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Opinion Open Access

Circumventing Polysorbate Induced Unwanted Immunogenicity and Anaphylaxis

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Opinion

The rapidly growing and increasingly effective use of Monoclonal Antibodies (mAbs) and other biotherapeutics in the treatment of neoplastic, autoimmune, and inflammatory diseases is an exciting development. Biotherapeutic formulations are significantly more complicated than small molecule drug formulations, contributing to high development and manufacturing costs. Because biotherapeutic proteins are large, structurally complicated, and somewhat fragile molecules (i.e., compared to small molecule drugs) they often require the inclusion of functional excipients in order to ameliorate undesirable properties such as aggregation or short shelf life, or allow for increased concentration permitting smaller administration volumes and reduced administration times. Biotherapeutic proteins can also be affected by differences in the manufacturing process and efficacy can be affected by differences in formulations.

For small molecule drugs, the FDA defines bioequivalence as "the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study." Similarly, EMA guidance on bioequivalence for small molecule drugs focuses largely on pharmacokinetic parameters, AUC, C_{max}, and T_{max}.

For proteins, however, matters are much more complicated because proteins are potentially immunogenic, a key component of drug safety assessment, and similar efficacy does not necessarily imply a similar safety profile between innovator and biosimilar products. The immune response to a biotherapeutic protein can be influenced by many factors including the nature of the protein itself, impurities, excipients, route of administration, and even idiosyncratic properties of the patient's own immune system. The consequences range from the clinically irrelevant to serious and life-threatening reactions. Unwanted immunogenicity is thus an important part of the evaluation of the safety of biotherapeutic products. Because animal studies have not been found to be predictive of the human immune response, data obtained from comparative efficacy studies is relied upon to detect marked increases in immunogenicity compared to the reference product. Such studies are typically powered to allow demonstration of efficacy or non-inferiority, so small, yet still critical; increases in immunogenicity are not likely to be statistically significant.

Because proteins are known to be potentially immunogenic in their own way, it is often assumed that immunogenicity observed for a biotherapeutic develops in response to the protein, ignoring the fact that other formulation components may be partially or even substantially responsible. Specifically, the polysorbates (PS-20 or PS-80–Tween-20 and Tween-80, respectively) are incorporated in approximately 70% of all mAb formulations as highly effective aggregation preventers. However, polysorbates contain polyoxyethylene moieties and unsaturated alkyl chains that spontaneously autoxidize in aqueous solution to form immunogenic and anaphylactogenic chemical species, including hydro- and alkyl-peroxides, epoxy acids, and reactive aldehydes such as formaldehyde and acetaldehyde. While immunogenicity of biotherapeutics is a serious and growing concern for the USA food and Drug Administration (FDA) and the European Medicines Agency (EMA), there has been little focus on the polysorbates as a potential and likely contributor to immunogenicity observed with many biotherapeutics in spite of the substantial body of literature that points directly in this direction.

Similarly, the root cause of anaphylaxis has received limited attention and, like immunogenicity, is generally assumed to be an unavoidable intrinsic property of biotherapeutic proteins themselves. Based on well-documented anecdotal reports from human clinical studies and extensive preclinical studies in animal models employing a broad spectrum of functionally independent indicators such as histamine release, hemodynamic effects, skin prick testing, enzyme-linked immunosorbent assay, IgE immunoblotting, flow cytometric detection of basophil activation, complement activation, determination of certain humoral factors, and the absence of polysorbate specific IgE (to confirm the non-immunologic nature of the anaphylactoid reactions), it has now become increasingly clear that the polysorbates are intrinsically anaphylactogenic. Hypersensitivity and anaphylaxis have been reported in the medical literature for a growing number of monoclonal antibodies, including rituximab, of atumumab, obinutuzumab, trastuzumab, cetuximab, tocilizumab, infliximab, etanercept, adalimumab, abciximab, golimumab, certolizumab, brentuximab, bevacizumab, and omalizumab, all of which contain a polysorbate surfactant, most often polysorbate-80 (Tween-80).

Both unwanted immunogenicity and anaphylaxis comprise major components of safety assessment. However, few if any attempts are made to differentiate biotherapeutic protein-related from polysorbate-related unwanted immunogenicity and anaphylaxis. Many non-ionic surfactants as alternatives the polysorbates, such as alkyl glycosides are under investigation by developers of both innovator biotherapeutics and biosimilars. Alkyl glycosides are simple, and stable molecules comprising a sugar and a single alkyl chain that rapidly metabolize to a sugar and fatty acid following parenteral administration. In preclinical studies, they have been shown to be equally effective but safer alternatives to the polysorbates. Reduction or elimination of unwanted immunogenicity and anaphylaxis by elimination of polysorbates will allow biotherapeutic developers to differentiate their biotherapeutic,

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biosimilar, or biobetter products from the large number of nearly identical competitor products, simultaneously providing a substantial commercial benefit and, more importantly, critical clinical benefits for all concerned–patients, physicians, and third-party payers.