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Review

Particle contamination of parenteralia and in-line filtration of proteinaceous drugs

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ABSTRACT

Protein drug products play an important role in the treatment of severe diseases. However, due to the instability of these complex molecules, protein aggregates can form which can compromise drug safety and efficacy including immunogenic reactions. In-line filtration during the administration of these drugs can serve as a final safeguarding step to protect patients from risks associated with proteinaceous particles. A unique analysis of more than 300 marketed protein drug products revealed that already around 16% of all these products are filtered during preparation or administration. Further, the research revealed that no standardized filtration practice exists. Broad variances regarding filter membrane or pore size are found and sometimes no specifications are mentioned at all. The benefits as well as possible negative impacts of filtration like filter shedding, extractables or drug adsorption are critically assessed. Several proposals to improve the current filtration practice and to expand the number of in-line filtered protein drug products are made. The suggestions include the demand for the specific usage of one filter membrane type, the establishment of a filtration routine for unfiltered protein drugs and a statistical analysis between filtered and non-filtered products with similar formulations to identify possible differences in the immunogenicity rate.

Contents

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1. Introduction

1.1. Regulatory specifications

Biopharmaceuticals have been rising for many years and their share on the total drug market will increase in the future to up to 20% (Walsh, 2014). They are commonly administered intravenously or subcutaneously (Jiskoot et al., 2012). Hence, protein drug products have to comply with the criteria set forth for parenteralia in the United States and European Pharmacopeia (European Directorate For The Quality Of Medicine, 2011c; The United States Pharmacopeial Convention, 2011a). One major aspect is that biopharmaceuticals need to be practically free from visible particles (European Directorate For The Quality Of Medicine, 2011c; The United States Pharmacopeial Convention, 2011a) and must not exceed limits for subvisible particles (European Directorate For The Quality Of Medicine, 2011a; Pharmaceuticals and Medical Devices Agency, 2011; The United States Pharmacopeial Convention, 2011b). Particles become visible above approximately 50 mm, and are well detected by the unaided eye at sizes of about 100 μm (Das, 2012; den Engelsman et al., 2011; Doessegger et al., 2012). At the moment particle number limits in the subvisible range are only defined for particles larger than 10 and 25 μm (European Directorate For The Quality Of Medicine, 2011a; Pharmaceuticals and Medical Devices Agency, 2011; The United States Pharmacopeial Convention, 2011b). However, in the recent years it has become common practice by the authorities to request data for particle sizes below 10 μm for this drug product class (Wang et al., 2012) and (The United States Pharmacopeial Convention, 2015). The European Pharmacopeia also contains a monograph called “Monoclonal antibodies for human use”, which allows the presence of protein particles in protein drug products (European Directorate For The Quality Of Medicine, 2011b). But these particles are only tolerated if they are well characterized and the data is accepted by the regulatory authorities (Doessegger et al., 2012; European Directorate For The Quality Of Medicine, 2011b). Nevertheless, these product inherent particles have to be reduced to a minimum (Doessegger et al., 2012; European Directorate For The Quality Of Medicine, 2011b).

1.2. Negative impacts of particles

Particles in parenteral solutions can derive among others from formulation components or other sources like silicone oil, cellulose fibers, cotton, glass microflakes, rubber, plastic or metal (Bethune et al., 2001; Doessegger et al., 2012; Paolo et al., 1990; Shaw and Lyall, 1985; Tran et al., 2006; Waller and George, 1986). Based on estimations of the year 1987, an adult intensive care patient gets more than 10^7 particles with a size larger than 2 μm infused within 24 h (van Lingen et al., 2004). Ten years earlier, in 1977, Mehrkens et al. found two million particles larger than 2 μm during the same infusion interval (Bethune et al., 2001). Many reports describe the negative impact of particle contamination. For example, a correlation between the frequency of site reactions and the particulate matter is witnessed. A high particle number results in an increased number of adverse effects (Doessegger et al., 2012). Further, particles affect mainly organs like eyes, brain, lungs, heart, kidney, spleen, stomach and intestine (Boehne et al., 2013; Paolo et al., 1990; Puntis et al., 1992; Waller and George, 1986), whereas large particles remain in the lung and small ones are transported within the systemic circulation (Boehne et al., 2013; Langille, 2013; Puntis et al., 1992). If particles are larger than 7 μm, capillary occlusion is a reason why these organs are harmed by particles, because the diameter of the smallest capillary vessel is around 7 μm (Hearse et al., 1986; Shaw and Lyall, 1985; Tran et al., 2006; Waller and George, 1986). Moreover, pulmonary granuloma is associated with the presence of particles in humans (Cant et al., 1988; Lehr et al., 2002; Shaw and Lyall, 1985; Shay et al., 1997; van Lingen et al., 2004). Granuloma formation is also observed for drugs like amphetamines, methadone or methylphenidate, intended to be administered orally but are misused intravenously (Doessegger et al., 2012; Jorens et al., 2009). This further indicates that particles are capable of inducing granuloma. Next, a large number of microthrombi are connected to particles with a size less than 2 μm, which also account for the majority of the particles in intravenous fluids, as Walpot and co-workers note (Lehr et al., 2002; Tran et al., 2006; Walpot et al., 1989).

1.3. Protein aggregate formation

Beside these non-proteinaceous particles, protein drugs can contribute to the particle burden of a formulation, because they are prone to chemical and physical degradation (Manning et al., 2010). Two very important chemical degradation pathways are deamidation and oxidation. Muromonab-CD3, human growth hormone or insulin are examples of pharmaceutical relevant drugs in which deamidation, a hydrolysis of asparagine or glutamine, is detected. Several factors like the amino acid sequence or pH have an impact. Oxidation processes can occur at any time. Among others light or metals can cause oxidation. Especially histidine, methionine, cysteine, tyrosine or tryptophan are sensitive towards oxidation. Physical degradation can be denaturation, caused for example by temperature or chemicals, or aggregation with different mechanism like chemically modified monomers or surface interfaces (Manning et al., 2010). Even the best formulation and storage condition cannot totally exclude such degradation products (Brange et al., 1992). External factors like temperature, pH, shaking, shearing, etc. can cause particle formation (Wang, 2005). Silicone oil, a non-proteinaceous particle, (Basu et al., 2013; Thirumangalathu et al., 2009) may foster protein aggregation by acting as heterogeneous nuclei (Mahler et al., 2009; Zölls et al., 2012). Generally, protein aggregates can be dimers or multimers in the lower nanometer range or may assemble to large particles even in the visible range above 100 μm (den Engelsman et al., 2011; Singh et al., 2010).

1.4. Immunogenicity of protein particles

In contrast to non-proteinaceous particles, aggregates formed by proteins require additional vigilance. For several monoclonal antibody drug products, for example adalimumab, abciximab, omalizumab or trastuzumab, immunogenic reactions are observed (Getts et al., 2010).

1.4.1. Causes for the immunogenic potential of proteins

Not surprisingly proteins with an amino acid sequence differing from the human homologue are immunogenic. Hence, in the case of protein drug products the immunogenicity issue has been detected first by proteins deriving from animal origin, like porcine and bovine insulins (Schellekens, 2002). The response of the immune system towards drugs deriving from animal, microbial or plant origin is rapid and occurs immediately after a single