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IMMUNOGENICITY

Presentation of immunogenicity-related information in regulatory dossiers

The purpose of this continuing professional development supplement is to explain how an integrated summary report can be created to consolidate the information required for assessment of immunogenicity-related risks of different types of biopharmaceuticals.

LEARNING POINTS

- The ICH M4 R2 guideline identifies Module 2.7.2.4 as the CTD location for a summary of information relating to the evaluation of immunogenicity. This summary cross-refers to bioanalytical reports located in Module 5.3.1.4 and as appendices to Clinical Study Reports in Module 5.
- In recognition of the importance of assessing a broad range of potentially interacting risk variables, including the intrinsic immunogenic potential associated with molecular design, manufacturing process conditions and patient genotype/phenotype, the EMA and FDA have recently provided additional guidance on the scope of information to be presented in an integrated summary of immunogenicity (ISI).
- The ISI effectively consolidates the location of relevant information into a single document, as well as encouraging a more systematic presentation of the applicant's rationale for the strategy applied to evaluate and mitigate risks for the particular product and the populations to be treated.
- The option to submit the ISI in Module 5.3.5.3 enables inclusion of an expanded amount of information such as tabular and graphical data analyses that show the relationship of the undesirable host immune response to the product with relevant clinical endpoints. This helps both the applicant and the regulatory assessor to interpret the clinical significance of signals detected using "super-sensitive" bioanalytical assays, thereby facilitating the overall clinical benefit–risk assessment and identification of patient sub-populations that might be at higher risk of an inferior treatment outcome.
- The ISI, unlike the ISE or ISS (integrated summaries of efficacy/safety), is intended to integrate results from individual clinical studies rather than aggregating data across different clinical studies. This aim reflects the primary objective to analyse the relationship of bioanalytical measures of the immune response with the pre-defined clinical endpoints for each clinical study – acknowledging a potential confounding influence of differences in clinical study design (patient population, dose regimen, duration of treatment, etc) and bioanalytical methodology on data interpretation.

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What is immunogenicity?

The term "immunogenicity" refers to the capacity of a therapeutic agent to induce an immune response in the recipient. The nature of the immune response depends on an interaction of multiple factors, including the structural features of the therapeutic agent, genotypic and phenotypic characteristics of the recipient and the particular conditions of use.[1,2]

Although the administration of therapeutic proteins generally results in a detectable immune response – in the form of anti-drug antibodies (ADA) and drug-specific B/T-lymphocytes in the systemic circulation – this may often be without any impact on the overall clinical benefit versus risk balance. Nevertheless, in rare cases, treatment-emergent ADA has reacted with both the therapeutic agent and endogenous factors leading to severe, life-threatening consequences.[3] Aside from potential risk associated with a treatment-induced immune response, human subjects may have pre-existing antibodies resulting from prior exposure to molecules that share common features with those of the therapeutic agent. Administration of the therapeutic agent against such a pre-sensitised background may then provoke serious adverse reactions in some subjects.[4]

Immunogenicity can be relevant for both sides of the benefit versus risk equation because ADA can reduce efficacy by enhancing clearance or by directly neutralising the activity of the therapeutic agent, as well as inducing immune-mediated adverse reactions.

Which types of medicinal product fall within the scope of this article?

This article concerns information relating to the assessment of undesirable immunogenicity of biopharmaceutical products to be submitted in support of clinical trial applications (CTA) and marketing authorisation applications (MAA) in International Council for Harmonisation (ICH) regions. The principles are applicable to originator and biosimilar versions of therapeutic proteins and peptides, as well as to gene and cell-based therapies. Vaccine products, for which immunogenicity is the intended therapeutic effect, are outside the scope of this article.

Why is this topic important for regulatory scientists?

There are a number of important activities for the regulatory specialist, most notably:

- Justification of the adequacy of the immunogenicity risk-based programme in regulatory submissions, including briefing material to support scientific advice meetings, CTA and MAA for most types of biopharmaceutical products
- Close collaboration with chemistry, manufacturing and controls (CMC) specialists to identify potential risks at the earliest stage of development and align manufacturing and product quality control decisions with an effective risk mitigation strategy
- Understanding of the suitability of bioanalytical methodology applied to monitor immune responses in nonclinical and clinical studies, including regulatory expectations for method validation
- Provision of advice to clinical team regarding sample timing for ADA testing and measurement of other relevant parameters (drug concentration, biomarkers of pharmacodynamic [PD] response, adverse events of special interest, etc) in clinical studies
- Incorporation in the statistical analysis plan of relevant terminology and data outputs for presentation in the MAA
- Integration of bioanalytical signals from nonclinical and clinical studies with relevant pharmacokinetics (PK), PD, efficacy and safety indices to describe the impact of immunogenicity on overall benefit versus risk
- Linkage of conclusions from clinical immunogenicity evaluation with other sections of the MAA dossier, including the risk management plan
- Updating of the immunogenicity summary to support authorisation in other therapeutic settings and maintenance of accuracy of prescribing information in respect of immunogenicity-related risks.

What is the ISI?

The ISI is intended to represent the "complete story" of how the applicant has evaluated and mitigated immunogenicity-related risks for the investigational medicinal product. The term "integrated" refers here to the linkage of bioanalytical signals (ADA) with clinical endpoints (PK, PD, efficacy and safety) within each clinical study, and to align with the potential risks including product quality-related factors, rather than aggregation of clinical data across all studies. Thus, the ISI concept is distinct from that of the integrated summary of efficacy (ISE) or integrated summary of safety (ISS). The value proposition for the sponsor is that the ISI can provide the regulatory assessor with the requisite information to understand the nature and extent of the risk at both the population and individual subject levels, thereby reducing uncertainty for clinical trial approval or marketing authorisation.

The ICH M4E R2 guideline[5] defines the summary information to be included in Modules 2.7.2.4 and 2.5.3 of the CTD format, with the associated bioanalytical method validation reports and standard operating procedures (SOPs) located in Module 5.3.1.4. Clinical study reports (CSRs) in Module 5.3 will also contain results from individual studies.

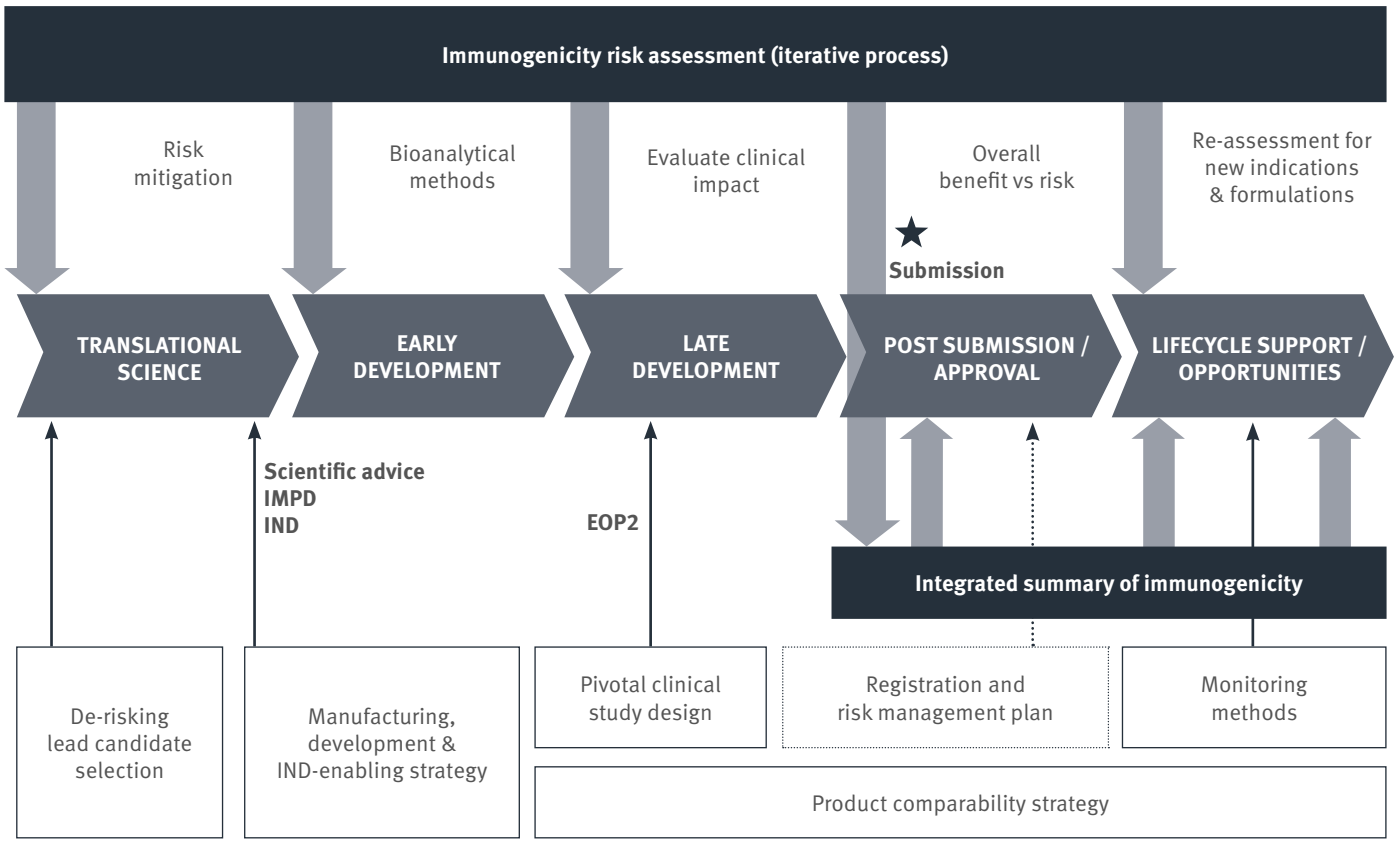
Guidance from both the European Medicines Agency (EMA)[2] and the US FDA[6] endorse the integrated summary concept and extend the scope of information defined in the ICH M4E R2 guideline to include:

- Risk assessment, ie, identification of potential risk factors and rationale for evaluation and mitigation
- Critical discussion of control of product quality-related factors, with a focus on product-related variants and process-derived impurities that may influence immunogenicity
- Clearer navigation through the development and validation of bioanalytical methodology in relation to assays applied to individual clinical studies (ie, to link the information contained in the reports submitted in Modules 5.3.1.4 and 5.3)
- More extensive descriptive analyses of the relationship between ADA signals and clinical parameters.

Section 10 of the EMA guideline[2] provides a list of topics to be addressed in the ISI, while the FDA guidance[6] identifies the most important elements for the regulatory reviewer – in a manner that is fully consistent with the EMA guidance. The case study associated with this article explains how the different elements can be assembled to build an effective ISI. A more detailed model format is described in a separate article.[7]

This supplement offers regulatory professionals an accessible way to use Regulatory Rapporteur as a starting point for recording their LLL hours and help gain or maintain MTOPRA status. Supplements will be archived online and will build up to become a repository of CPD exercises – pitched at different levels of regulatory experience – that members can access free as and when they require them.

FIGURE 1
Evolution of immunogenicity-related regulatory documentation during the product lifecycle



Where in the CTD format should the ISI be located?

Because the amount of information to be submitted may exceed size limitations for Module 2 summaries in the CTD format, both EMA and FDA guidelines[2,6] explicitly permit submission of the ISI in Module 5.3.5.3. A brief summary of the results and conclusions of the clinical immunogenicity evaluation can be submitted in Module 2.7.2.4 and cross-refer to the ISI in Module 5.3.5.3 for the complete information.

In the author's experience, the length of the ISI for a novel biological entity is often between 160 to 200 pages of A4 format. In the case of abbreviated programmes, eg, for biosimilars and line extensions, the ISI might be shorter and accommodated more easily in Module 2.7.2.4. Both the EMA and FDA have been flexible in allowing applicants to use their judgement about dossier location in order to encourage completeness of information to be reviewed.

How should the risk-based programme be described?

Regulatory guidance[2,6] encourages the creation of a formal immunogenicity risk assessment document early in the product development process. A comprehensive framework of the scope of information to consider is provided in the EMA and FDA guidance[2,6,] bearing in mind that the risk assessment needs to be adapted to both the specific structural and functional properties of the investigational medicinal product (IMP) and the intended clinical population. The aim of the risk assessment is to identify potential product and patient-related risk factors and thereby design appropriate monitoring and control measures into the development programme.

A summary report can be created to serve as a source document for information to be included in CTAs and briefing documents for scientific advice procedures. This document should be updated during clinical development and then used as the first section of the ISI for submission in the MAA dossier. Figure 1 illustrates the iterative process of immunogenicity risk assessment process as manufacturing process and clinical development progresses towards the MAA and linkage to the ISI.

Currently, there is no standard format for the risk assessment document. The format summarised in Figure 1 of the case study could be used as a starting point because this incorporates sub-headings that

Quiz: Test your knowledge

Once you have read the supplement, complete the self-assessment exercise at **topra.org/CPDsupplements** and answer the questions online. Successful completion and submission of the assessment form means that you can claim your lifelong learning (LLL) hour for the task, which members can add to their CPD recording tool.

Immunogenicity can be relevant for both sides of the benefit versus risk equation because ADA can reduce efficacy by enhancing clearance or by directly neutralising the activity of the therapeutic agent, as well as inducing immune-mediated adverse reactions

reflect the different points to consider described in the relevant regulatory guidelines.[1,2,5,6]

The immunogenicity risk assessment may be submitted in the CTA dossier. In terms of the CTD format, section 2.7.2.4 would be the most relevant location for this information. Alternatively, it could be submitted as a sub-section of the overall benefit–risk justification for the clinical study, or as an appendix to the CTA dossier. It is recommended that sponsors seek endorsement from regulatory agencies about choice of methodology and clinical study design for monitoring immunogenicity. Even if validated bioanalytical methods are not yet available, the CTA dossier should provide a justification for the proposed extent of monitoring and bioanalytical methods to be developed and validated.

Which factors contribute most to successful regulatory outcomes?

Immunogenicity depends on the intrinsic molecular features of the IMP and the manner in which these interact with the innate and adaptive immune systems, against a background of variable immune tolerance.[8] Accordingly, explaining how molecular design and mode of action of the product (and its target) contribute to immunogenic potential in the relevant therapeutic context represents the foundation for the risk profile.

Because fundamental choices made at the levels of molecular design and host cell substrate to be used for expression of a recombinant protein can be critical variables, the rationale for and impact of the decisions made merits clear discussion in the ISI. Although not being accurately predictive of immune responses across a clinical population, *in silico* and *in vitro* tools are available that allow a first estimation of relative intrinsic immunogenic potential of a defined primary amino acid sequence.[9-11] Therefore, presentation of data generated using these tools can provide a starting point for assessing relative risk.

Since formulation decisions can influence immunogenicity by affecting the stability of the monomeric form of the investigational medicinal product, and host cell-derived impurities can contribute to incremental immunogenicity, it is relevant to provide a summary of analytical and stability test results for such attributes in the ISI – or, at least, to provide a cross-reference to the relevant data located in Module 3 of the dossier.

The bioanalytical methods applied to monitor the ADA response generate an indirect index of immunogenicity, which is inferred from the difference between pre- and post-treatment signals in ligand-binding assays that measure antigenicity.

These assays are not quantitative because there are no absolute reference standards for calibration and the assays are subject to many other sources of analytical bias. Most importantly, these assays often detect signals at levels that are well below that associated with a clinical impact.[12] Therefore, the most important benefit of the ISI is the opportunity to position the bioanalytical signals into a relevant clinical context by integrating the results from ADA testing with indices of PK, PD, efficacy and safety. This requires advance planning to define the requisite data inputs for the ISI – which can be defined either in the statistical analysis plan for the clinical study (and, therefore, captured in the tables, figures and listings in the clinical study report) or in a pre-defined secondary data analysis plan (sometimes referred to as the "ISI SAP") that is not part of the formal clinical protocol. Industry publications provide advice for terminology and data presentation that can be used for defining suitable analyses.[13,14]

While inclusion of detailed information on bioanalytical methodology in the ISI might seem to duplicate content in the method validation reports to be submitted in Module 5.3.1.4, it can be extremely difficult for the regulatory assessor to follow the evolution of methodology applied to different clinical studies. Accordingly, the bioanalytical section of the ISI can be used to navigate the regulatory assessor through the history, clarifying how changes in methodology have affected assay performance/ADA detectability.

Given the important influence of genotypic and phenotypic variables on the magnitude of immune responsiveness, the results of the clinical immunogenicity evaluation should include a critical review of the impact at both the individual subject and population levels. In particular, comparison of clinical parameters (PK, PD, efficacy and safety) for the sub-populations with the lowest versus highest ADA titer values can be instructive for identification of subjects at highest risk. Appropriate warnings and precautions may then be included in the prescribing information.

Conclusion

The ISI represents a "living document" that provides a complete picture of the immunogenicity-related information that will need to be assessed by regulatory reviewers. This format can be created early in the development cycle to guide strategic decisions and then updated during clinical development to support regulatory interactions, initial marketing authorisation and line extensions for new therapeutic indications.

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CASE STUDY

Creating an integrated summary of immunogenicity report

Introduction

The purpose of this case study is to illustrate the creation of an integrated summary of immunogenicity report (ISI) that fulfils the recommendations described in current regulatory guidance for the scope of information needed to facilitate assessment of immunogenicity-related risks to support marketing authorisation of novel and biosimilar versions of biopharmaceutical products. A model format for documenting the output of the immunogenicity risk assessment that can be presented to support clinical trial applications and scientific advice procedures is also described. An updated version of this risk assessment may then used as the first part of the ISI to be submitted in the marketing authorisation application (MAA) dossier.

1. Immunogenicity risk assessment

The primary purpose of the risk assessment is to identify potential risks for the molecular entity and the target clinical population, and then to define an appropriate plan for evaluation and mitigation of these potential risks. Creation of a formal document that summarises the intrinsic and extrinsic factors that could influence the immunogenicity of an investigational medicinal product should commence at the time of the lead candidate selection stage of development because this will guide important risk evaluation and mitigation decisions. This document serves as the source for summaries to be presented in the briefing books in pre-CTA meetings and

FIGURE 1

Model format for immunogenicity risk assessment to be presented in CTA dossier

Immunogenicity risk assessment for CTA dossier

1. Intrinsic immunogenic potential
2. Systems biology
3. Subject-related factors
   - i. Immunological competence of the subject
   - ii. Prior sensitisation/history of allergy
   - iii. Genetic factors
   - iv. Extent of immune tolerance to structurally related endogenous factors
   - v. Co-morbidities associated with disease state
4. Product quality
5. Nonclinical evaluation (*in vitro* and *in vivo*)
6. Conditions of use
7. Strategy for effective risk evaluation and mitigation
   - i. Tabular summary aligning potential risks to proposed evaluation and mitigation measures
   - ii. Bioanalytical strategy
     - Hierarchical test scheme
     - Proposed assay formats and controls
     - Parameters validated/to be validated
     - Potential utility of biomarkers of PD response
   - iii. Clinical sampling scheme (including follow up)

for the CTA dossier itself. The example in Figure 1 has been used by the author and could serve as a starting point for refinement and addresses the scope of information recommended in the regulatory guidance referred to in the main article.

For biosimilar applications, the analysis of risk factors would be guided primarily by the experience accumulated for the originator product allied to potential for incremental risk associated with any detected qualitative and quantitative differences in the product quality profile of the biosimilar candidate. Representative analytical results pertaining to potentially important variables for incremental immunogenicity risk may also be included. Nonclinical evaluation includes data from *in vitro* analyses using human cells and, for products that have structural and functional commonality across different species, *in vivo* data from non-human species might be relevant for hazard identification. The forward-looking plan for risk evaluation should include clinical study design considerations, as well as proposals for bioanalytical methodology.

Figure 2 illustrates the way in which a tabular summary format could be used to present the output of the risk assessment process for one potential consequence of immunogenicity for a therapeutic protein expressed in a yeast host cell substrate. The risk identification process links to the definition of a suitable bioanalytical strategy for monitoring pertinent risks, as well as clinical trial design considerations, which can then be discussed with regulatory agencies as part of scientific advice procedures during development.

2. Integrated summary of immunogenicity (ISI)

Regulatory guidance defines the scope of information to be presented in the ISI in a manner that allows flexibility to accommodate different product types, risk profiles and extent of the programme. The outline format shown in Figure 3 identifies the recommended inputs, including the updated risk assessment (Section 1 of ISI), and illustrates how these can be organised to address regulatory expectations.

Section 2 of the ISI provides an opportunity to explain the suitability of the methodology applied for risk evaluation at different stages of clinical development – what methods were chosen, and why – and how the data were interpreted. Effectively, Section 2 of the ISI can draw together the most critical information from the bioanalytical method validation reports submitted in Module 5.3.1.4, and help the regulatory assessor understand how different iterations of methodology fit into the clinical development programme.

Section 3 of the ISI should present the results from each clinical study in a manner that describes immune response dynamics (incidence and magnitude of anti-drug antibody/neutralising anti-drug antibody) relative to clinical points (pharmacokinetics, pharmacodynamics, efficacy and safety). Section 4 of the ISI provides the main conclusions and links to the risk management plan.

Figure 4 indicates the relationship of the ISI to other sections of the CTD format that are relevant for the immunogenicity assessment. Summary information and conclusions from the ISI can be used to populate clinical summaries. ISI section 1 will cross-refer to relevant sections of Module 3 for product quality-related information; ISI section 2 will cross-refer to the bioanalytical method validation reports in Module 5.3.1.4; and ISI section 3 will cross-refer to the clinical study reports in Module 5.3.

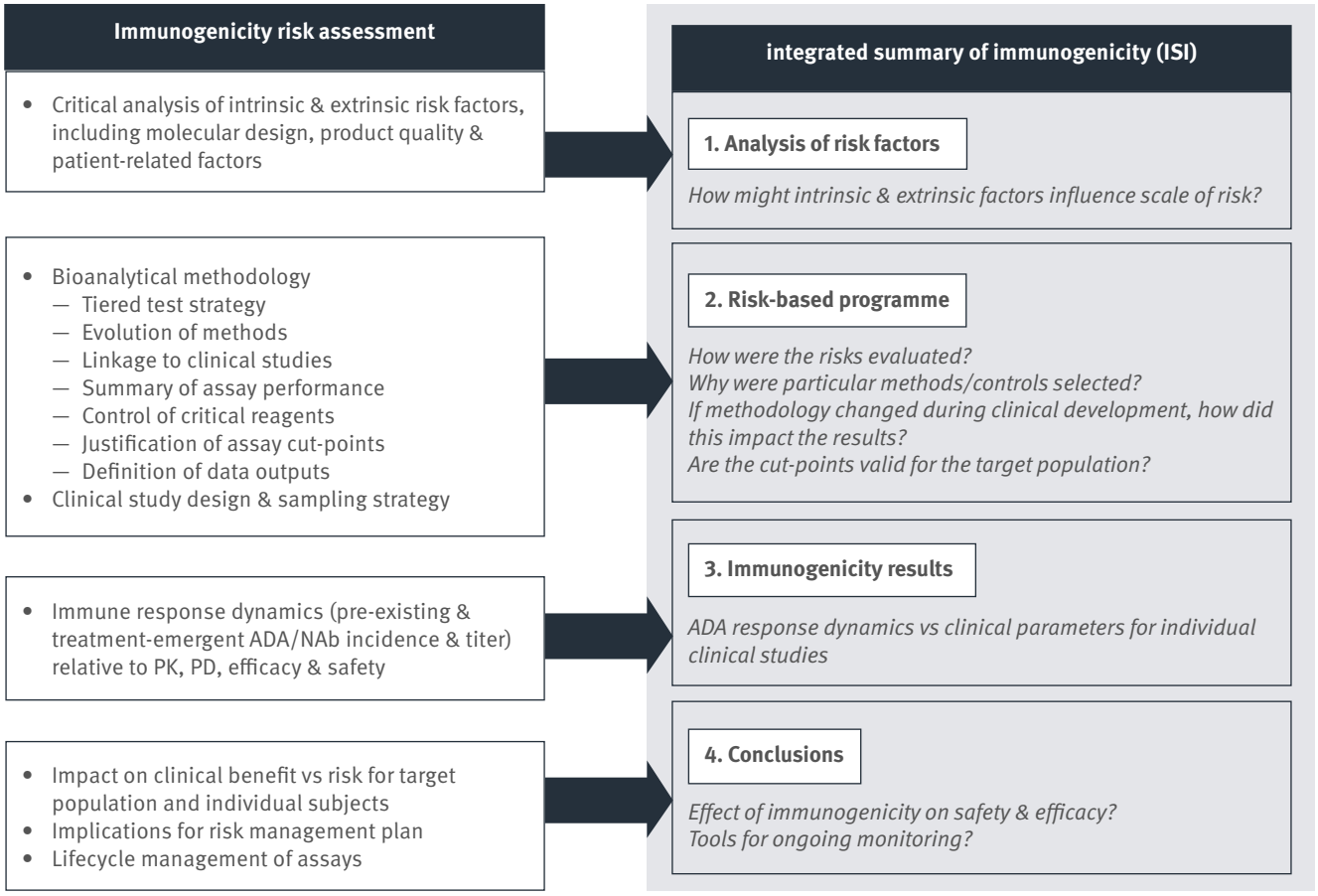
FIGURE 2

Summary of output from risk assessment

Potential consequence	Risk evaluation	Risk mitigation
Allergic-type hypersensitivity/ anaphylaxis	**Pre-clinical** • Comparative *ex vivo* basophil activation testing (healthy humans vs atopic subjects) **Clinical** • Monitoring of timing and severity of clinical symptoms of infusion-related reactions relative to pre-existing and treatment-emergent ADA with cross-reactivity to non-human glycans (additional specificity tier incorporated in ADA testing scheme) • Measurement of serum tryptase levels • Follow-up investigation of IgE ADA and *ex vivo* basophil activation test in subjects with potential immune-mediated AEs in Phase 3 study	1. Molecular design to minimise non-human glycans associated with expressed protein 2. Absence of *ex vivo* basophil activation in naïve or treated subjects 3. Negligible serum tryptase in treated patients 4. No subjects fulfilling NIAID FAAN criteria for anaphylaxis 5. No severe systemic hypersensitivity reactions reported in clinical programme 6. AEs not related to drug-specific IgE

ADA = Anti-drug antibody; AE = Adverse event; FAAN = Food Allergy and Anaphylaxis Network; NIAID = National Institute of Allergy and Infectious Disease

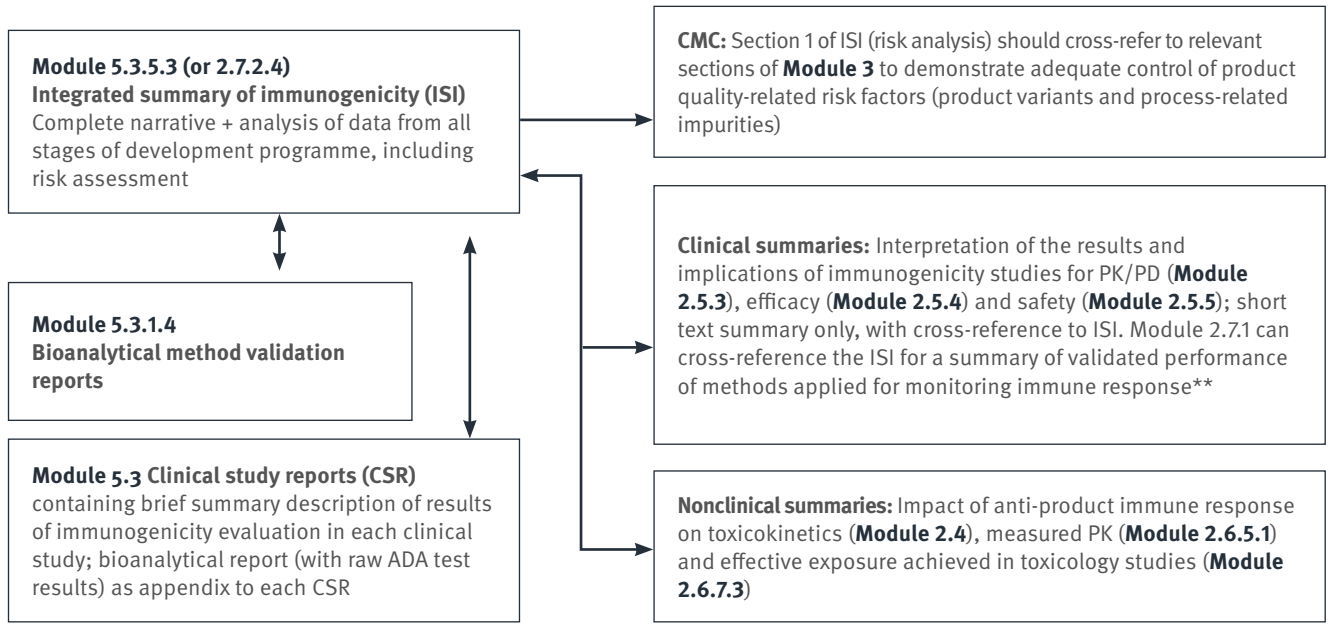
FIGURE 3
Model format for integrated summary of immunogenicity*



ADA: Anti-drug antibody; NAb: Neutralising anti-drug antibody

*A more detailed model format for the ISI is provided in reference 7 cited in the main article.

FIGURE 4
Relationship of ISI to other CTD sections



ADA: Anti-drug antibody

**Module 2.7.1 then describes PK & biomarker assay methods only.

MCQs (complete the quiz online at http://bit.ly/RR_CPD)

1. In which section of the CTD format has the main summary of information relating to the evaluation of immunogenicity been traditionally (ie, according to the ICH M4 R2 guideline) located?

- ○ **A.** 5.3.1.4
- ○ **B.** 5.3.5.3
- ○ **C.** 2.7.2.4

2. Why have the EMA and FDA updated their guidance to extend the range of information to be presented in the immunogenicity summary?

- ○ **A.** To link interpretation of the clinical results to the immunogenicity risk profile of the product and patient population
- ○ **B.** To simplify the format for presenting results
- ○ **C.** To extend the scope of the products for which immunogenicity assessment is expected

3. What is the main benefit of locating the integrated summary of immunogenicity in Section 5.3.5.3?

- ○ **A.** Immunogenicity data is of most interest to clinical reviewers
- ○ **B.** More information can be included in a single dossier location to enable a multi-disciplinary data-driven assessment of impact of immunogenicity on overall clinical benefit and risk, compared with location in Module 2
- ○ **C.** The main focus of the immunogenicity assessment has changed from a review of bioanalytical methodology to interpretation of the clinical impact of the bioanalytical signals

4. How is the clinical impact of immunogenicity assessed?

- ○ **A.** The relationship of detected anti-drug antibody levels to incidence and severity of treatment-emergent adverse events is assessed for each clinical study; impact on PK or efficacy is far less important
- ○ **B.** A multi-disciplinary team of assessors reviews the bioanalytical results in relation to PK, PD, efficacy and safety from all clinical studies and puts this information into the context of the potential risk profile for the product and the target population
- ○ **C.** Efficacy results for the neutralising antibody positive subjects is compared with efficacy in the neutralising antibody negative subjects

5. The term "integrated" signifies what in respect of the immunogenicity summary?

- ○ **A.** The pooling or aggregation of clinical results from different studies, as for the integrated summary of efficacy and integrated summary of safety
- ○ **B.** Assessment of clinical impact by analysis of bioanalytical measures relative to the pertinent clinical endpoints for each individual clinical study, in association with justification of suitability of methodology and the product quality control strategy
- ○ **C.** Merging of CTD sections 2.7.2.4 and 5.3.1.4