The AAPS Journal (2023) 25:43
https://doi.org/10.1208/s12248-023-00796-4

EDITORIAL

Compendium of Immunogenicity Risk Assessments: an Industry Guidance Built on Experience and Published Work

The AAPS Journal Theme Issue: Compendium of Immunogenicity Risk Assessments: an Industry Guidance Built on Experience and Published Work

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Received: 31 January 2023 / Accepted: 15 February 2023 / Published online: 20 April 2023

For nearly 20 years (1, 2), a risk-based approach to assess immunogenic potential and resultant clinical consequences of administration of therapeutic proteins has evolved to what we practice today. Currently, we evaluate both intrinsic and extrinsic factors: protein sequence for T cell epitopes, antigen presentation by MHC, and *in vitro* cellular response assays to predict immunogenicity risk as well as evaluate other product- or patient-related risk factors. Our industry has been very prolific in the implementation of in silico and *in vitro* tools to predict immunogenicity risk and characterization (3–9). We now implement immunogenicity risk assessment (IRA) tools to drive decisions on bioanalytical and clinical strategy in the development of biotherapeutics. Furthermore, the FDA immunogenicity bioanalytical guidance (10) and the EMA immunogenicity guidance (11) have helped improved practices on immunogenicity bioanalytical assessments and highlighted the importance of IRAs. However, the process for immunogenicity risk assessment is still not harmonized, as the tools used differ in the parameters captured as well as the tabulation and reporting of overall immunogenicity risk varies, the latter involving the use of formats such as an Excel™ file, a gradient table with classifications, or a Word™ document.

The AAPS Therapeutic Product Immunogenicity Community leadership started an initiative to assess approaches on how to consider an immunogenicity risk assessment evaluation and provide colleagues with concrete examples based on drug type. These efforts were published in a theme issue of The AAPS Journal, "Compendium of Immunogenicity Risk Assessments: an Industry Guidance Built on Experience and Published Works." Overall, five manuscripts were published in this theme issue to provide examples on strategy and presentation of immunogenicity risk assessment for PEGylated therapeutics (12), a low-risk monoclonal antibody (13), an engineered human cytokine analogue expressed in different cell substrates (14), a fusion protein (15), and multi-domain specific biotherapeutic molecules (16). All manuscripts developed an IRA based on fictional biotherapeutic(s), however utilized the authors' experience, and discussed how intrinsic factors, systems biology/mechanism of action, treatment, product quality attributes, and non-clinical findings would impact immunogenicity risk and presented a bioanalytical and clinical strategy to address such risks. A common theme seen in the IRAs was how the clinical immunogenicity risk assessment would influence the immunogenicity strategy with the goal of maximizing safety; for example, in anticipation of clinically impactful consequences of immunogenicity, the IRA would propose more frequent monitoring and characterization of immunogenicity, potentially additional diagnostic measures or even develop a clinical intervention plan. The need for ongoing information sharing on this topic continues to be evident as seen with the recent publication on immunogenicity potential for oligonucleotide-based drugs (17).

There is clear interest across the industry in this topic. Since publication of this compendium, the manuscripts have been repeatedly referenced, with one of the manuscripts accessed more than 3400 times, and a total of 26 cross-references (taken from journal metrics). In a recent AAPS eLearning webinar, "Immunogenicity Risk Assessment and Integrated Summary of Immunogenicity" (December 6th, 2022), the participation was very strong, with over

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400 registrants, and with the majority of webinar survey respondents indicating their companies are preparing immunogenicity risk assessments. This highlights the point that companies are in different places in the spectrum of their experience with immunogenicity risk assessment. We hope readers find this compendium useful in their endeavors to document immunogenicity risks and encourage participation, if needed, by posting questions on the AAPS immunogenicity community page.

Given all the experience in immunogenicity of biotherapeutics over the years, assessing immunogenicity risk and clinical relevance continues to be areas we should focus on. It is a potential risk to patients receiving our drugs that we need to acknowledge and mitigate, as appropriate. Knowledge gaps may still exist in other functional areas within research and development (R&D) regarding the roles and importance of their contribution in establishing IRAs. Close collaboration with chemistry manufacturing controls (CMC), discovery biology, non-clinical and clinical safety, and clinical pharmacology are paramount to the authoring of a comprehensive IRA. Such interactions will become more important when alignment on quality attributes for new modalities such as cell and gene therapies will be needed. The standard product quality attributes (e.g., aggregation) may not be relevant, but residuals from process development during manufacturing such as viral proteins and cell-derived contaminants can contribute to the immunogenicity risk, and should be considered. In addition, processes within companies for the authoring and frequency of updates to the IRA may still be evolving and look different or be tailored according to the immunogenicity risk. It will be important for our community to continue to share learnings in this space through AAPS forums and research articles; of particular importance would be to present an example on how to develop an IRA for cell therapies given the novelty and complexity of such products.

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