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Nonclinical Assessment of Immunogenicity from Regulatory Perspective

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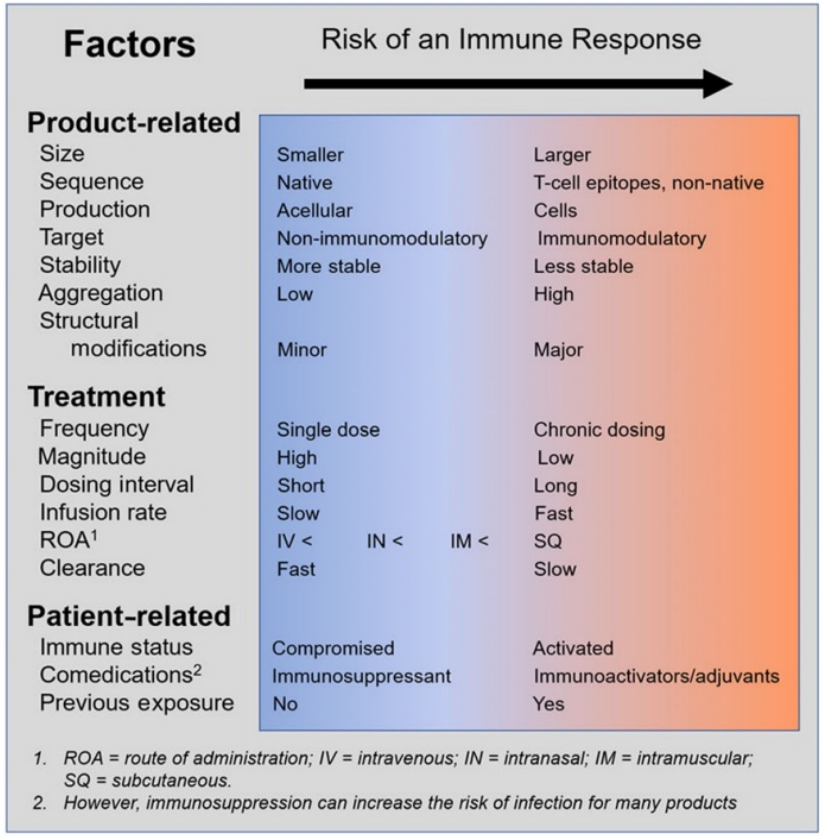
Immunogenic risk factors

Drug nature

Treatment (dosing and administration)

Patient related factors and disease type



Vandivort T. C. et al., 2020

The need of immunogenicity assessment depends on immunogenicity risk factors

- Biotherapeutic protein products and their copies (biosimilars)
- Several non-biologic drug classes
  - Peptides
  - Oligonucleotides
  - Some combination products
- Gene therapies
- Presence of impurities

Clinical consequences

- Loss of efficacy (in case of neutralization Abs)
- Effects on drug clearance
- Acute immunological adverse events (infusion reactions, cytokine storm, allergic reactions, hypersensitivity)
- Non-acute responses type III and IV hypersensitivity reactions (antigen-antibody complex-mediated, cell-mediated reactions), serum sickness and contact dermatitis
- Autoimmunity (cross-reactivity with endogenous proteins)

Guidelines: Immunogenicity

- **ICH S6**
  - *One aspect of immunotoxicological evaluation includes assessment of potential immunogenicity*
  - *Measurement of antibodies associated with administration of these types of products should be performed when conducting repeated dose toxicity studies in order to aid in the interpretation of these studies.*

- ***EMA -*** Guideline on the Quality, Non-clinical and Clinical Aspects of Gene Therapy Medicinal Products
  - *Delivery of GTMPs can result in immune responses of the innate and adaptive immune system. These aspects should be considered by the applicant during the non-clinical development.*
  - *Toxicity should be assessed for the whole GTMP in order to determine unwanted consequences of the distribution and persistence of the vector, its infection/transduction/transfection, the expression and biological activity of the therapeutic gene(s) and vector genes, if applicable, as well as immunogenicity or unwanted pharmacological effects.*

Assessment of immunogenicity

(according to ICH S6 and Addendum)

- ADAs should be assessed during repeated toxicity assays if there is:
  - evidence of altered pharmacodynamic (PD) activity
  - unexpected changes in exposure in the absence of a PD marker
  - evidence of immune-mediated reactions (immune complex disease, vasculitis, anaphylaxis, etc.).
- Characterization of neutralizing potential is warranted when ADAs are detected and there is no PD marker to demonstrate sustained activity in the *in vivo* toxicology studies.

- Validated assays should be used
- In addition, a testing of antibody independent immunogenicity might be required (CRS, complement activation) on case by case basis
- Routine testing on case by case basis
- Assay selection and sampling time points should be carefully designed (mechanism of action considered, presence of soluble target, adequate cut-off determination, matrix, controls, statistics)

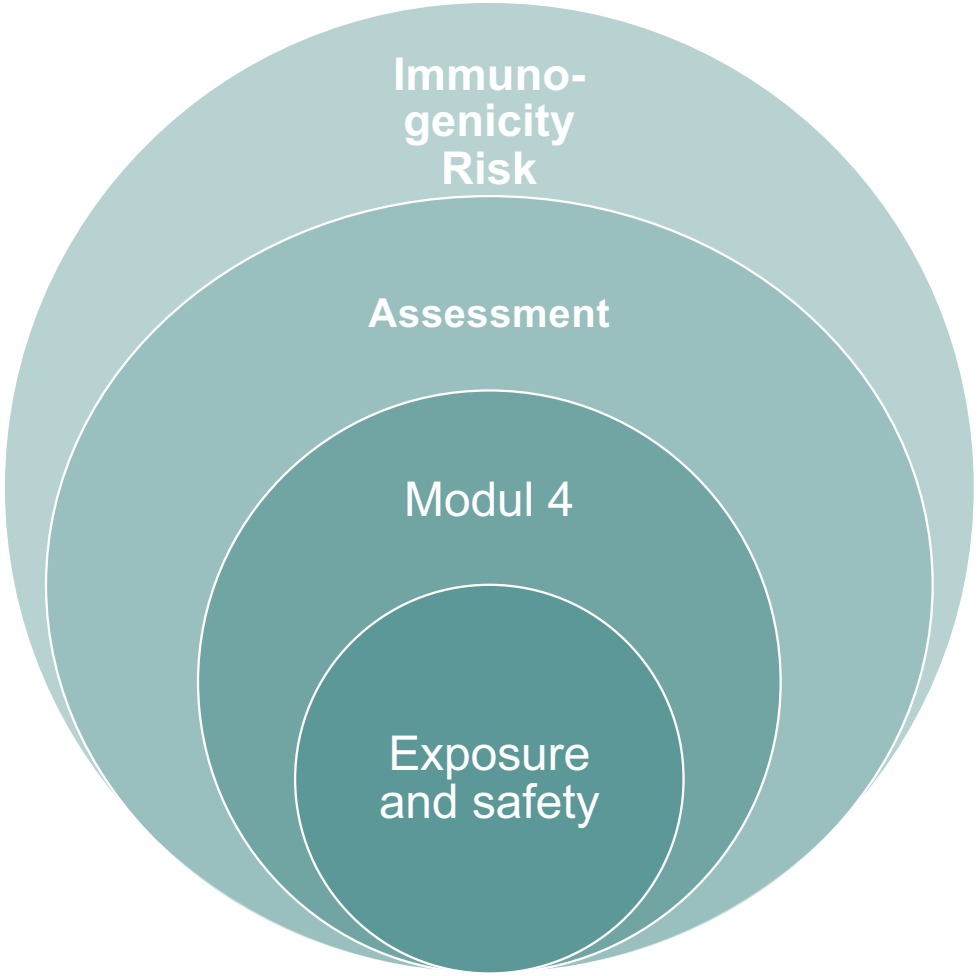
Nonclinical immunogenicity investigation

- Assessment of immunotoxicity and immunogenicity are regulatory requirements in nonclinical and clinical testing.

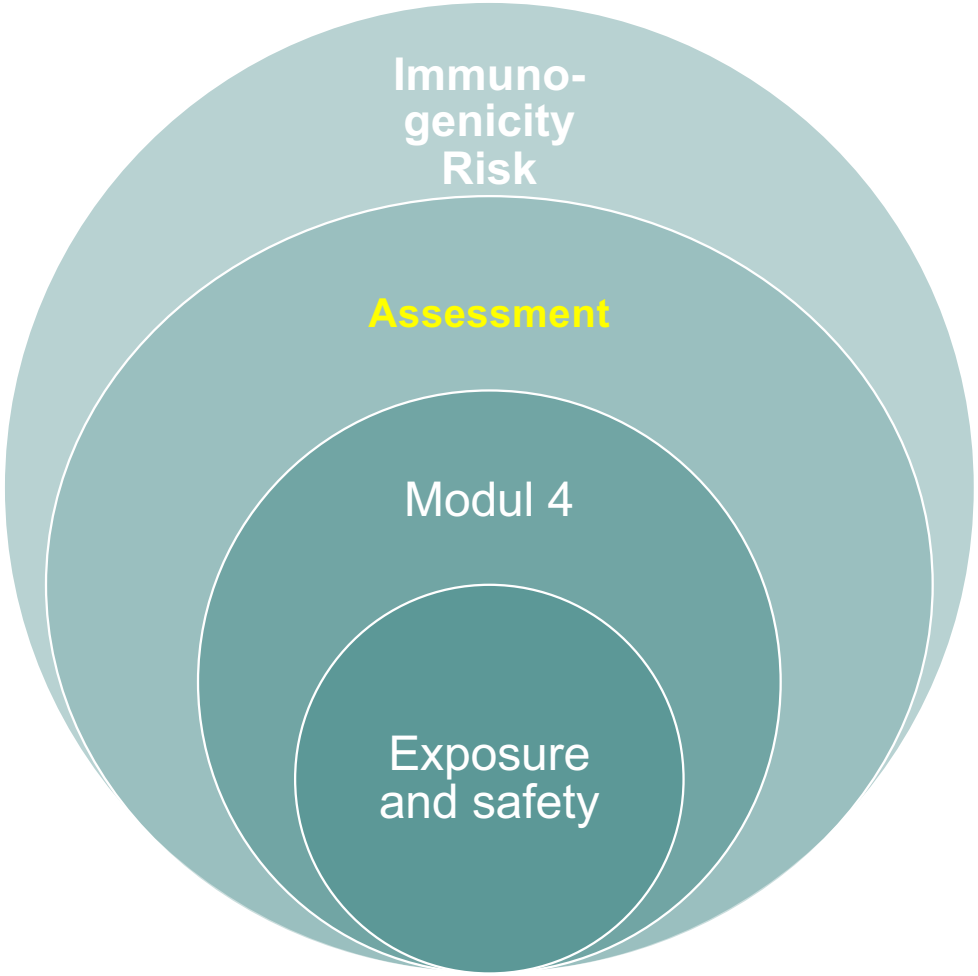
- **The induction of antibody formation in animals is not predictive of a potential for antibody formation in humans. (ICH S6)**

Why bother at all?
Why and when are immunogenicity studies needed ?
When do they actually add value to safety?
What about non-antibody mediated immunogenicity?

How to address immunogenicity from the nonclinical perspective?



How to address immunogenicity from the nonclinical perspective?



Nonclinical assessment of immunogenicity: a multidisciplinary approach

Quality data (Module 3)

- Type of product (low/high risk)
- Chemical or post-translational modifications?
- Impurities?
- **Available data:**
  - ***in silico* tools data (epitope prediction models)?**
  - ***In vitro* data (HLA binding; T cell assays)?**
    - **Validated methods?**

Nonclinical data (Module 4)

- **Pharmacology data**
- **Pharmacokinetic data**
- **Toxicity data**

Clinical data (Module 5)

- Type of disease
- Observed immunogenicity?
  - ADA development
  - *Ex vivo* assays
  - Cytokine release
- Patient health status

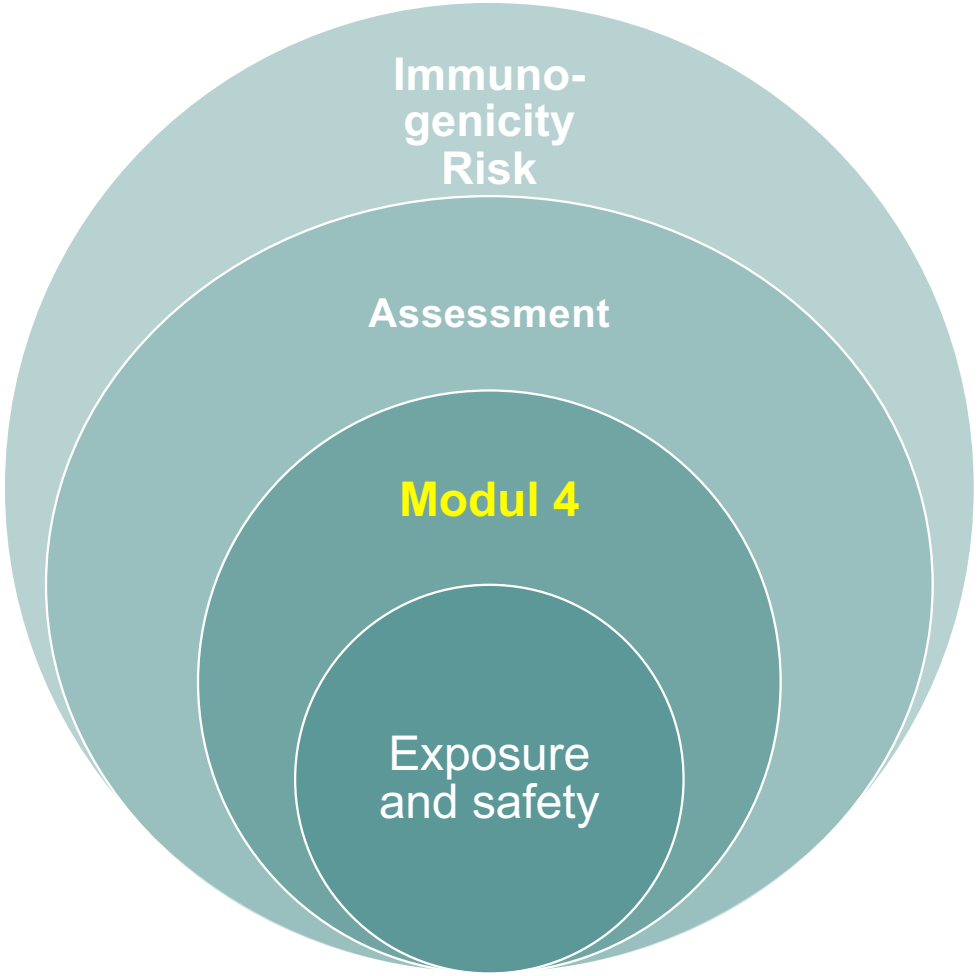
Objectives of nonclinical immunogenicity assessment

- Immunogenicity assessment serves to address the risk of adverse immune response (non-antibody maediated immunogenicity) by identifying a potential cause of concern.

- It allows mitigation of an unwanted immune response in human before clinical trials.
  - For biologics and more complex modalities, immunogenicity is one of the main reasons for failure in FIH trials

- It supports the interpretation of toxicology studies.

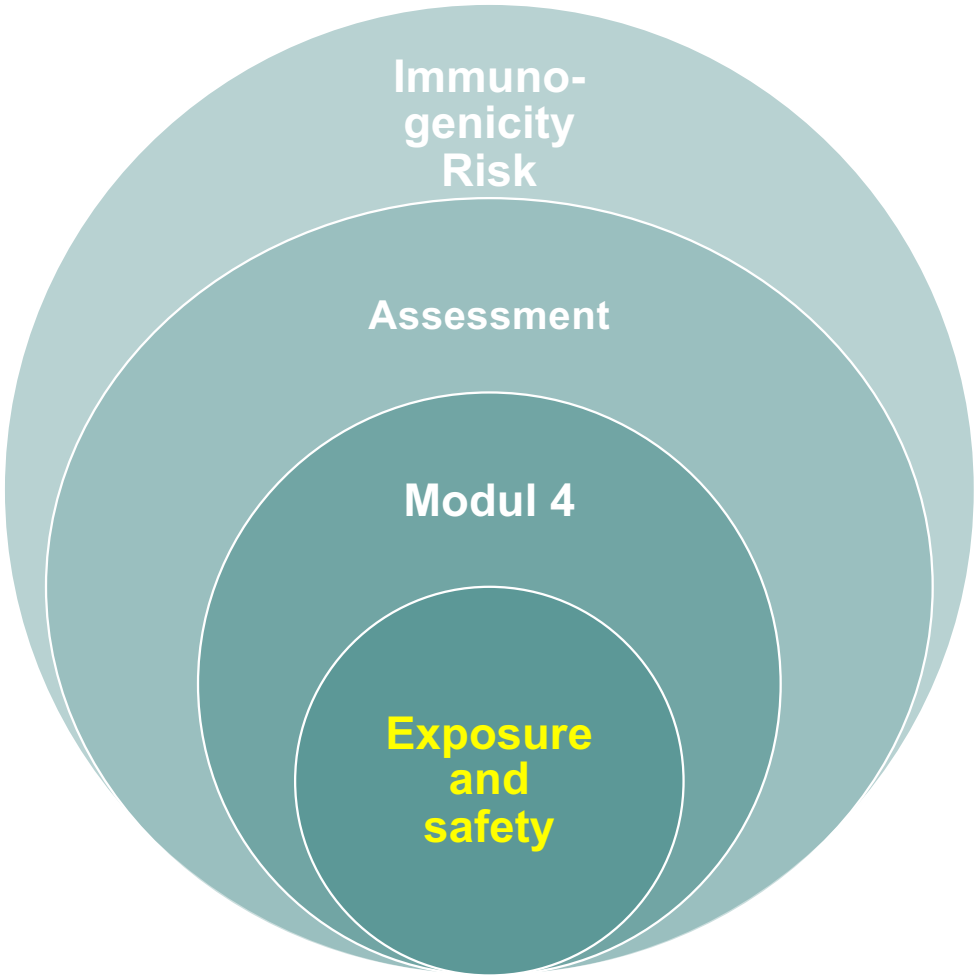
How to address immunogenicity from the nonclinical perspective?



Module 4

Pharmacology data	Pharmacokinetic data	Toxicity data
• Mechanism of action • Off-target binding? • Complement activation?	• Changes in PK • ADA formation	• Clinical signs • Findings in haematology or histopathology • Signs of inflammation

How to address immunogenicity from the nonclinical perspective?



Effects on exposure

Sufficient exposure of the drug in the toxicology study is necessary for the appropriate safety assessment and the calculation of safety/exposure margins.

Points to consider when evaluating data:

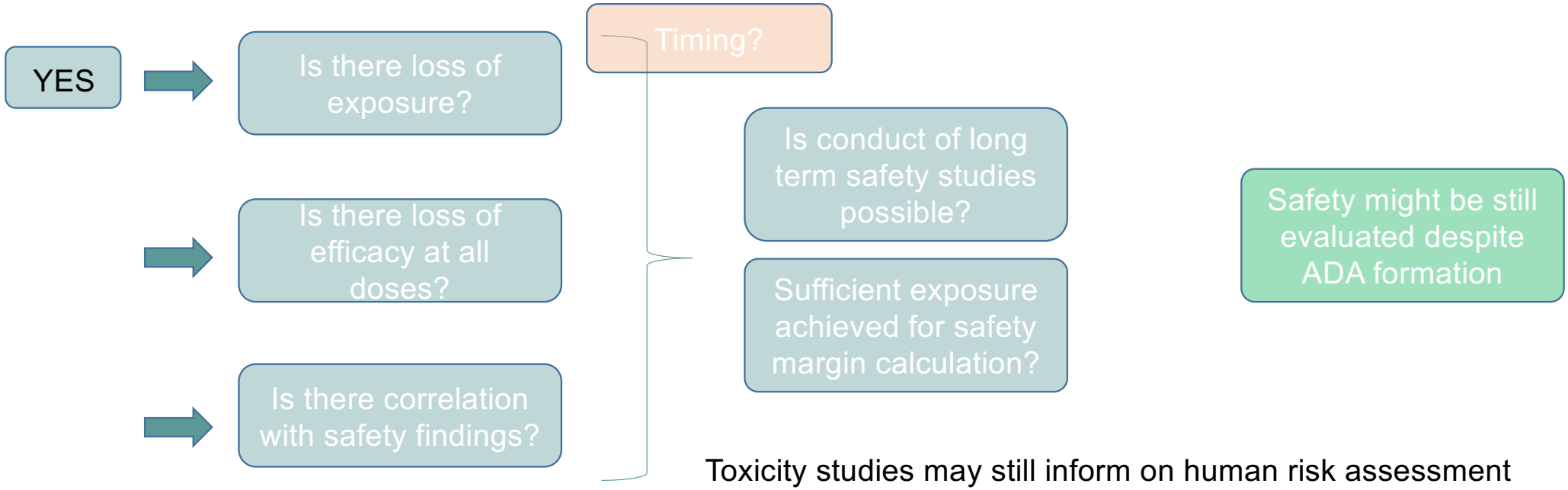
Was the effect observed in all animals?

- It is recommended to exclude ADA positive animals for TK analysis to understand the impact of ADAs and correlate with safety data

  →This approach is more appropriate for studies, when PD, safety and TK are evaluated in the same animal.

ADA formation does not preclude safety evaluation

Were ADAs measured in a toxicity study?

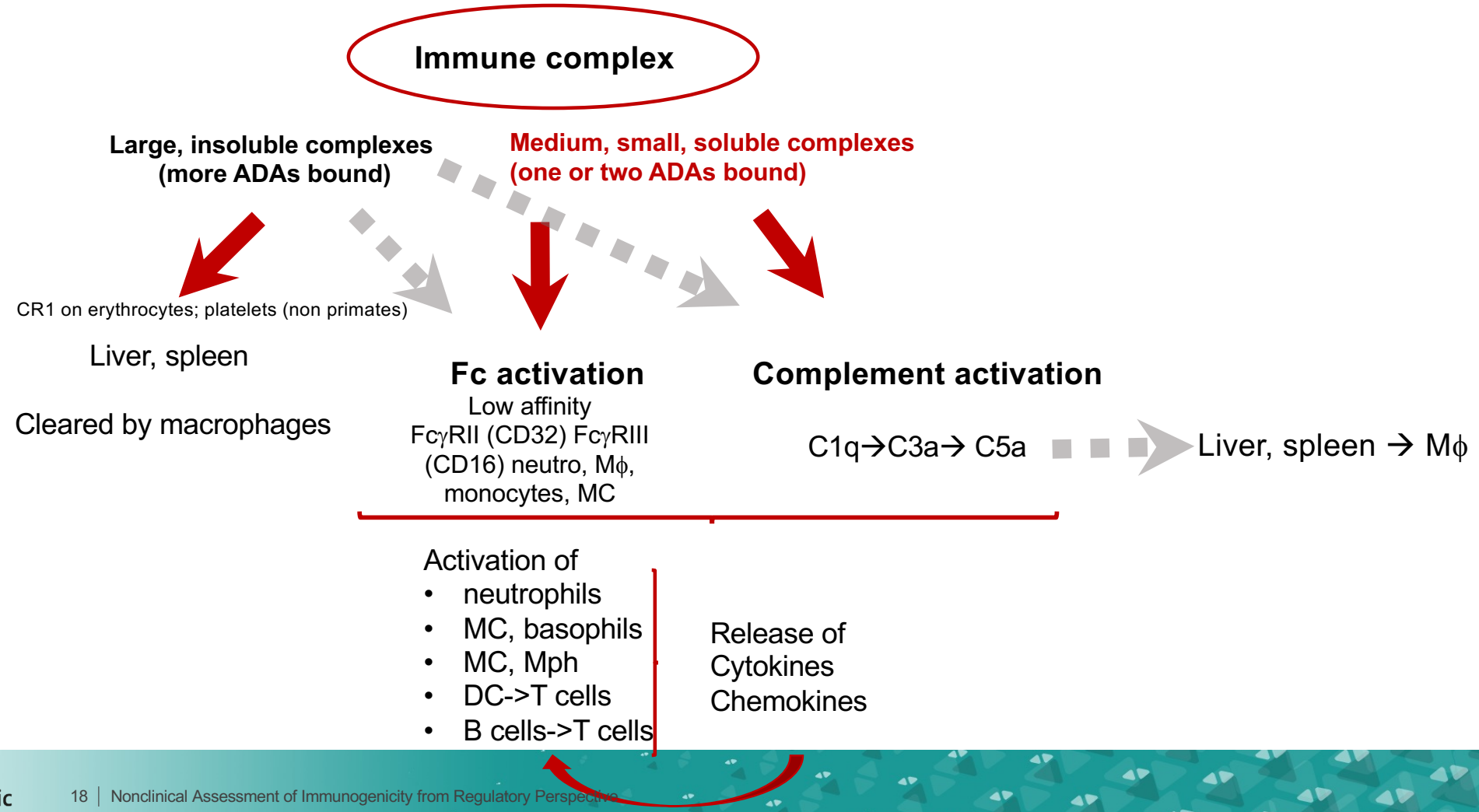


Toxicity studies may still inform on human risk assessment despite ADA formation.

Toxicity findings

- Haematology changes (immunotoxicity, changes in cell number)
- Effects on lymphoid organs
- Hypersensitivity, anaphylaxis
- Immune complex (IC) formation
- Signs of inflammation (vasculitis, arthritis, granulomelitis …) or necrosis?
  - Correlation with ADA findings or IC formation sites?
  - Correlation with complement activation?

Immune complexes and immune system activation



Interpretation of immunogenicity findings in toxicity studies

- Prediction of potential immune-associated adverse events in the clinic is limited, however the understanding of immunogenic potential can help in design of clinical trials and on the decision of clinical monitoring.

- Important for clinical trials

- Post approval commitment →included in risk management plan

New multi-specific molecules

- Often no relevant species and long term safety cannot be assessed
- Carry enhanced risk of immunotoxicity/genicity due to:
  - Introduction of new AA sequences, new epitopes
  - Bringing together two or more different targets in a non-natural way
  - Molecules can bind immune cells, trigger T cell activation
- Assessments should include:
  - Good understanding of pharmacology
  - Evaluation of immunotoxicity and immunogenicity
  - Discussion of the risk of clinical consequences and mitigation strategies

Example A: Bi-specific monoclonal antibody for oncology indication

Quality data (Module 3)

- New structure → high risk

Nonclinical data (Module 4)

- No relevant toxicology species or surrogate molecule
- High immunogenicity in animals, → no long term studies or assessment of off-target toxicity
- **Determination of safety margin not possible.**

Extensive evaluation of MoA was conducted using ex vivo samples

Clinical data (Module 5)

High immunogenicity
- ADA development
- Cytokine release syndrome

Risk mitigation strategies were included during FIH trials

Acceptable due to indication and risk mitigation strategy

Example B: Bi-specific monoclonal antibody for chronic treatment

Quality data (Module 3)

- New structure →high risk

Nonclinical data (Module 4)

Pharmacology

- MoA: binding to the endothelial cell surface protein

Pharmacokinetics

- Typical for mAb

Nonclinical data (Module 4)

- Toxicity studies conducted in relevant species
- High immunogenicity in animals but sufficient exposure
- IC formation and vasculitis due to IC deposition
- **Detailed discussion of the location of vasculities and IC was requested due to localisation of target**
- **Correlation between ICs deposition and vasculitis was found, but did not include target binding; not relevant for humans as low ADAs in clinical trials**

Clinical data (Module 5)

- Acceptable immunogenicity
- No signs of inflammation in clinics

Immunogenicity will be tracked as a postmarketing commitment

What do we expect?

- Adequate presentation of immunogenicity information in submitted documents is important as it facilitates efficient review

- Weight of evidence approach considering:
  - drug specific risk factors
  - nonclinical data (*in vitro* and *in vivo*)
  - literature
  - discussion of a broad range of immune-related responses (both antibody-dependent and independent)
  - conclusions and risk-mitigation strategies proposal based on these results

Future aspects?

- New reliable and validated methods
- For biologics and more complex modalities; immunogenicity is one of the principal reasons for failure in FIH trials
- Guideline revision (?)

Thank you for your attention