Anaphylaxis and the inclusion of polysorbates in biotherapeutics.

Edward. T. Maggio*

Aegis Therapeutics LLC, 11770 Bernardo Plaza Court, San Diego, CA 92128, USA

Editorial

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INTRODUCTION

The formulation and manufacturing of parenteral biotherapeutic products occur at the interface of science and regulatory concerns. Science dictates the formulation composition, often including the addition of certain excipients in order to stabilize the biotherapeutic protein, ameliorate undesirable properties such as aggregation or short shelf life, or allow for increased concentration permitting smaller administration volumes, thus placing the final product in a condition better suitable for administration to patients. Biotherapeutic formulations are significantly more complicated to formulate than small molecule drug formulations, often requiring the inclusion of a host of functional excipients. Since no biotherapeutic formulation can be perfect in all respects, regulatory concerns are intended to balance the risks of life-saving technological enhancements against the known limitations or deficiencies associated with commercial biotherapeutic products with the aim of achieving an acceptable compromise with respect to product safety.

The rapidly growing use of monoclonal antibodies (mAbs) in the treatment of neoplastic, autoimmune, and inflammatory diseases is an exciting development, but one that has led to a significant increase in hypersensitivity reactions worldwide, complicating their use as first-line therapies and limiting patient survival and quality of life. Anaphylaxis is often attributed to some undefined intrinsic property of the protein biotherapeutic, often ignoring potential contributions from other formulation components. In particular, polysorbates PS-20 or PS-80 (Tween 20 and Tween 80, respectively) are incorporated in approximately 70% of all mAb formulations in order to prevent aggregation. They are highly effective in this role. However, polysorbates contain ether linkages (within polyoxyethylene moieties) and unsaturated alkyl chains that spontaneously self-oxidize in aqueous solutions to form immunogenic (neoantigenic) and anaphylactogenic (anaphylaxis stimulating) chemical species, including hydro- and alkyl-peroxides, epoxy acids, and reactive aldehydes such as formaldehyde and acetaldehyde. While

*Corresponding author: Edward. T. Maggio, Aegis Therapeutics LLC, 11770 Bernardo Plaza Court, Suite 353, San Diego, CA 92128, USA, Tel: +1 858- 618 1400, Fax: +1 858 618 1441, Email: emaggio@aegisthera.com

the immunogenicity of biotherapeutics is a serious and growing concern for the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA), the root cause of anaphylaxis has received limited attention and is generally assumed to be an unavoidable intrinsic property of the biotherapeutic proteins themselves, ignoring the broader potential negative contributions of functional excipients such as the polysorbates.

It has now become increasingly clear that the polysorbates are intrinsically anaphylactogenic. This has been demonstrated in humans in well-documented anecdotal reports in the clinical literature and extensively in animal model studies 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). In humans, hypersensitivity and anaphylaxis have been reported in the medical literature for a growing number of monoclonal antibodies, including rituximab, ofatumumab, obinutuzumab, trastuzumab, cetuximab, tocilizumab, infliximab, etanercept, adalimumab, abciximab, golimumab, certolizumab, brentuximab, bevacizumab, and omalizumab, all of which contain a polysorbate surfactant. A complete review of the clinical and preclinical evidence of the anaphylactogenic nature of the polysorbates may be found in the December 2017 issue of JEFC (1).

Both unwanted immunogenicity and anaphylaxis comprise major components of safety assessment, however, few if any attempts are made to differentiate drug-related from excipient-related anaphylaxis. Replacement of anaphylactogenic and immunogenic functional excipients with equally effective but safer alternatives will allow biotherapeutic developers to differentiate their biotherapeutic, biosimilar, or biobetter product from the large number of nearly identical competitor products, simultaneously providing a substantial commercial benefit as well as critical clinical benefits for all concerned - patients, physicians, and third party payers.

REFERENCES

1 Maggio E.T., Reducing or Eliminating Polysorbate Induced Anaphylaxis and Unwanted Immunogenicity in Biotherapeutics, Journal of Excipients and Food Chemicals, Vol 8, No 3, pp 52-61, 2017