal sterilization is generally the preferred method. Because sterile products manufacturing requires specialized expertise, many pharmaceutical companies rely on contract service providers. Choosing a CDMO with demonstrated success developing and commercializing robust terminal sterilization processes is essential to ensure patient safety.

GROWING DEMAND FOR STERILE DRUGS

Demand for sterile injectable drugs has been increasing steadily in recent years and will continue to do so, according to Transparency Market Research. The firm predicts that the global sterile injectable drug market will expand at a compound annual growth rate of 11.1% from $348.5 billion in 2016 to $901.3 billion in 2025.[1]

Expansion of the market for biologic drugs, which can only be injected, is one key driver. There is also growing demand for small-molecule parenteral products, including heart medications, antibiotics and analgesics, as well as standard intravenous glucose, potassium and saline solutions. Intravenous infusion provides an immediate therapeutic effect by rapidly delivering medication directly into the bloodstream, with most treatments occurring in hospitals.

Sterile injectables can be formulated as concentrated admixtures, which are often freeze-dried in glass vials and require dilution before administration, or as diluted, premixed solutions packaged in flexible plastic bags.

NUMEROUS STERILIZATION METHODS

To ensure patient safety, parenteral/injectable drug products must be sterilized to destroy any potential microbial contaminants (fungi, bacteria).

The most common sterilization method involves heating under pressure in the presence of water to generate steam; this method is recommended by various pharmacopeias. Generally, steam sterilization is performed in an autoclave and can be used for drug products, medical devices, plastic bags and other single-use equipment, glass containers, surgical dressings and more.

Sterilization can also be achieved via dry heating. Much higher temperatures (180–200 °C) are required for this method; however, these temperatures are not suitable for most drug products. Dry heating is also not appropriate for aqueous solutions and is most commonly used to sterilize glassware, metal and other surfaces.

Exposure to radiation is another sterilization method used throughout the industry. Gamma radiation is the most common, though other options include infrared and ultraviolet radiation and high-velocity electrons. Radiation is typically used for the sterilization of single-use components/systems, but it can be used for packaged drug products.

Treatment with gases is also a sterilization alternative. Such gases include ethylene oxide, formaldehyde, glutaraldehyde, propylene oxide, hydrogen peroxide and chlorine dioxide. This method is more commonly used to sterilize clean-room suites.

Sterilization via filtration is the only option if the other processes are not suitable for the specific product or component. In filtration, the final drug product solution is passed through a filter that has been produced under aseptic manufacturing conditions and designed with appropriate pore sizes/surface chemistries that remove bacteria via size exclusion, entrapment, electrostatic attraction and other modalities.

CAREFUL SELECTION IS ESSENTIAL

Sterilization is often performed under harsh conditions. Selection of an appropriate sterilization method requires an in-depth understanding of the physicochemical properties of the drug substance and the characteristics of the final formulated product. Sterilization methods using high heat or radiation will, for instance, cause degradation of most biologic drug substances. For biopharmaceutical products, therefore, sterile filtration under aseptic conditions is required.

Small-molecule APIs may also be sensitive to heat or radiation. In some cases, one of these methods may be suitable. In others, it may only be necessary to slightly reduce the sterilization temperature and extend the process time.

WHY TERMINAL STERILIZATION

Terminal sterilization is the preferred method for drug products because, in this process, sterilization takes place after the product has been filled into the primary packaging. Because of this, there are no further opportunities for contamination due to human intervention. As mentioned above, terminal sterilization with moist heat (i.e., steam) is recommended by all pharmacopeias, typically with heating to 121 °C at 15 psi for 15 minutes.

EMPHASIS ON VALIDATION

Because sterilization is a crucial process in the manufacture of drug products and a key step in ensuring patient safety, the process must be controlled to ensure that the product is of the intended quality based on information collected during the manufacturing process. Monitoring is necessary to ensure compliance with specific good manufacturing practice (GMP) requirements and sterility assurance.

Extensive testing is conducted during the development process to identify appropriate sterilization conditions for a given API/drug product. The amount of time during which the unsterilized product can sit in the product package without an increase in microbial contamination is thus determined. The temperature, pressure and time for sterilization must also be measured for each product.

Once an effective sterilization process is developed, it is then subjected to validation. Three key parameters are considered during this process: the sterilization temperature, the sterilization time, the pressure and the bioburden reduction. Another important parameter to take into consideration is the holding time between vial/bag filling and sterilization.

The time allowed between filling and sterilization depends on the nature of the parenteral solution and its propensity to culture microbes. For some solutions, e.g., concentrated salt solutions, there is little likelihood that microbes will grow. For others, however, e.g., glucose solutions, there is a high likelihood of microbial growth. The hold times for the latter solutions must be kept to a minimum.

It is also essential during sterilization that the desired temperature is reached within all areas of the autoclave and is maintained throughout the process. For successful validation, it is necessary to demonstrate that all positions within the autoclave, including the coldest locations, reach the required temperature for the required length of time.

Similarly, the appropriate pressure must be maintained during the steam sterilization process. It is the combination of temperature and pressure that generates the conditions necessary to achieve sterilization. Therefore, if the right pressure is not reached and maintained, complete sterilization may not be achieved.

Finally, the effectiveness of the sterilization process with respect to reducing the bioburden to specified levels must be validated. Biological indicators are placed in the product containers before sterilization, and confirmation of their destruction following completion of the process provides the evidence needed.

In fact, many different chemical parameters are evaluated before and after sterilization to confirm the effectiveness of the sterilization process. Ultimately, several key analytical methods are selected and validated for use during commercial manufacturing.

SELECTION OF AN APPROPRIATE STERILIZATION METHOD REQUIRES AN IN-DEPTH UNDERSTANDING OF THE PHYSICOCHEMICAL PROPERTIES **OF THE DRUG SUBSTANCE AND THE CHARACTERISTICS OF THE FINAL FORMULATED PRODUCT.**

TERMINAL STERILIZATION AT GRIFOLS

Grifols uses many different sterilization processes across its various operations. For parenteral drug products, however, we use terminal steam sterilization wherever possible owing to its reliability and in accordance with pharmacopeia guidelines. We have the capacity to sterilize approximately 70 million units per year, including both Grifols products and products produced for our customers.

We view sterilization as the most critical process that we manage. As such, we have established a robust validation process to ensure that each drug product produced by Grifols meets the highest quality standards. Terminal sterilization of parenteral

THREE KEY PARAMETERS ARE CONSIDERED DURING VALIDATION: **THE STERILIZATION TEMPERATURE, THE STERILIZATION TIME, THE PRESSURE AND THE BIOBURDEN REDUCTION.**

drug products is performed at 121 °C when possible. For heat-sensitive APIs, a lower temperature is used for a longer process time. For example, lipid emulsions undergo degradation at 121 °C but can withstand sterilization at 115 °C.

For medical devices and product components, such as plastic (twist-off) stoppers used in the manufacture of premixed parenterals, gamma radiation is used as a cost-effective, easy-to-implement method that does not require drying (which is the case with steam). Steam sterilization is performed in-house. Sterilization by gas or gamma radiation is performed by third-party providers with the necessary specialized equipment and expertise.

SPECIALISTS IN PREMIXED BAGS

Both governments and the pharmaceutical industry prefer that parenteral drug solutions be prepared by the manufacturer, rather than the hospital/caregiver, to reduce risk and ensure greater patient safety. The use of premixed bags eliminates the need for dilution and ensures compliance with the Joint Commission on the Accreditation of Healthcare Organizations (JCAHO) standards and U.S. Pharmacopeia 797 guidelines.

Grifols has extensive expertise in the production of parenteral drug products in premixed bags. We have been manufacturing bags of glucose, saline and other intravenous solutions for cardiovascular drugs, analgesic drugs, antibiotics, etc. for many years. As a CDMO, we apply this experience to the formulation of small-molecule parenteral products in premixed bags and have successfully manufactured many drugs based on a number of different APIs.

While standard saline/glucose solutions and small-molecule drug products manufactured in premixed bags require terminal sterilization, the processes for each can be quite different. Saline and glucose solutions are not easily degraded. Historically, sterilization of these solutions has been performed using overkill cycles with long process times.

Drug products based on APIs cannot typically withstand the conditions traditionally used for IV solutions. Because sterilization must be accomplished without causing any degradation of the API, terminal sterilization processes have to be customized to in order to meet the specific properties of each small-molecule drug product.

The sterilization of drug products in premixed bags also requires consideration of the potential impact of the plastic bags used to contain the products. Recently, regulatory agencies have emphasized the need for drug manufacturers to confirm that no leachables or extractables are generated during terminal sterilization at high temperatures.

Grifols is working closely with its plastic suppliers to ensure that the plastic bags we use for our premixed drug product solutions do not have leachable/extractable issues that can impact patient health. Our approach includes not only careful selection of resin composition, but also the design and control of sterilization processes that minimize the potential for leachable and extractable formation – while still ensuring effective sterilization.

LONG HISTORY OF QUALITY STERILIZATION PERFORMANCE

Grifols has been producing sterile products for nearly 75 years and performing terminal sterilization for nearly 50 years. In fact, we mainly produce sterile injectable products. Our customers bring their projects to us because we have extensive experience autoclaving IV solutions and a wide range of small-molecule parenteral drug products with varying properties, as well as challenging nutritional products and medical devices. Our knowledge base includes designing customized sterilization cycles with respect to temperature, pressure and time.

Grifols has also demonstrated the ability to develop effective validation processes for terminal sterilization of parenteral products. In 2007, we became the first Spanish company to obtain regulatory approval for parametric release of parenteral solutions in glass and flexible containers from our EMA- and FDA-certified production plants in Barcelona and Murcia, Spain. We expect to have the parametric release approval from the U.S. FDA in a short period of time.

Parametric release is authorized for companies that have historically shown excellent sterility test results and high consistency in their overall quality systems. It is a guarantee that the product has attained the desired quality and is based on information collected during manufacturing according to GMP.

It also reflects the culture of quality, effective quality systems and commitment to continuous improvement and ongoing achievement to the highest quality levels that drives Grifols. P

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