

## Addressing immunogenicity-related risks in an integrated manner

At least 80% of the regulatory questions related to immunogenicity risks could be avoided by more effective presentation of data. *Paul Chamberlain* explains how biopharmaceutical companies can achieve this.

It is quite rare for immunogenicity-related concerns in themselves to represent the primary reason for a negative opinion for EU marketing authorisation of a biopharmaceutical. Nevertheless, if the overall clinical benefit is marginal, the risks associated with undesirable immunogenicity may assume a decisive role.

Many questions arise during the review of regulatory dossiers because the data do not correlate and/or the rationale for the applied strategy is not adequately explained in the dossier. Thus, the potential impact of undesirable immunogenicity on overall clinical benefit and risk is not clear to the reviewer. As a consequence, the reviewer may be inclined to raise a "major concern" based on the detection of a treatment-emergent anti-drug antibody (ADA) response, regardless of the clinical significance of these bioanalytical signals.

The multiplicity of factors that can influence the rate of occurrence and severity of undesirable immunogenicity of biopharmaceutical products creates a need for applicants to address a diverse range of data elements in an integrated manner. In this context, the term "integrated" refers to two dimensions:

- interpretation of bioanalytical signals in relation to their clinical significance; and
  - data summary that demonstrates that the applicant has sufficiently addressed the pertinent factors to enable a reliable judgement about the impact on overall clinical benefit and risk of the treatment, and has then proposed a risk management plan (RMP) for mitigating the remaining uncertainty.
- The common technical document (CTD) format does not require the submission of an "integrated summary" to address immunogenicity-related risks, although, as discussed in this article, the structure of the dossier has the flexibility to accommodate such a document. Equally, while not formally required as part of dossiers to support clinical trial applications, it could be envisaged that there are cases where inclusion of an integrated "immunogenicity risk assessment" module in an investigational medicinal product dossier (IMPd) might be very helpful.

Arguably, at least 80% of the regulatory questions related to immunogenicity risks could be avoided by more effective presentation of data.

This article describes a practical approach that has been applied successfully in connection with registration procedures for

different biopharmaceutical products. The principles described apply equally to submissions to the European Medicines Agency and the US Food and Drug Administration.

### Hierarchy of concerns

As pointed out by Dr Amy Rosenberg in a seminal presentation given in 2002<sup>1</sup>, it is possible to stratify the potential clinical significance of the risks associated with the undesirable immunogenicity of biopharmaceutical products. Thus, we know that the following situations would represent the "highest risk" category:

- potential for bypassing immune tolerance to an endogenous protein;
- induction of ADAs that cross-react with an endogenous protein leading to a functional deficit; and
- severe systemic adverse drug reactions (ADRs) mediated by treatment-emergent ADAs or pre-existing, cross-reactive antibodies.

We also know that the detection of persistent ADAs can be a causal factor for loss of efficacy and infusion-related reactions<sup>2</sup>, and that loss of efficacy might be correlated with a measurable reduction in trough concentration of the drug product due to enhancement of clearance by ADAs<sup>3,4</sup>.

On the other hand, we know of products that can induce a relatively high magnitude of ADAs in 100% of recipients without an associated loss of efficacy or appearance of immune-mediated adverse events<sup>5</sup>. Moreover, we know that all registered biopharmaceutical products, with the possible exception of filgrastim, do induce ADAs in some human subjects.

So, we can start from a position where we could reasonably assert that detection of treatment-emergent ADAs does not automatically equate with a clinical risk. Rather, the detection of an ADA signal is an expected outcome and represents a useful sentinel for monitoring the rate of occurrence of host immune responses to the product. This incidence and the magnitude of this signal need to be evaluated relative to pharmacokinetic, pharmacodynamic, efficacy and safety indices in order to ascertain the clinical significance.

A second fundamental is that ADAs are not necessarily a bad thing. It is conceivable that ADAs could serve to augment an endogenous pool of natural inhibitors, to prevent systemic

activity of a highly active drug product that is administered directly to its site of action<sup>6</sup>. Indeed, the existence of naturally occurring antibodies to endogenous proteins demonstrates that antibodies may serve an essential homeostatic role in "immune networks"<sup>7</sup>.

Identification of structural motifs that have affinity to bind to human MHC Class II, the first step in antigen presentation to T-cell lymphocytes, provides a rational basis for the detection of such antibodies. We know that naturally occurring cytokines such as erythropoietin contain MHC binding regions<sup>8</sup>, and that their immunogenic potential is usually suppressed by immune tolerance mechanisms; these tolerance mechanisms, however, might be "bypassed" under the conditions of use (injection of large quantities of recombinant proteins) or physico-chemical characteristics (eg aggregates)<sup>9</sup>.

A third fundamental is the uncertainty that remains from the pre-registration database about the long-term effects of a host immune response against the treatment, or of administration to a wider population.

We know that a product can be associated with dramatically different outcomes depending on the nature of the treated human subjects, as exemplified by more frequent induction of auto-reactive host antibodies to PEG-rHuMGDF in immunocompetent healthy volunteers compared with immunocompromised chemotherapy patients<sup>10</sup>. Accordingly, it will usually be necessary to define a RMP that addresses the uncertainty associated with wider use, including "off-label" applications, as well as providing appropriate characterisation of ADRs or loss of efficacy that have a plausible linkage to the host immune response.

The take-home message is that the applicant needs to apply the "hierarchy of concerns" in an intelligent manner to interpret the signals and to reach a conclusion about their clinical significance. It is not reasonable to expect a regulatory reviewer to be able to assimilate all of these interdependent considerations by trawling through a typically disparate data presentation.

### Linkage to product life-cycle

Although the EU guideline on immunogenicity assessment of biotechnology-derived therapeutic proteins<sup>11</sup> refers to the data requirements to be submitted in support of

marketing authorisation, the extent of the information required will have an impact on product development strategy from the lead candidate selection stage onwards. Prior to entering the clinic, important information on relative risk to human subjects may be obtained by identifying the intrinsic and extrinsic risk factors that are relevant for that particular product. This could enable minimisation of risk by re-engineering the protein sequence, and/or by optimising manufacturing or formulation conditions. The initial risk assessment should also lead to a definition of a bioanalytical strategy that includes assays of appropriate specificity and sensitivity, and ensures that the suitability of methodology is subsequently validated by cross-reference to *in vivo* correlates (including PK and PD markers) of an undesirable host immune response to the product.

The application of *in silico* techniques to identify potentially immunogenic motifs has been demonstrated to have predictive utility<sup>12</sup>. Data from such analyses could represent a valuable starting point for discussion of the intrinsic immunogenicity of any recombinant DNA-derived biopharmaceutical product. This does not mean that the identification of MHC Class II binding motifs will automatically translate into a clinically significant risk factor. Rather, it may provide the most plausible explanation as to why ADAs are detected in the clinic, and thereby help to balance potential concerns about the influence of extrinsic factors – such as product formulation and analytical profile – on clinical outcomes.

It is clear, then, that it is advantageous to initiate the process of “immunogenicity risk assessment” as early as possible in the life-cycle of a product, and then to refine this as a function of the data input from pre-clinical, clinical and post-marketing phases. The information could be collated to provide a source for regulatory submissions as well as a tool to facilitate the strategy of the project team. Table 1 suggests how this information is relevant to activities at different stages of product development.

### The “risk assessment” process

The risk assessment process is not a predictive science, but aims to:

- identify the risks for safe and effective use of a product;
- stratify these risks according to the potential severity;
- estimate the likelihood that treated subjects will develop undesirable immune responses to the product; and
- propose a suitable risk management strategy that balances severity versus probability.

Since most biopharmaceutical products induce immune responses in treated subjects, with

Lead candidate selection	<ul style="list-style-type: none"> <li>• Risk identification &amp; stratification</li> <li>• Review need for <i>in silico</i> and/or <i>in vitro</i> data</li> <li>• Internal strategy document to align bioanalytical plan with product characteristics</li> </ul>
Investigational medicinal product dossier/ Investigational new drug	<ul style="list-style-type: none"> <li>• Immunogenicity risk assessment module</li> <li>• Integrated summary of toxicological findings</li> <li>• Overall risk and benefit assessment</li> </ul>
Scientific advice	<ul style="list-style-type: none"> <li>• Justification of design of product comparability exercise to support manufacturing and/or formulation changes</li> <li>• Minimisation of immunogenicity-related risks during investigational studies</li> <li>• Adequacy of clinical evaluation to support registration</li> <li>• Suitability of bioanalytical methods and sample timing</li> </ul>
CTD format MAA / BLA	<ul style="list-style-type: none"> <li>• 2.7.2.4 Special studies</li> <li>• 2.7.3 Summary of clinical efficacy</li> <li>• 2.7.4 Summary of clinical safety</li> <li>• 5.3.1.4 Reports of bioanalytical and analytical methods for human studies</li> <li>• 5.3.5.3 Integrated summary of immunogenicity</li> </ul>
Post-marketing	<ul style="list-style-type: none"> <li>• Pharmacovigilance reporting</li> <li>• Variations/line extensions</li> <li>• Product labelling updates</li> </ul>

widely varying clinical consequences, it is important that the risk assessment process is sufficiently broad and rigorous to identify and estimate the pertinent risks. This may be achieved using a “standardised” approach that is adapted to the particular characteristics of the product and its intended use.

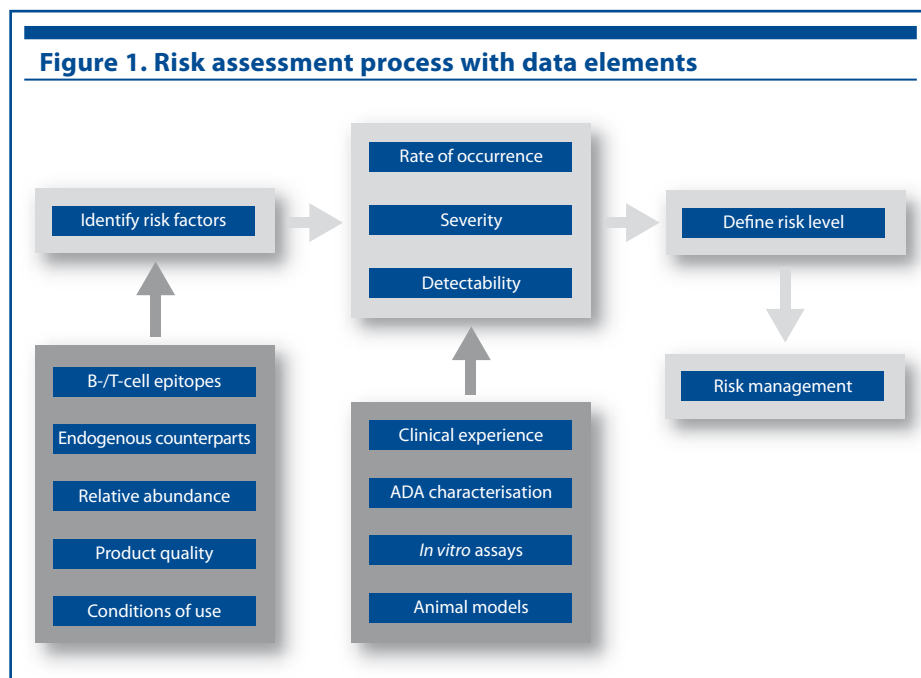
Figure 1 illustrates the application of risk assessment methodology to the undesirable immunogenicity of biopharmaceutical products. The first stage in the process is the identification of risk factors; this is followed by the “integration” step in which a rate of occurrence, estimated from input data (dark grey boxes), is interpreted relative to the

potential severity of the clinical consequences and to the limitations of the methodology to detect signals of clinical significance. The output is defined in Figure 2, namely a “calculated risk” and recommendations for managing the defined risk and the uncertainty.

### Questions approach to data input

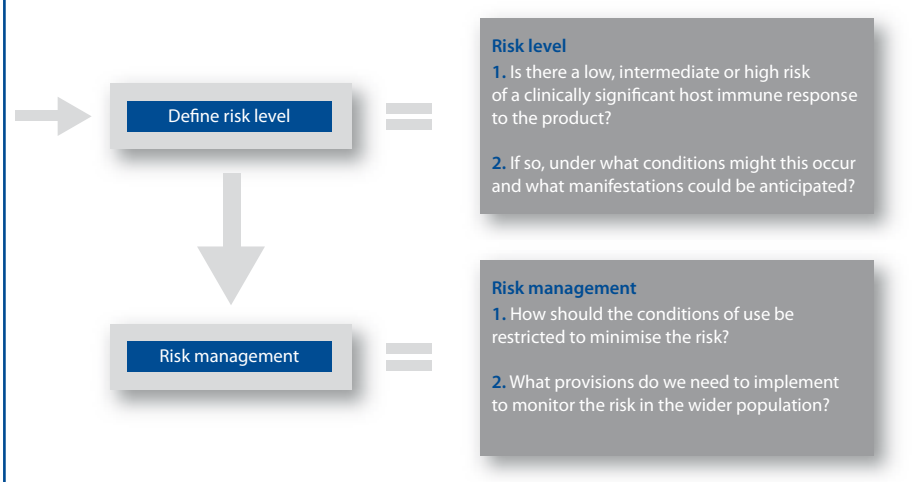
When faced with an apparently overwhelming number of “points to consider”, the best approach is often to define a set of core questions that could be applied in most situations, and which embrace the essentials.

Although still a work in progress, I have found that a common set of questions can be



**Figure 1. Risk assessment process with data elements**

**Figure 2. Output of risk assessment process**



**Table 2. Identification of risk factors**

Questions	
1.	Does the product contain immunogenic motifs?
2.	How could the nature or location of the target affect immunogenicity?
3.	What is the relative abundance of endogenous counterparts of the product, or of physiologically relevant inhibitors of the endogenous counterparts?
4.	How is the product manufactured and characterised?
5.	What is the comparability of the drug product used at different stages of clinical development?
6.	How is the product to be used?

**Table 3. Estimating rate of occurrence**

Questions	
1.	What immunogenicity-related signals have been detected in clinical studies using the drug product or related products?
2.	Does the incidence of immune-mediated adverse drug events increase with the appearance of ADAs?
3.	Can relative immunogenic potential be estimated from <i>in silico</i> and <i>in vitro</i> methods?
4.	Could prior exposure to the product, or to related products, affect immunogenicity?
5.	Is there concomitant medication that might alter immunogenicity?

**Table 4. Understanding severity**

Questions	
1.	Is there a potential for bypassing immune tolerance to an endogenous factor?
2.	Could ADAs cross-react with, and neutralise the function of, endogenous factors that share structural motifs?
3.	Does the severity of immune-mediated adverse drug events correlate with the magnitude of the ADAs?
4.	How does the appearance of ADAs affect PK and PD parameters?
5.	Is efficacy reduced in ADA-positive subjects?
6.	Are the ADAs transient or persistent?
7.	Is there any evidence for immune memory to the product?
8.	Are there data from relevant animal models that indicate functional effects of ADAs?

applied to any product scenario to generate the input data to inform the immunogenicity risk assessment process.

The questions that are relevant for the risk identification stage are shown in Table 2.

These questions enable two outputs: (i) integration of the properties of the product with the way in which it will be manufactured and used; and (ii) text that can be used (eg presented in sections 1 and 2 of an "integrated summary of immunogenicity", as described below) to explain the basis for assessment of the immunogenicity risks according to the properties of the particular product.

The same approach may then be applied to define the data input for the second stage, namely the integration of rate of occurrence relative to severity, using the questions shown in Tables 3 and 4, respectively.

The structure of these questions defines a format for data presentation in regulatory dossiers. For example, responses to the above questions provide the content for Sections 3 and 4 of the integrated summary of immunogenicity, as described below.

### Questions approach to data output

The most critical outputs of the immunogenicity risk assessment are responses to the questions shown in Table 5, which seek to estimate the clinical significance of the input data relative to the strength of the database available.

The responses provide the conclusion of the impact assessment, which may be presented as Section 5 of an integrated summary of immunogenicity.

The applicant should then propose an RMP that effectively addresses the uncertainty associated with the existing data, taking into account the nature of the risks identified and the conditions of use of the product. Again, this can be achieved using a question-based approach, as shown in Table 6.

This output corresponds to the immunogenicity-related information that should be included in the RMP in Module 1 of the CTD format<sup>13</sup>; the same information might be included as Section 6 in an integrated summary of immunogenicity, thereby providing a clear rationale to the regulatory reviewer for the proposed measures.

### Integrated presentation in dossiers

#### CTD format

The ICH guidelines<sup>14</sup> on the format of the CTD indicate that information related to the evaluation of immunogenicity should be presented according to Table 7.

#### Integrated summary format

In the US, regulation requires the submission of integrated summaries of efficacy and safety; the Food and Drug Administration recommends

inclusion of these in Section 5.3.5.3 of the CTD format. EU regulatory agencies also appreciate the submission of integrated summaries, particularly in relation to clinical safety.

The integrated summary actually represents an “integrated analysis” of the data accumulated across different studies. It provides the reviewer with a self-supporting description of the data comprising a text summary with tables and appendices containing the datasets.

The text portion may be used also for the clinical efficacy and safety summaries in Sections 2.7.3 and 2.7.4, respectively, if this text fulfils the requirements specified in the ICH M4E guideline. The key distinction is that the integrated summaries in Section 5.3.5.3 provide the datasets and accompanying analyses used to derive the conclusions in Module 2; data are not permitted in Module 2 of the CTD format and size limitations restrict the extent of discussion of the data.

Accordingly, for products for which there are treatment-emergent immunogenicity signals of potential impact on the overall assessment of clinical benefit and risk, it may be advantageous to submit an integrated summary of immunogenicity in Section 5.3.5.3. Although such a document is not defined in current regulatory guidance, there are precedents for including an integrated summary of immunogenicity in biologics licence application submissions to the FDA.

<b>Table 5. Defining the level of risk</b>	
<b>Questions</b>	
1.	What is the scale of risk of clinically significant immunogenicity in the human target population?
2.	Could the risk of undesirable immunogenicity affect the overall clinical benefit and risk balance?
3.	What are the most likely clinical manifestations of undesirable immunogenicity?
4.	What is the level of uncertainty due to limitations of the pre-registration database?

<b>Table 6. Risk management plan</b>	
<b>Questions</b>	
1.	Are there potential patient sub-populations to whom this product should not be administered?
2.	Under which circumstances might it be necessary to modify or stop treatment?
3.	What monitoring methods should be applied to investigate suspected host immune responses to the product?
4.	Is it necessary to collect additional data, eg from a patient registry, to monitor long-term risks in a wider population?
5.	What are the risks associated with off-label use?

The discussion of immunogenicity in other sections of the CTD format could then cross-reference the integrated summary of immunogenicity in Section 5.3.5.3 as the main source of the immunogenicity risk analysis. If an integrated summary of immunogenicity were not included in the CTD, Section 2.7.2.4 of the dossier should be used to present a text summary of all pertinent factors impacting on the immunogenicity risk assessment;

cross-references should be provided to the supporting data located in other parts of the dossier.

As a general rule, I would recommend inclusion of an integrated summary of immunogenicity in Section 5.3.5.3 because this enables the applicant to present both the argumentation and data analyses in a single wdocument; this would include discussion of intrinsic immunogenicity, quality, non-clinical,

<b>Table 7. Location of immunogenicity-related data in CTD format</b>	
<b>CTD section no.</b>	<b>Information to include</b>
<b>CLINICAL</b>	
2.7.2.4 – Special studies: immunogenicity risk assessment	<ul style="list-style-type: none"> <li>• Conclusions from analysis of correlation of immunogenicity with PK, efficacy &amp; safety parameters</li> <li>• Bioanalytical strategy: rationale for methods used (screening, confirmatory &amp; neutralising assays, additional characterisation, sample timing, etc)</li> <li>• Tabular summary indicating format and performance of bioanalytical methods and text description of statistical basis for calculating cut-off point for screening and confirmatory assays</li> <li>• Description of nature (incidence, magnitude, persistence, cross-reactive and neutralising potential) of anti-product immune response</li> <li>• Overall assessment of immunogenicity-related risks, including consequences for re-treatment</li> </ul>
2.5.3 – Overview of clinical pharmacology	Impact of immunogenicity on human PK/PD, including potential interference of anti-drug antibodies in bioanalytical assays; cross-reference to 2.7.2.4
2.7.3 – Summary of clinical efficacy	Potential impact of immunogenicity on conclusions regarding efficacy; short text summary only – provide cross-reference to data and to 2.7.2.4
2.7.4 – Summary of clinical safety	Potential impact of immunogenicity on conclusions regarding safety; short text summary only – provide cross-reference to data and to 2.7.2.4
5.3 – Clinical study reports	Immunogenicity data for individual studies, appended to the relevant Study Report
5.3.1.4 – Reports of bioanalytical and analytical methods for human studies	Validation reports for assays used for immunogenicity evaluation across different clinical studies
<b>NON-CLINICAL</b>	
2.4 – Non-clinical overview	Impact of anti-product immune response on toxicokinetics
2.6.5.1 – Pharmacokinetics overview	Conclusion regarding impact of host anti-product immune response on measured PK parameters
2.6.7.3 – Toxicokinetics overview	Conclusion regarding impact of host anti-product immune response on the effective exposure achieved in toxicology studies

and bioanalytical aspects in the context of their clinical significance.

The format of the integrated summary of immunogenicity follows intuitively from the structure of the questions applied to define the input and output data of the "immunogenicity risk assessment". Thereby, the data presentation is integrated with the underlying process. Table 8 illustrates the section headings for the integrated summary of immunogenicity template.

## Bioanalytical aspects

Many applicants make the error of omitting to explain the rationale for their immunogenicity testing strategy and summarise the analytical performance of the methods.

Simple inclusion of the assay validation reports in the dossier, without any descriptive or summary text in relevant parts of the dossier, will invariably lead to questions concerning the adequacy of the bioanalytical approach.

Accordingly, a clear presentation of the applicant's rationale for the design of the bioanalytical methodology used for the non-clinical and clinical immunogenicity evaluation is essential to the regulatory assessor. This should include:

- type of assays used (eg ELISA, bridging ELISA, radio-immunoprecipitation, BIAcore, bioassay);
- sequence of testing, eg screening assay followed by confirmatory assay followed by bioassay for neutralising capacity of confirmed positives;
- additional characterisation, eg test for anti-host cell protein antibodies, test for cross-reactivity with native counterparts of active substance;
- consistency of assay conditions applied across different non-clinical and clinical studies; and
- nature of positive control antibody used to estimate sensitivity.

Although guidance from the American Association of Pharmaceutical Scientists<sup>15</sup> defines standards for best bioanalytical practice, applicants may apply different approaches and methods according to product-specific considerations<sup>16,17</sup>. However, applicants should remember that regulatory reviewers are not comfortable with having to "second-guess" the reasons why an adequate assay for neutralising antibodies has not been presented, or why an assay that detects a restricted subset of ADA isotypes has been used. While there may well be perfectly acceptable scientific reasons, the regulatory reviewer deserves a clear explanation.

## Concluding comments

The task of the regulatory specialist is to understand the requirements of the multi-disciplinary team of experts that will be assessing the risks of undesirable immunogenicity relative to overall clinical benefit.

In the context of a question-based approach, the priorities to address may be summarised in Table 9.

These priorities may be most effectively addressed by presentation of data in an integrated summary of immunogenicity. The same document can be used as a repository of input and output data to inform the strategy for monitoring and minimisation of immunogenicity-related risks during product development, commencing from the lead candidate selection stage.

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**Table 8. Section headings for integrated summary of immunogenicity**

1. PRODUCT-RELATED RISK FACTORS
    - 1.1 INTRINSIC IMMUNOGENICITY
      - Product profile
      - Sequence homology
    - 1.2 CONTROL OF PRODUCT QUALITY
      - Process-related impurities and suitability of analytical/control methods
      - Aggregates and particulates
      - Stability of active ingredient in drug product formulation
      - Comparability during clinical development
  2. POTENTIAL IMMUNOGENICITY-RELATED CLINICAL RISKS
    - Cross-reactive antibodies
    - Drug hypersensitivity responses
    - Abrogation of efficacy due to neutralising antibodies or enhanced clearance
  3. BIOANALYTICAL METHODS
    - 3.1 RATIONALE FOR CHOICE OF METHODS
    - 3.2 PK ASSAY
    - 3.3 ADA SCREENING & CONFIRMATORY ASSAYS
      - Assay format and performance characteristics (Tabular summary)
      - Interpretation of ADA test results: (i) incidence; (ii) magnitude
      - Drug tolerance limit
    - 3.4 ASSESSMENT OF CROSS-REACTIVE POTENTIAL
    - 3.5 NEUTRALISING ANTIBODY ASSAY
    - 3.6 CONCLUSION: SENSITIVITY TO DETECT CLINICALLY SIGNIFICANT ADAs
  4. IMMUNOGENICITY-RELATED SIGNALS
    - 4.1 NON-CLINICAL
      - 4.1.1 OVERVIEW OF NON-CLINICAL PROGRAMME
      - 4.1.2 ADA vs PK vs PD
      - 4.1.3 ACUTE HYPERSENSITIVITY
      - 4.1.4 OTHER POTENTIAL ADA-MEDIATED TOXICITY
    - 4.2 CLINICAL
      - 4.2.1 STUDIES CONTRIBUTING TO IMMUNOGENICITY DATABASE
      - 4.2.2 STUDY DESIGN: SAMPLE TIMING FOR ADA MEASUREMENT vs TREATMENT SCHEDULE
      - 4.2.4 DRUG HYPERSENSITIVITY REACTIONS OR SUSPECTED IMMUNE-MEDIATED ADVERSE EVENTS
        - Incidence & severity relative to timing of drug administration
      - 4.2.5 ADA RESPONSES
        - Time-course of ADA response relative to treatment schedule
        - Persistence of ADA response following cessation of treatment
        - Neutralising potential of ADAs
        - Impact of re-treatment
      - 4.2.6 ADA vs PK/PD parameters
      - 4.2.7 ADA vs EFFICACY
      - 4.2.8 ADA vs SUSPECTED IMMUNE-MEDIATED ADVERSE EVENTS
  5. IMPACT OF IMMUNOGENICITY ON OVERALL ASSESSMENT OF CLINICAL BENEFIT AND RISK
  6. RECOMMENDATIONS FOR RISK MANAGEMENT PLAN
- DATA APPENDICES

Table 9. Priorities of regulatory reviewer	
Questions	
1.	Has the applicant identified all pertinent risks?
2.	Have studies been designed correctly to enable a reliable estimate of the rate of occurrence of clinical outcomes?
3.	Do the monitoring methods have appropriate specificity and sensitivity?
4.	Has the applicant correlated the bioanalytical signals with the relevant clinical endpoints?
5.	Is the proposed risk management plan adequate?
6.	Are there sufficient data to make a reliable judgement on overall clinical benefit and risk for use in the intended population?

**References**

- Rosenberg AS, Immunogenicity of Biological Therapeutics: A hierarchy of concerns, In "Immunogenicity of Therapeutic Biological Products", ed. Brown F and Mire-Sluis AR, Dev Biol Basel, Karger, 2003, Vol 112, 15-21
- Subramanyam M, Case Study: Immunogenicity of natalizumab. In "Immunogenicity of Biopharmaceuticals", ed. van de Weert & Moller, Springer, 2008, Chapter 10, 173-187
- Cassinotti A & Travis S, Incidence and clinical significance of immunogenicity to infliximab in Crohn's disease: a critical systematic review, Inflamm Bowel Dis, 2009, 15, 1264-1275.
- Bartelds GM et al, Clinical response to adalimumab: relationship to anti-adalimumab antibodies and serum adalimumab concentrations in rheumatoid arthritis, Ann Rheum Dis, 2007, 66, 921-926
- FDA Arthritis Advisory Committee, 16 September 2009, Xiaflex for Dupuytren's contracture; www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisDrugsAdvisoryCommittee/ucm125994.htm
- Ibid
- Shoenfeld Y, Toubi E, Protective autoantibodies: Role in homeostasis, clinical importance and therapeutic potential, Arthritis & Rheumatism, 2005, 52, 2599-2606
- Tangri S et al, Rationally engineered therapeutic proteins with reduced immunogenicity, J Immunology, 2005, 174, 3187-3196
- Sauerborn M et al, Immunological mechanism

underlying the immune response to recombinant human protein therapeutics, Trends in Pharmacological Sciences, 2010, 31, 53-59

- Li J et al, Thrombocytopenia caused by the development of antibodies to thrombopoietin, Blood, 2001, Vol 98, 3241-3248
- EMA/CHMP, Guideline on Immunogenicity assessment of biotechnology-derived therapeutic proteins, CHMP/BMWPI/14327/2006
- Koren E et al, Clinical validation of the "in silico" prediction of immunogenicity of a human recombinant therapeutic protein, Clin Immunol, 2007, 124, 26-32
- EMA/CHMP, Guideline on Risk Management systems for medicinal products for human use, EMA/CHMP/96268/2005
- ICH Harmonised Tripartite Guidelines M4E & M4S
- Shankar G et al, Recommendations for the validation of immunoassays used for detection of host antibodies against biotechnology products, J Pharmaceut Biomed Anal, 2008, 48, 1267-1281
- See Reference 11
- FDA, CBER/CDER, Draft Guidance for Industry: Assay development for immunogenicity testing of therapeutic proteins, December 2009

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