A Risk Analysis Approach to Producing Environmentally Sensitive Parenterals

Jun 25, 2018 11:58:08 AM PA0-M06-18-CL-007

Tags: CDMO Parenterals Grifols

Production of parenteral drugs is a complex and challenging process, and when APIs used in formulation are sensitive to oxygen, moisture or light, issues in manufacturing are multiplied. Using risk analysis and a quality-by-design (QbD) approach across all aspects of the manufacturing process, from the choice of environmental controls to the selection of packaging components, can ensure the consistent production of even the most sensitive high-quality parenteral drug products.

Complex and Challenging

The manufacture of sterile parenteral products is generally more complex than the production of oral dosage forms. In addition to assuring the stability of the API in the formulated product, manufacturers must demonstrate compatibility between the drug substance/product solution and all packaging components (glass/plastic containers, rubber stoppers, etc.). For any container, E&L studies must be performed with extractable and leachable testing necessary to ensure that no components of the container (including additives, such as antioxidants, stabilizers, plasticizers, lubricants, solvents and/or dyes) contaminate the drug product. Sterilization processes must be performed to guarantee the sterility of the formulated product, but without causing any degradation of the product or an adverse effect on the container.

This complexity is magnified if the active pharmaceutical ingredient (API) in a parenteral product can react with the oxygen or can be degraded if exposed to light. If proper precautions are not taken, significant consequences may arise. In addition to changing the color of the solution, and reducing the shelf life, the toxicity profile can be affected, leading to reduced efficacy and safety.

The most challenging APIs and parenteral products are those that are oxygen-sensitive; there are generally more readily available, less complicated solutions for protecting APIs and formulated products from exposure to light and moisture. Removal of all residual oxygen in the air throughout the entire production process, from the initial vessel-filling step to final packaging is more difficult, and special equipment and operator expertise is needed to ensure these parenteral products are successfully manufactured.

Identifying Environmental Sensitivities

At Grifols, we produce parenteral products and provide contract manufacturing services. For the Grifols products that we manufacture, physical property data is already available for the API, however, for projects brought to us by our clients, the level of available information can vary significantly. In some cases, clients have conducted stability studies to evaluate the impact of changes in pH, oxygen, light and temperature on their APIs and identified potential sensitivities. In others, little information is available and these studies can be performed in-house.

All of the information generated about a project is shared at periodic meetings with the full project team, which includes representatives from R&D, production, QA/QC, etc. This knowledge sharing is essential to ensure that appropriate processes are developed. Operators working on projects that involve sensitive products, which require special handling, receive additional training specific to the needs of the project, including the consequences of exposure.

Using a QbD Approach

For all the projects at Grifols, we design quality into the process from the start. Such a quality-by-design (QbD) approach is particularly beneficial for the production of parenteral products based on sensitive APIs because it ensures that the quality target product profiles (QTPP) are well defined from the start, allowing for identification of the critical quality attributes (CQAs) of the product that can be impacted by material attributes and process conditions.

Identification of the CQAs is used to determine which material attributes will be critical to the process and which have the potential to affect the stability of the API during preparation of the solution, filling, sterilization, packaging and storage. In addition to the API, excipients, and primary (such as the flexible plastic bags at Grifols) and secondary container closure system (such as clear or aluminum overwrap) and packaging materials (Cardboard box) are characterized.

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About the Company

Grifols ›

Grifols is a global healthcare company founded in Barcelona, Spain in 1940, focused on the development of plasma-derived therapies, diagnostics, and hospital pharmacy products. We offer our experience in intravenous products through Grifols Partnership, the contract manufacturing service specialized on development and manufacturing products that require advanced technology and complex production processes such as sterile solutions, mainly in flexible bags and vials.

Indeed, the selection of the appropriate primary and secondary container closed system is essential for environmentally sensitive formulations. Polymer compositions that are both compatible with the parenteral drug product and act as oxygen, light or moisture barriers must be used for primary and/or secondary packaging. For highly sensitive products, the use of secondary packaging, such as an aluminum overwrap may be recommended. For highly oxygen-sensitive APIs, the addition of oxygen scavengers between the primary and secondary bags may be required to reduce residual oxygen levels and extend product shelf lives.

Risk Analysis in Process Development

Once the critical materials have been identified, the next step in the QbD approach is to develop a deep understanding of the process in order to identify the critical process parameters (CPPs) that can impact the CQAs. The relevant design space for the process is determined by conducting a design of experiments (DoE) investigation at the lab scale.

For all processes, scalability is a primary concern from the start. This consideration, along with the choice of materials and required process conditions, determines which processing equipment will be appropriate for each step in the manufacturing process.

For the initial step – the preparation of the solution formulation – environmentally sensitive products generally require additional protections. For oxygen-sensitive products, a deoxygenating process is carried out, for instance, the air in the mixing vessel or the air in the solution, which is typically removed by flushing or stripping with nitrogen. Thus, for this type of product, the process requires a supply of nitrogen, which should be identified at the process development stage.

QbD results are applied in conjunction with our process understanding to the filtration, filling and sterilization steps as well, with different options evaluated in order to develop optimum and robust solutions. In these risk analyses, all sources of variability are considered that may impact the CQAs. With environmentally sensitive products, some of the steps that are not critical for standard products can have an impact on CQAs. Consequently, the risk analyses conducted for these challenging products are more extensive. The performance of a comprehensive risk analysis is crucial to the development of effective processes for environmentally sensitive products because they enable us to identify the sources of potential problems and implement measures to prevent those issues from arising.

Once the limits and potential areas of concern have been identified, the next step is to determine the process conditions and controls needed to ensure the process will be robust and scalable. As an example, after filling of a light-sensitive product into the primary flexible bag, it may be determined that an overwrap must be added within a time limit to ensure that no degradation of the product occurs.

It is also worth noting that at Grifols, we have implemented automation solutions throughout our manufacturing facilities to reduce the potential for human error and process variability. Automation also helps reduce the likelihood that environmentally sensitive products will be exposed to the air, light or moisture. We have found that increased automation leads to more robust manufacturing processes.

The Analytical Factor

Analytical methods for environmentally sensitive compounds are needed to ensure that the degradation of the API does not occur at any time throughout the manufacturing, filling and terminal sterilization processes. In many cases, these methods—which are intended to detect potential degradation products—must be developed in-house.

However, as is the case during process development, analytical method development for environmentally sensitive products can present challenges. Sample-handling solutions are needed to ensure that the samples are not exposed to the environment. Methods must also be designed to ensure that degradation does not occur during the analysis.

Long-term Experience

Grifols Partnership, the CDMO business of Grifols, has been manufacturing parenteral products for over 75 years and has extensive experience working with both non-sensitive and highly sensitive APIs. We have acquired broad expertise in the development of robust processes for the production of all numerous types of sensitive products and we apply this knowledge to each new client project. The use of QbD, DoE and risk analysis approaches combined with our quality culture ensures the production of parenteral products of the highest quality—regardless of the sensitivity of the API.

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Oriol Riera holds a degree in pharmacy from the University of Barcelona. He has more than 25 years experience in the pharmaceutical development of medicinal products and plastic containers for medicinal products on an international level, and more than 8 years experience using a quality-by-design (QbD) approach from early development to technology transfer. His experience is focused on parental drug products design (QTPP, cQA) and process design (DoE, cPP, Risk Analysis) as well as formulation, manufacturing process development, sterilization process design and E&L studies.

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HG/CM/0618/0024

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