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Particulate Matter Control in Difficult to Inspect Parenterals

PDA Particulate Matter Control in Difficult to Inspect Parenterals Technical Report Team

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1.0 Introduction

Detection of foreign particulates and other defects in transparent parenteral solutions filled into clear containers is challenging under the best conditions, but is virtually impossible with opaque formulations and/or container types. Product/container combinations that obscure particulates are commonly known as "difficult-to-inspect" parenterals.

In spite of the challenges, regulators around the world expect 100% unit inspection. These requirements are laid out primarily in the pharmacopeias: The United States (USP), European (Ph. Eur.), Japanese (JP), and other world pharmacopeias have outlined inspection conditions and expectations that require manufacturers to examine 100% of all parenteral units for visible foreign particulates, including difficult-to-inspect parenteral (DIP) products. The World Health Organization (WHO) has a regulation for it, as well.

Any finished product unit that exhibits visibly detectable particulates during a qualified inspection must be rejected from the batch before it is released to distribution. USP General Chapter <790> Visible particulates in injections is a unique standard, because it defines the term "essentially free" of foreign particulate matter following the mandatory 100% in-process inspection and calls for a statistically-derived, acceptable quality limit-based inspection at the time of batch release ***(1).*** Other major pharmacopeias use slightly different, but equivalent terms. Ph. Eur. uses "practically-free" and JP uses "free from readily visible," yet neither of these mentions a final acceptable quality limit (AQL) inspection ***(2,3).*** Alternate statistically based attribute sampling plans, such as rejectable quality level (RQL), may be employed if they are shown to be equivalent or better than the AQL as a defect control process. Additionally, USP General Chapter <1> Injections and implanted drug products (parenterals)—product quality tests and USP <790> are currently the only pharmacopeial standards that also require a supplemental destructive inspection or testing for difficult-to-inspect parenteral products ***(1,4).***

In-process manufacturing inspection has been designed to ensure that the quality of the batch is maintained by detecting and removing defective units. However, many difficult-to-inspect parenteral dosage forms diminish the ability to detect common defects such as visible intrinsic or extrinsic foreign particulate matter using 100% in-process inspection that controls residual defects. Difficult-to-inspect parenteral dosage forms include opaque and deeply colored solutions, lyophilized cakes, powders, concentrated suspensions, and emulsions. Difficult-to-inspect parenteral container types might include plastic syringes, blow-fill-seal packaging, flexible bags, specialty containers, and medical devices. These types of products require some form of supplemental analysis or destructive inspection or testing and monitoring as part of the control strategy to ensure a product meets not only the USP <790> definition of "essentially free from visible particles," but also the harmonized subvisible particle acceptance guidance outlined in major world pharmacopeias ***(4).*** To accomplish this, a lifecycle-based particulate and physical defect management approach, along with a destructive inspection and trending strategy, are essential for detecting, identifying, and preventing foreign particulates in parenterals. It should be stressed that without robust controls over each element of the up-stream supply chain, as well as all of the manufacturing steps leading to the finished dosage form, the DIP product may not result in adequate particulate defect removal equivalent to a clear solution in a similar container system that can be readily visually inspected. Emphasis should be placed on the effectiveness to reduce impact to product quality and patient risk which is best achieved at the earliest points in the lifecycle process.

When beginning an initial destructive testing process, some difficult-to-inspect parenteral products might not immediately meet the expectations stated in USP <790>. In all cases, process monitoring data and historical trending is required to evaluate and optimize appropriate process control levels for both visible and subvisible particulates. Short- to long-term action plans may be necessary to update the supporting upstream lifecycle controls for facilities, raw materials, components, product contact equipment, maintenance cycles and inspection or testing procedures in order to meet current regulatory expectations and good manufacturing practices.

1.1 Purpose

This technical report describes best practices for difficult-to-inspect parenteral product lifecycle management, destructive testing, and trending to supplement portions of the guidance given in USP General Chapter <1790> Visual inspection of injections ***(5).*** USP provides some guidance on acceptance criteria based on a statistical sampling plan designed for destructive testing.

In 2015, the PDA Task Force on Particulate Matter Control in Difficult-to-inspect Parenterals initiated an industry survey on opaque or difficult-to-inspect parenteral products that established current particle testing practices, and statistical sampling for both APIs and finished products ***(6).*** The survey, literature and pharmacopeial references along with the collective expertise of Task Force contributors form the basis for the information provided in this technical report.

1.2 Scope

Although the current USP guidance does not completely address difficult-to-inspect parenteral products, this technical report is intended to provide logical pathways to DIP inspection and testing to support continual process improvement in the industry.

Critical physical container defects (cracks or seal integrity) that could compromise sterility should also be removed by a 100% non-destructive inspection. Neither this physical container/closure defect inspection nor enhancements or modifications of specific inspection conditions are within the scope of this report.

2.0 Glossary

"As Marketed"

Term used to describe the state or appearance of the product during 100% or AQL visual inspection (prior to labeling). As marketed refers to the product in-situ or the form in which it is distributed, for example clear liquid, lyophilized, powder, opalescent liquid, etc.

Automated Inspection

Consists of mechanical handling and presentation of product containers combined with automated inspection of the filled containers using image analysis and/or light obscuration.

Difficult-to-inspect Parenterals (DIP)

When the nature of the product or package limits the ability to perform a thorough inspection for particles ***(1).***

Emulsions

A dispersed colloidal system consisting of two immiscible liquid phases generally stabilized with one or more suitable agents. Injectable emulsions are sterile liquid dosage forms of drug substances dissolved or dispersed in a suitable emulsion medium. Injectable emulsions are for parenteral administration of poorly water-soluble drugs ***(7).***

Gels

Gels (sometimes called jellies) are semisolid systems consisting either of suspensions of small inorganic particles or of organic molecules interpenetrated by a liquid. Gels can be classed either as single-phase or two-phase systems ***(7).***

Good Manufacturing Practices (GMP)

Best practices in manufacturing of pharmaceuticals or biopharmaceuticals. From a regulatory standpoint, GMPs (21 CFR 210) are regarded as the minimum current good manufacturing practice for methods to be used in, and the facilities or controls to be used for, the manufacture, processing, packaging, or holding of a drug to assure that such drug meets requirements of safety, identity, and strength and meets the quality and purity characteristics that it purports or is represented to possess.

Implants

Implants are long-acting dosage forms that provide continuous release of an API for periods of months to years. They are administered by the parenteral route. For systemic delivery, they may be placed subcutaneously or, for local delivery, they can be placed in a specific region in the body ***(7).***