Integrated Summary of Immunogenicity

Paul Chamberlain and Josefin-Beate Holz on behalf of the Early Development Group at NDA Group

Why do we need an Integrated Summary of Immunogenicity?

Immunogenicity related data are being presented in multiple parts of the drug dossier (e.g. manufacturing, non-clinical, clinical). From a reviewers perspective, it is often difficult to understand the rationale of the immunogenicity studies and to find the relevant data. This leads to unnecessary questions by the assessor which could critically impact the timeline and the outcome of the review.

The priorities of regulatory reviewers are to answer the following questions:

1. Has the applicant identified all pertinent risks?
2. Have all 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 signal 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?

"Telling the whole story"

The regulator needs to determine:

• Potential risks associated with unfavourable effects

• Suitability of methodology applied to detect clinically relevant immunogenicity

• Scale of impact, if any, on overall clinical benefit vs. risk for each intended clinical population

• Whether risk level associated with uncertainty has been effectively mitigated

The applicant's task is to:

• Provide a risk-oriented, evidence based analysis to understand the nature of risks, allied to uncertainty at the time of marketing authorization

• Propose a Risk management plan to mitigate uncertainty in post-authorization phase

ISI – Relationship to other sections of CTD format

Module 5.3.5.3
Integrated Summary of Immunogenicity
→ Rationale for strategy
→ Control of CMC variables
→ ADA detection methodology
→ Results from clinical evaluation
→ Conclusions for relative immunogenicity

- **Module 1.8.2** Risk Management Plan
- **Module 2.7.1** Focus on PK assay methodology
- **Modules 2.7.3 & 2.7.4** Impact on overall clinical efficacy & safety
- **Module 5.3.1.4** Bioanalytical method validation reports
- **Modules 5.3.3 & 5.3.5** Clinical Study Reports, with raw ADA data from ADA testing

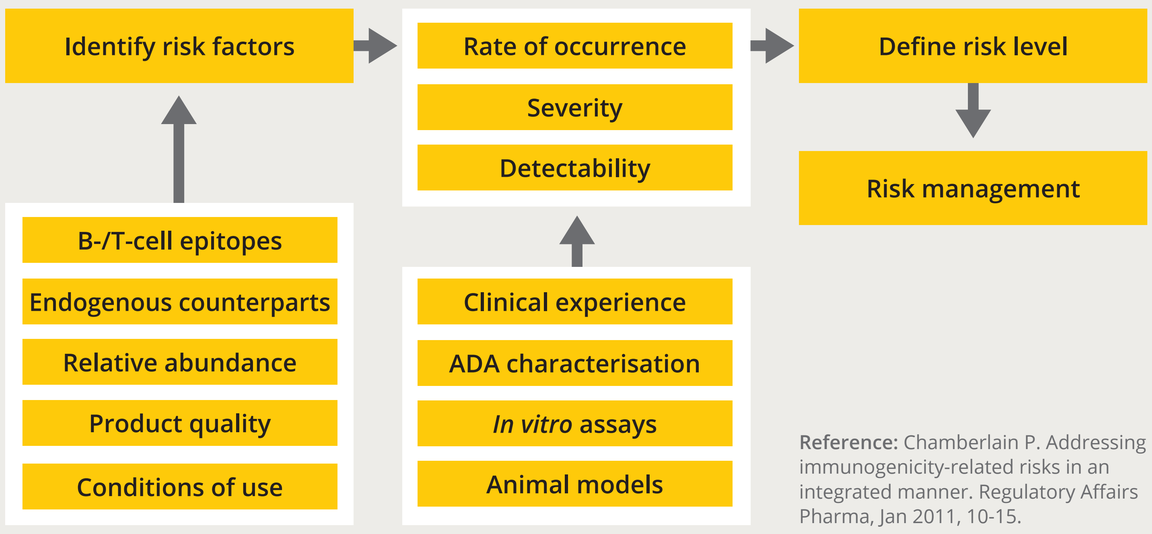
ISI Structure – Main Headings

1. Analysis of risk factors
2. Risk-based immunogenicity program
3. Immunogenicity results
4. Conclusions on the risk(s) of immunogenicity

ISI - Risk Assessment Process

1. Previous experience of product / product class
2. Physicochemical & structural aspects
3. Conditions of use
4. Patient- & disease related factors

Figure 1. Risk assessment process with data elements



Reference: Chamberlain P. Addressing immunogenicity-related risks in an integrated manner. Regulatory Affairs Pharma, Jan 2011, 10-15.

Figure 2.Output of risk assessment process

Define risk level =

Risk level
1. Is there a low, intermediate or high risk of a clinically significant host immune response to the product?
2. If so, under what conditions might this occur and what manifestations could be anticipated?

Risk management =

Risk management
1. How should the conditions of use be restricted to minimise the risk?
2. What provisions do we need to implement to monitor the risk in the wider population?

ISI - Risk Based Immunogenicity Program

1. Bioanalytical (ADA assay) strategy
2. Clinical evaluation plan
3. Justification of risk-evaluation relative to product-specific risk assessment

BIOANALYTICAL PARAMETERS	CLINICAL PARAMETERS	
Humoral immune response ADA Incidence & Titer Neutralizing capacity Time-course of formation **Specificity:** Biosimilar vs. Reference Process-related impurities Pre-existing vs. post-treatment IgE ADA only if suspected Type I hypersensitivity ADRs	Cmax, T½, drug trough concentration	**PK**
	Biomarkers of response	**PD**
	1° & 2° clinical endpoints	**Efficacy**
	Timing & severity of immune-mediated AE's	**Safety**

Bioanalytical methodology – Explain what was done ..... and why

- Clear summary of methods for each clinical study
- Discussion on relative sensitivity ± clinically-relevant drug levels and specificity to detect different moieties of protein or conjugate (if applicable)
- Justify assay cut-points, matrix interference, choice of positive controls and QC levels

ISI – Immunogenicity Results

Data correlations needed!

- Incidence of ADA, including nAbs
- ADA titers vs. time
- Cross reactivity
- ADA vs. PK
- ADA vs. PD, efficacy and safety
- Impact of pre-existing ADA's

ISI Structure and Headings

1. PRODUCT-RELATED RISK FACTORS
1.1 INTRINSIC IMMUNOGENICITY
1.2 CONTROL OF PRODUCT QUALITY
2. POTENTIAL IMMUNOGENICITY-RELATED CLINICAL RISKS
3. BIOANALYTICAL METHODS
3.1 RATIONALE FOR CHOICE OF METHODS
3.2 PK ASSAY
3.3 ADA SCREENING & CONFIRMATORY ASSAYS
3.4 ASSESSMENT OF CROSS-REACTIVE POTENTIAL
3.5 NEUTRALIZING ANTIBODY ASSAY
3.6 CONCLUSION: SENSITIVITY TO DETECT CLINICALLY SIGNIFICANT ADA
4. IMMUNOGENCITIY-RELATED SIGNALS
4.1 NON-CLINICAL
4.2 CLINICAL
5. IMPACT OF IMMUNOGENICITY ON OVERALL ASSESSMENT OF CLINICAL BENEFIT AND RISK
6. RECOMMENDATIONS FOR RISK MANAGEMENT PLAN
DATA APPENDICES

Aligning immunogenicity risk assessment to product life-cycle

Table 1. Aligning immunogenicity risk assessment to product life-cycle

Lead candidate selection	• Risk identification & stratification • Review need for *in silico* and /or *in vitro* data • Internal strategy document to align bioanalytical plan with product characteristics
Investigational medicinal product dossier/ Investigational new drug	• Immunogenicity risk assessment module • Integrated summary of toxicological findings • Overall risk and benefit assessment
Scientific advice	• Justification of design of product comparability exercise to support manufacturing and /or formulation changes • Minimisation of immunogenicity-related risks during investigational studies • Adequacy of clinical evaluation to support registration • Suitability of bioanalytical methods and sample timing
CTD format MAA / BLA	• 2.7.2.4 Special studies • 2.7.3 Summary of clinical efficacy • 2.7.4 Summary of clinical safety • 5.3.1.4 Reports of bioanalytical and analytical methods for human studies • 5.3.5.3 Integrated summary of immunogenicity
Post-marketing	• Pharmacovigilance reporting • Variations/line extensions • Product labelling updates

Conclusion

The task of the regulatory specialist is to understand the requirements of the multidisciplinary team of experts that assess the risks of undesirable immunogenicity relative to overall clinical benefit.

In the context of a question based approach, the priorities of the reviewer may be most effectively addressed by presentation of data in an integrated summary of immunogenicity (ISI). The same document can be used as a repository of input and output data to inform the strategy for monitoring and minimization of immunogenicity-related risks during product development, commencing from the lead candidate selection stage.

NDA Group:
Translational Development Team


Paul Chamberlain
Biopharmaceuticals & Immunogenicity Expert


Jenny Sims
Non Clinical Expert


Niamh Kinsella
CMC & Regulatory Expert


Paula Salmikangas
ATMP Expert


Josefin-Beate Holz
Clinical Expert