European Journal of Pharmaceutics and Biopharmaceutics 99 (2016) 54–64

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

journal homepage: www.elsevier.com/locate/ejpb

Review Article

The pharmaceutical vial capping process: Container closure systems, capping equipment, regulatory framework, and seal quality tests

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ARTICLE INFO

Article history:
Received 20 May 2015
Revised 23 November 2015
Accepted in revised form 24 November 2015
Available online 30 November 2015

Keywords:
Capping
Crimping
Residual seal force
Container closure integrity
Process control

ABSTRACT

Parenteral drug products are protected by appropriate primary packaging to protect against environmental factors, including potential microbial contamination during shelf life duration. The most commonly used CCS configuration for parenteral drug products is the glass vial, sealed with a rubber stopper and an aluminum crimp cap. In combination with an adequately designed and controlled aseptic fill/finish processes, a well-designed and characterized capping process is indispensable to ensure product quality and integrity and to minimize rejections during the manufacturing process.

In this review, the health authority requirements and expectations related to container closure system quality and container closure integrity are summarized. The pharmaceutical vial, the rubber stopper, and the crimp cap are described. Different capping techniques are critically compared: The most common capping equipment with a rotating capping plate produces the lowest amount of particle. The strength and challenges of methods to control the capping process are discussed. The residual seal force method can characterize the capping process independent of the used capping equipment or CCS. We analyze the root causes of several cosmetic defects associated with the vial capping process.

1. Introduction

Parenteral drug products are protected by appropriate primary packaging components. The most commonly used primary packaging for parenteral drug products to date is the rubber stopper and glass vial, sealed with an aluminum crimp cap. The design and choice of primary packaging components, and their combination, requires careful assessment. This includes dimensions, specifications, qualification, manufacturability, and process fit of the CCS in its entity – and not each component individually to ensure product stability and quality.

Parenteral drug products are sterile products, as per pharmacopeial requirements. In the 1970s, a national wide epidemic of septicemias in US hospitals was caused by contaminated, insufficiently sealed infusion products [1]. Since then, CCI has been increasingly recognized as a critical quality attribute of parenteral drug products and received significant attention by the authorities. Several guidelines including USP chapter ⟨1207⟩ [2] and technical reports (TR) were released to address the CCI of parenteral drugs [3,4]. In addition to protecting from possible microbiological contamination, the CCS can provide protection of its content from other external stresses (e.g. oxygen in the case of therapeutic proteins).

Ensuring CCI over the product shelf-life including manufacture, storage, shipment, and intended use is one of the most critical aspects in the development and commercialization of parenteral drug products. The drug product manufacturing processes, can also impact seal quality, and thus can be considered a unit operation with potential critical process parameters. Several minor or cosmetic defects associated with the capping process, which do not necessarily lead to leakage and CCI failure, are responsible for the majority of rejections and recalls in commercial manufacturing. For example, scratches on the crimp cap induced by the capping plate, scratches on the vial neck caused by a too long crimp cap skirt, dimpling rubber stoppers, or lose flip-off buttons are recognized and rejected in the 100% visual inspection.

Abbreviations: CCI, container closure integrity; CCS, container closure system; CT, computer tomography; mCCI, microbial container closure integrity; pCCI, physical container closure integrity; PDA, parenteral drug association; RSF, residual seal force; TR, technical report; USP, United States Pharmacopeia.

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http://dx.doi.org/10.1016/j.ejpb.2015.11.016
0939-6411/

The process of the vial closing is a complex interplay of the vial, rubber stopper and crimp cap but also the capping equipment, including the choice of processing parameters and ranges.

In this review we describe the challenges regarding CCI and manufacturing defects, such as cosmetic issues associated with the capping process. Different aspects of the primary packaging components and their impact on the capping process are highlighted. Finally, commercially available capping equipment and methods to monitor the vial capping process are discussed.

2. Primary packaging components

The prevalent CCS system for parenteral liquid and freeze-dried drug products is the glass vial sealed with an elastomeric rubber stopper and an aluminum crimp cap (Fig. 1). In this review, we focus on this particular CCS configuration.

2.1. Glass vials

Glass vials can be manufactured from glass tubings or molding. Today, glass vials from glass tubings are typically preferred over glass vials from molding as they have less cosmetic defects, are lighter, and show better dimensional consistency [5].

The manufacturing of glass vials includes several steps. After the vial shaping process, surface imperfections are removed by a fire polishing process. Finally, the vials are annealed in a lehr oven to reduce stresses within the glass.

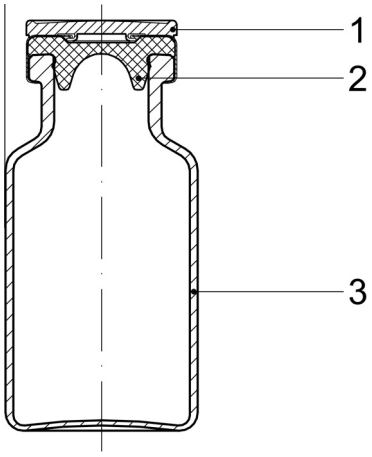

Fig. 1. The drug product vial sealed with a rubber stopper and an aluminum flip-off crimp cap: 1 – Aluminum flip-off crimp cap with a plastic flip-off button, 2 – rubber stopper and 3 – vial.

2.2. Rubber stoppers

The elastomeric rubber stopper is a complex part of the primary packaging [6]. The two important designs are the serum rubber stopper and lyophilization rubber stopper (Fig. 2) [7].

The chemical composition of the rubber stopper is an interplay of the different components of the rubber formulation, which determines the final chemical and physical properties, and any components possibly generated during stopper manufacture. For example, physical and chemical properties influence rubber's hardness, modulus, compression set, permeability to gas [8–10], and the profile of extractables/leachables [11–13].

The rubber formulation usually consists of a proprietary blend of an elastomer, a filler, an activation agent, a vulcanization agent, and color pigments.

In addition to the complex chemical rubber formulation, rubber stoppers are often coated to reduce the leaching of rubber components into the drug product [11], e.g. using a proprietary Flurotec® (laminated ethylene or tetrafluoroethylene) coating [14]. The ability of a rubber stopper to close a vial is a function of the rubber's mechanical properties and dimensional fit. Mortan et al. described the viscoelastic properties of elastomeric rubber stoppers [9]. The intermediate response (combination of viscous and elastic) of a rubber stopper during the capping process ensures a sufficient seal. The viscous behavior allows the rubber stopper to flow into imperfections of the vial sealing area. The elastic behavior of the rubber stopper generates a pressure of the rubber stopper against the vial sealing area; which is known as the RSF (discussed below).

The key parameter, which characterizes the viscoelastic properties of a rubber, is the hardness, which is usually measured by a shore durometer [15]. Today, rubber stoppers are available from approximately shore A hardness 40 up to shore A hardness 80. Another important parameter of a rubber is the compression set. The compression set test measures the elastic properties of a rubber after prolonged compression stress. Therefore, a rubber stopper featuring a high compression set applies less force to a closure after storage [16].

2.3. Crimp caps

The crimp cap is the third part of the container closure system. During the capping process, the capping equipment applies a vertical force against the vial/rubber-stopper/crimp cap combination to compress the rubber stopper. Second, the skirt of the crimp cap is folded under the vial flange, which fixes the rubber stopper in the compressed position pressing the rubber stopper against the vial sealing area. A variety of different crimp caps are commercially available. Crimp caps typically consist of (a tamper evident) aluminum and feature an injection site or are completely removed via a tear-off procedure before usage. The injection site can be further protected by different plastic buttons (flip-off). Those can have

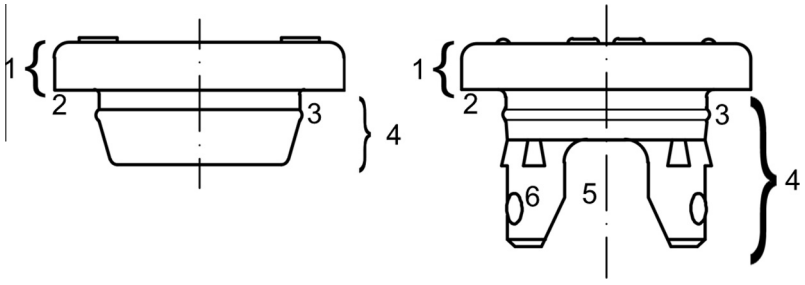

Fig. 2. Serum and lyophilization rubber stoppers: 1 – rubber stopper flange, 2 – sealing area, 3 – no-pop ring, 4 – rubber stopper plug, 5 – lyophilization rubber stopper vent and 6 – lyophilization rubber stopper nibs.