White Paper

Risk Assessment for Single-Use Pharmaceutical Manufacturing Systems

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In order to help ensure patient safety, biopharmaceutical companies must identify possible risks and mitigate exposure to those risks. Risk assessment programs are conducted to support this critical objective by identifying materials and consumables suitable for incorporation into manufacturing processes.

Adoption of single-use systems adds a new layer of complexity to risk assessment. Single-use technology is now present in higher risk aseptic processing applications, such as the final sterile filtration step after formulation of the drug substance, and this can present new challenges for traditional risk assessment programs.

Because current regulatory guidelines only offer general direction for risk assessments, drug manufacturers may not be certain of how best to approach the process. In fact, various industry groups are attempting to develop more detailed standard qualification requirements for single-use pharmaceutical manufacturing systems based upon current, relatively general regulations such as the following examples from the FDA and European Commission:

- "Equipment shall be constructed so that surfaces that contact components, in-process materials, or drug products shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements." and "Production equipment shall not present any hazard to the products."[1]
- "The parts of the production equipment that come into contact with the product must not be reactive, additive or absorptive to such an extent that it will affect the quality of the product and thus present any hazard."[2]

This white paper offers insight into current and expected industry and regulatory requirements for single-use pharmaceutical manufacturing systems, such as more detailed extractables and material qualification data. A review of single-use system quality and regulatory documentation based on these requirements is presented, which will make risk assessments, based on ICH Q9 guidance, more efficient for the sterile drug product manufacturer.

Residual Impurities

The origin of the impurity may determine which guidelines and associated control limits to follow in the final evaluation of the drug impurity. Relevant guidelines may include:

- ICH Q3A (Impurities in New Drug Substances)
- ICH Q3B (Impurities in New Drug Products)
- ICH Q3C (Impurities: Guideline for Residual Solvents)
- ICH Q3D (Impurities: Guideline for Elemental Impurities)
- ICH M7 (Assessment and control of DNA reactive impurities in pharmaceuticals to limit potential carcinogenic risk)
- PQRI-PODP (under development)
- PQRI-OINDP, EMA (Guideline on plastic immediate packaging materials; 2005)

The FDA's 1999 Container Closure Guideline covers leachables; in terms of extractables, there are no regulatory guidelines for single-use manufacturing systems. There are, however, evolving industry proposals from the BioPhorum Operations Group (BPOG). BPOG is a group of representatives from 28 member companies that works on initiatives important to the biopharmaceutical industry. A disposable working group was formed in 2012 to help standardize protocols for extractables for single-use systems. Consensus standardized extractables testing protocols for single-use systems were published in the November 2014 issue of Pharmaceutical Manufacturing. Recently, a draft of an update to USP <661> included a sub-section USP <661.3> entitled "Plastic Components and Systems used in Pharmaceutical Manufacturing."

Residual Solvents

The scope of the guideline ICH Q3C (CPMP/ICH/283/95 "Note for Guidance on Impurities: Residual Solvents", current version Q3C (R5), issued as EMA/CHMP/ICH/82260/2006) is to recommend acceptable amounts for residual solvents in pharmaceuticals for the safety of the patient. The guideline recommends use of less toxic solvents and describes levels considered to be toxicologically acceptable for some residual solvents.

Residual solvents in pharmaceuticals are defined as organic volatile chemicals that are used or produced in the manufacture of drug substances or excipients, or in the preparation of drug products. The solvents are not completely removed by practical manufacturing techniques.

Appropriate selection of the solvent for the synthesis of drug substance may enhance the yield, or determine characteristics such as crystal form, purity, and solubility. Therefore, the solvent may sometimes be a critical parameter in the synthetic process. This guideline does not address solvents deliberately used as excipients nor does it address solvates. However, the content of solvents in such products should be evaluated and justified.

According to the guideline ICH Q3C it is our understanding that the topic of reporting residual solvent applies to drug substances, excipients and in the preparation of drug products.

Although ICH Q3C does not apply to filters and single-use products used in the drug manufacturing process, solvents are sometimes used during the filter membrane manufacturing process. Depending on membrane type, Class 2 and Class 3 solvents are utilized in the manufacturing process. To mitigate the risk of residual solvents for all filter membranes, a flush volume is recommended, based on testing to determine the volume needed to decrease the total organic carbon (TOC) levels below 500 ppb.

Elemental Impurities

Elemental impurities in drug products can arise from a number of different sources and via a number of different means, including the active pharmaceutical ingredient, excipients, the vehicle, and leaching of elemental entities that are present in the drug product's manufacturing or packaging systems. Thus, knowledge about the presence, level, and likelihood of leaching of elemental entities in manufacturing and packaging systems is relevant to understanding how these systems contribute to a drug product's total elemental impurity burden.

The recently endorsed ICH Q3D (step 4) guideline outlines a process to assess and control elemental impurities in the drug product using the principles of risk management as described in ICH Q9.

Section 5.7 of the ICH Q3D (step 4) guideline highlights special considerations for biotechnologically derived products. For these products, the risk of elemental impurities being present at levels that raise safety concerns at the drug substance stage are considered low. The topic relevant for manufacturing systems, including filters and single-use products, focuses on typical purification schemes used in biologics manufacturing such as extraction, chromatography steps and dialysis or ultrafiltration-diafiltration (UF/DF). These purification schemes have the capacity to clear elements introduced in cell culture/fermentation steps or from contact with manufacturing equipment to negligible levels. As such, specific controls on elemental impurities leading up to the drug substance are generally not needed.

For manufacturing systems composed of polymeric materials, such as filters and single-use products, a joint team from the Extractables and Leachables Safety Information Exchange (ELSIE) Consortium and the International Pharmaceutical Aerosol Consortium on Regulation and Science (IPAC-RS) has conducted a review of the available literature on elemental entities in pharmaceutically relevant polymers and the presence of these elemental entities in material extracts and/or drug products. Based on this broad and comprehensive survey of the literature, the results illustrated that in most cases, levels of extracted elemental entities and leached elemental impurities in the materials assessed are low and are unlikely to significantly contribute to the elemental impurity profile of a final drug product. Nevertheless, a comprehensive risk management process for drug product safety and quality should consider the potential for elemental impurities from drug product packaging and manufacturing systems

Particulates: Sub-visible

Apart from the pharmacopoeias, no other regulatory guidance exists for sub-visible particles. The guidelines were essentially created to control levels of extrinsic particles. For example, USP <788> states "Particulate matter in injections and parenteral infusions consists of extraneous mobile undissolved particles, other than gas bubbles, unintentionally present in the solutions."

USP <788> is harmonized with EP 2.9.19, JP 6.07, ICH Q4B Annex 3 (R1), and WHO 5.7.1. The guideline does not however cover sub-visible protein particles in biotechnology products. Two test methods are described: Light obscuration and microscopic particle count tests. While light obscuration is preferred it may not be applicable for preparations with reduced clarity, increased viscosity (i.e. emulsions, colloids, and liposomal preparations) or the propensity to produce bubbles.

Particulates: Visible

Particulate matter is defined as mobile randomly sourced, extraneous substances, other than gas bubbles, that cannot be quantitated by chemical analysis. Pharmacopeia requirements for visible particles remain contradictory:

- EP Monograph on monoclonal antibodies: *"…without visible particles unless otherwise justified"*
- EP Monograph on parenteral preparations: *"…and practically free from particles"*

- USP on foreign and particulate matter: *"…is essentially free from visible particulates"*
- JP on foreign insoluble matter test for injections: *"…and free from readily detectable foreign insoluble matters"*

The USP has recently updated Chapter <1> 'Injections' and two new Chapters <790> and <1790> 'Visible Particulate in Injections'. USP <790> defines what '*essentially free*' means and <1790> will be an informational chapter regarding sources of particles and detection methods

Integrity Assurance

Ensuring structural integrity of single-use systems is critical to reducing stakeholder risk. These risks include loss of valuable product from leaks in the system, contamination based on microbial ingress and threat to operator safety based on toxic or hazardous product.

Single-use systems used in the manufacturing of biopharmaceuticals may involve multiple components and may require significant amount of handling and other forms of stress. The integrity assurance level can be enhanced by employing comprehensive risk-based quality procedures.

Many factors impact single-use system integrity and include material selection, component design, assembly design, assembly manufacturing (process and facility), sub-component testing, final testing (supplier and end user), transportation/handling and actual use. All of these must be qualified in order to ensure the integrity of the single-use assembly.

Single-Use Systems

The qualification of single-use suppliers, materials, components and completed assemblies require attention to several factors. It is important to use a scientific risk-based approach to qualify both materials and completed assemblies for single-use systems in pharmaceutical development and manufacture.

The assessment of risk must be based on the complexity of the system and its intended use (e.g. product contact versus non-product contact, upstream versus downstream use, short-term contact versus long-term storage). In addition, scientific principles must be applied to:

1. Identify and monitor extractable materials from films and other components.
2. Investigate potential interactions with product CQAs or significant process parameters like cell culture media.
3. Assess the effects of assembly processes such as welding, fusing, mechanical stress and sterilization (e.g. gamma irradiation) on the materials during manufacturing.

In assessing the suitability of the single-use system with respect to potential leachables in the final product, extractables may be considered potential leachables. Finally the design and functional integrity of the completed single-use system must be verified and maintained by appropriately trained end users via suitable processes for construction, packaging, shipping and deployment.

The supplier of the single-use system must provide sufficient data to qualify the materials and components used to assemble the final single-use system. In this regard, the end user may use the documents from the supplier to meet most of the verification criteria required to make sure that the single-use system is fit for the intended application and purpose. This requires a thorough qualification of the supplier by the end user to ascertain an acceptable supplier quality system, documentation, and an appropriate level of technical capability that extends all the way to the original sources of materials to the supplier.

Conclusion

The process of proactively assessing risk is fundamental to the drug manufacturing process. While regulatory guidelines describing risk assessment are in place, they can be somewhat vague and continue to evolve. To assess the risk for implementation of single-use systems, the drug manufacturer must develop a detailed understanding of the design, supply chain, manufacturing and distribution of the single-use systems themselves, as critical material attributes could ultimately negatively affect the drug product or its production process.

Since understanding the quality and variability of raw materials is critical, this information for single-use systems is best obtained via a formal partnership between end user and supplier. This will help ensure that the quality of the single-use systems is not only appropriate for pharmaceutical manufacturing but also comparable or better than traditional multi-use systems.

Quality specifications, compliance to standards and regulations, along with risk assessment support material is best consolidated in a documentation dossier. Different types of dossiers are important to support you throughout the different stages of your operations: qualification, risk assessment, and process optimization.These value-added activities, no longer performed by the drug manufacturer, will contain elements of both the supplier's and end user's quality systems. Overall, a partnership between supplier and end user will help support the risk assessment and control strategy for implementation of single-use systems.

References

4. FDA, Code of Federal Regulations, Part 211, "Current Good Manufacturing Practice for Finished Pharmaceuticals", Part 211.65, "Equipment Construction", 2005
5. European Commission, EUDRALEX Volume 4, "Good Manufacturing Practices, Medicinal Products for Human and Veterinary Use", Chapter 3, "Premise and Equipment", 2003

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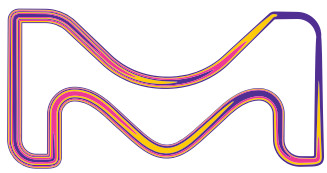

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