Practical advice to perform immunogenicity risk assessments for INDs/IMPDs, BLAs/MAAs

EIP Training Course

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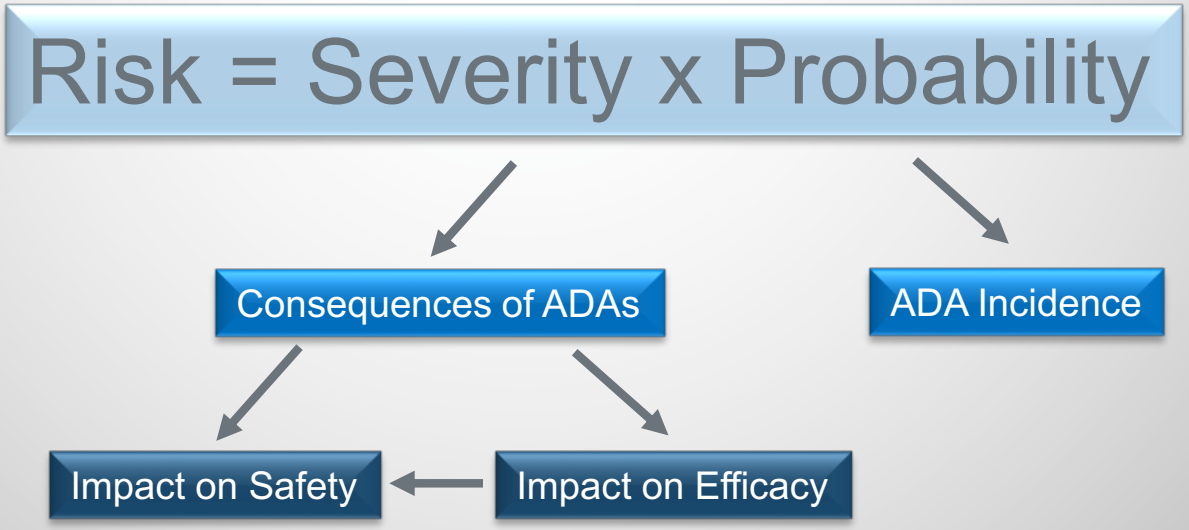
Immunogenicity Risk Assessment

- Immunogenicity risk assessment (IRA) allows the anticipation of potential clinical consequences even in the absence of clinical data



Immunogenicity Risk Assessment

Risk Factors

- Immunogenicity risk factors form the basis for immunogenicity risk assessment
  - They include product, process, posology- and patient-related risk factors
  - They either influence the incidence or clinical sequelae of an ADA response (or both)
- The risk to safety is considered of prime importance
  - A few subjects with severe ADA-related clinical consequences are of more concern than many ADA-positive individuals without apparent clinical impact
  - Focus is given to the potential severity of clinical consequences of immunogenicity rather than the probability of occurrence of ADA responses
- Prediction of immunogenicity is distinct from risk assessment (but is part of it)
  - Prediction tools might help predicting the probability of an ADA response but not its clinical sequelae

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Immunogenicity Risk Assessment

Example

IMMUNOGENICITY RISK FACTOR		Lower Risk	Moderate Risk	Higher Risk
Product related risk factors	Similarity to unique endogenous counterpart(s)	No similarity	Partial similarity	Complete similarity
	Primary Sequence	Fully human	Human with mutations / Partially human	Non human
	Glycosylation pattern	Fully human	Partially human	Non-human
	Mode of action	Immunosuppressive	Not applicable	Immunostimulatory
Process related risk factors	Expression system	Mammalian		Yeast/Bacterial
	Aggregates	Relatively low level	To be determined	Relatively high level
	Impurities	Relatively low	To be determined	Relatively high
Posology related risk factors	Dosing regimen	Single dosing	Multiple dosing / Chronic dosing	Intermittent dosing
	Dose	Rather high	To be determined	Relatively low
	Route of administration	IV	IM / IP	SC / Inhaled
	Clearance in humans	Relatively fast	To be determined	Relatively slow
Patient related risk factors	Immune status of patients	Immune-compromised	Normal immune system	Activated immune system
	Concomitant medication	Immunosuppressive co-medication	Not applicable	Immunostimulatory co-medication
	Concentration of endogenous counterpart	Relatively high	Not applicable	Relatively low

Moderate immunogenicity risk

Prediction of Immunogenicit vs. IRA

- **Prediction of immunogenicity is not a synonym for Immunogenicity Risk Assessment (IRA)**
  - Predicted T-cell epitopes are one immunogenicity risk factor (amongst product related risk factors)

IMMUNOGENICITY RISK FACTOR		Lower Risk → Higher Risk				
Product related risk factors	Similarity to endogenous counterpart(s)	No similarity	Partial similarity			Complete similarity
	Degree of foreignness	Fully human	Human with mutations	Partially human		Non human
	Glycosylation pattern	Fully human	Partially human			Non-human
	Mode of action	Immunosuppressive	Not applicable			Immunostimulatory
Process related risk factors	Expression system	Mammalian				Yeast/Bacterial
	Aggregates	Relatively low level				Relatively high level
	Impurities	Relatively low				Relatively high
Clinical related risk factors	Dosing regimen	Single dosing	Multiple dosing	Chronic dosing		Intermittent dosing
	Dose	Very high				Relatively low
	Route of administration	IV	IM	IP	SC	Inhaled
	Clearance in humans	Relatively fast				Relatively slow
Patient related risk factors	Immune status of patients	Immune-compromised	Normal immune system			Activated immune system
	Concomitant medication	Immunosuppressive co-medication	Not applicable			Immunostimulatory co-medication
	Concentration of endogenous counterpart	Relatively high				Relatively low

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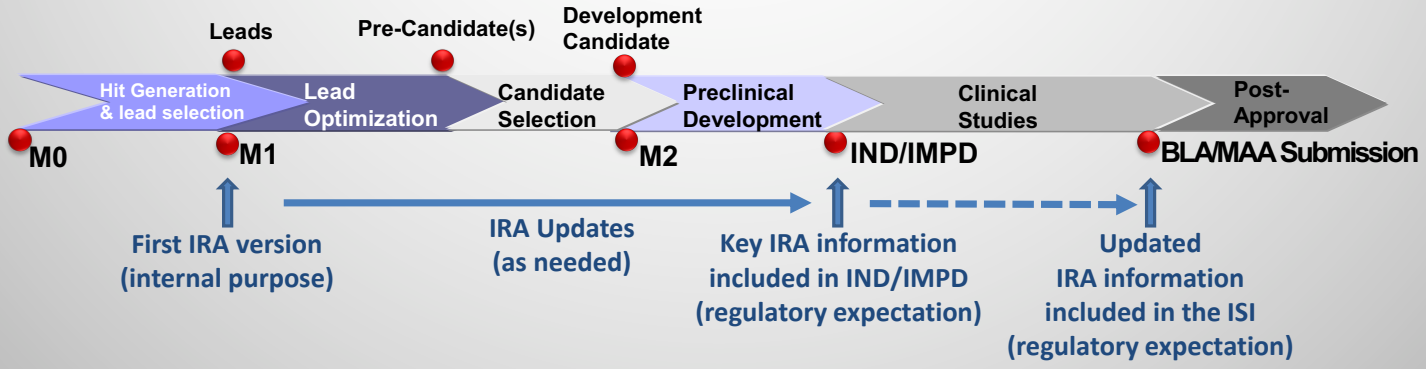
Immunogenicity Risk Assessment

Regulatory Expectations

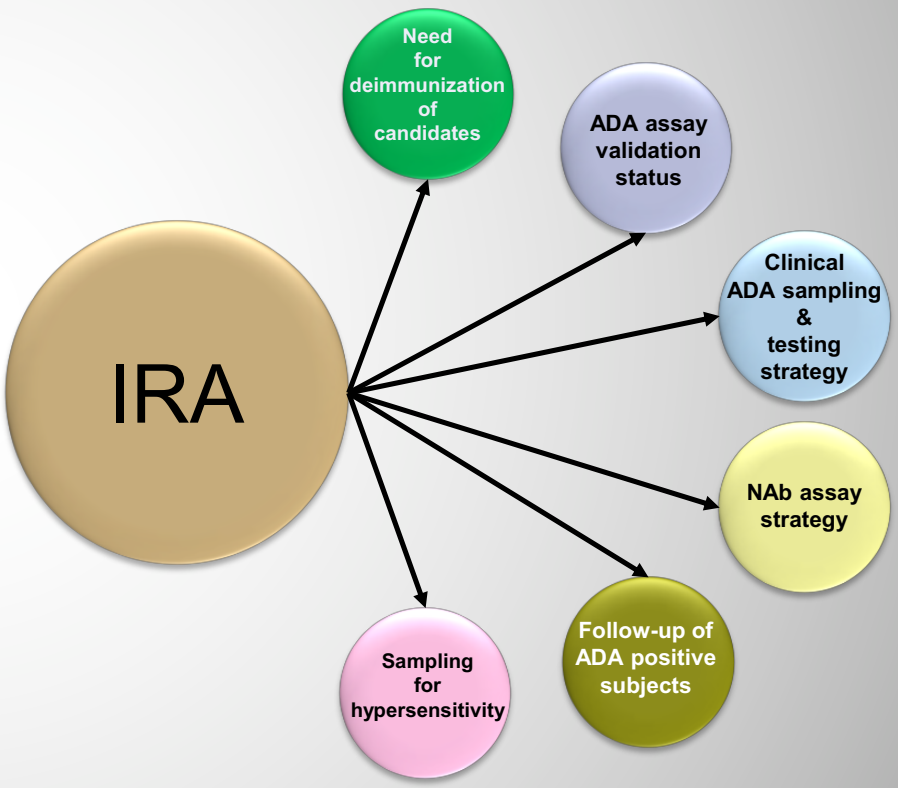
- First version of the immunogenicity risk assessment (IRA) is created at lead selection
  - Main purpose at that stage is to determine the potential need for de-immunization
- From a regulatory point of view an IRA should be provided along with an IND/IMPD to support FIH and at BLA/MAA filing as part of the Integrated Summary of Immunogenicity (ISI)
  - The IRA is most valuable at IND/IMPD stage as it allows the identification of potential clinical consequences even in the absence of clinical data and supports the immunogenicity sampling/bioanalytical strategy
  - At BLA/MAA filing an IRA becomes less important due to the availability of real clinical immunogenicity data overruling initial theoretical concerns
  - Formal interim updates of the IRA document (between FiH and BLA/MAA filing) might be performed but are usually not requested by health authorities



Immunogenicity Risk Assessment

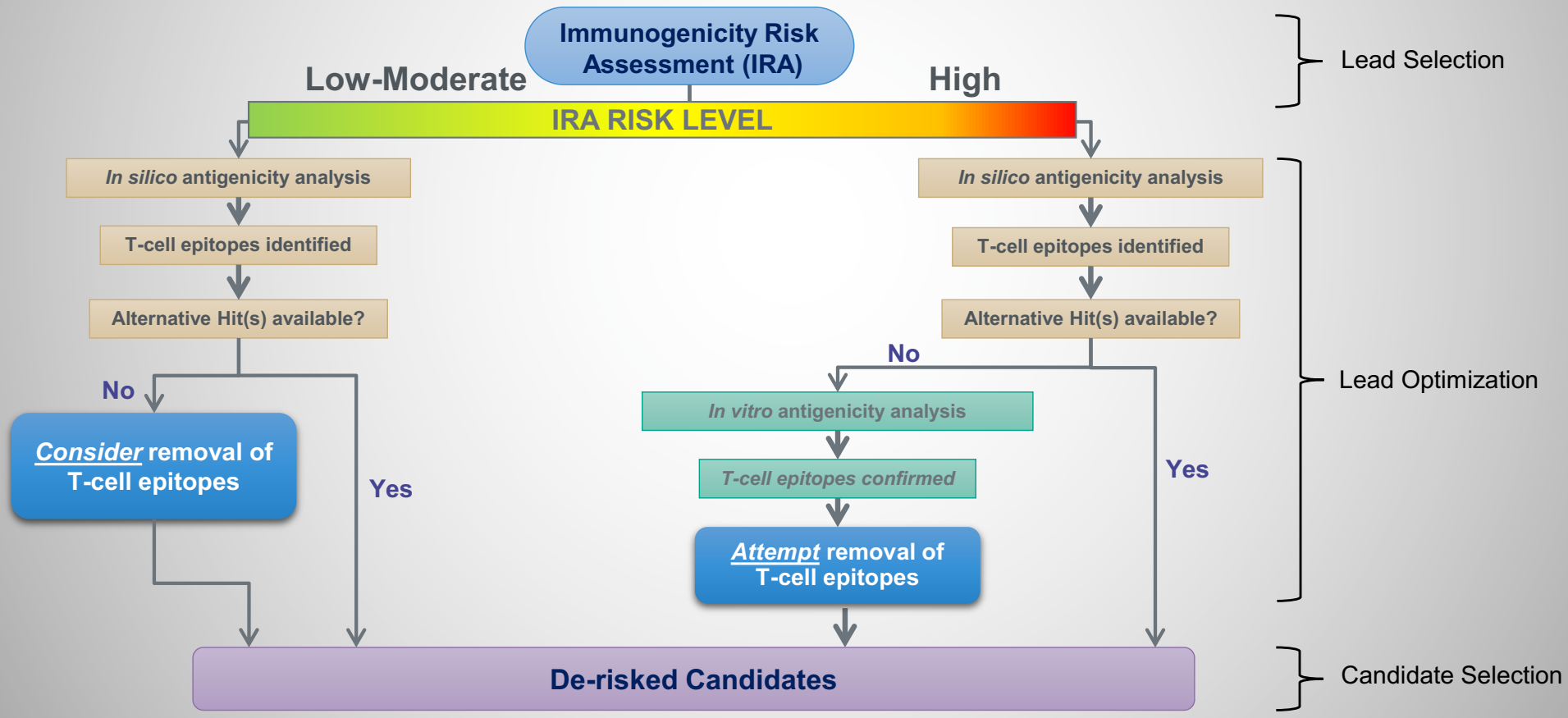
Risk-based Approaches

- Ranking of Biologics according to their immunogenicity risk category enables:
- A tailored approach to determine
  - The need for deimmunization
  - The clinical immunogenicity sampling and testing strategy (including the requirement for a neutralizing (NAb) assay)
  - The necessity of a post study follow-up of ADA positive subjects
  - The obligation to draw ad-hoc samples to assess hypersensitivity reactions



Risk-Based Approach

Need for Deimmunization



Risk-Based Approach

ADA Assay Validation Status

- FDA immunogenicity testing guideline (2019) does only request fully validated immunogenicity assays for
  - High risk products in respect to immunogenicity (already for phase 1)
  - Pivotal clinical trials (for all products)

For Other Risk Level Products

- Sponsor may store patient samples to be tested when suitable assays are available
- Phase 1 and phase 2 study samples may be tested using "fit-for purpose" assays
- Pivotal study/phase 3 samples need to be tested using fully validated assays
- Provide data supporting full validation of the assays at license

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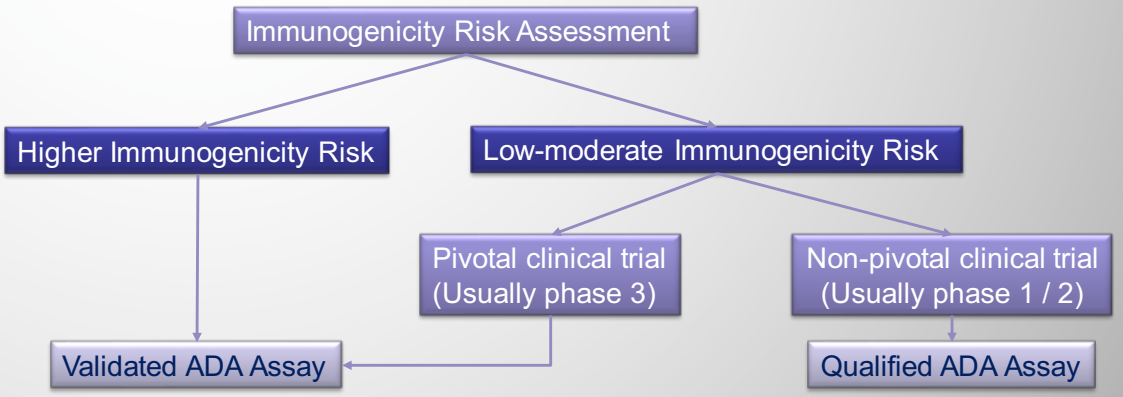

João A. Pedras-Vasconcelos; EIP Meeting Lisbon 2017

Risk-Based Approaches

Clinical Sampling and Testing Strategy

ADA Testing/Sampling Strategy for Low-Moderate Risk Therapeutic Proteins	ADA Testing/Sampling Strategy for High Risk Therapeutic Proteins
Frequency of Sampling Within Study	**Frequency of Sampling Within Study**
• Minimum/optimum sampling frequency to allow decent understanding of the ADA incidence and ADA kinetics	• High sampling frequency throughout all phases of clinical development to guarantee the safety of study participants • Consider post study follow-up of ADA positive subjects
Assessment of ADAs	**Assessment of ADAs**
• Detection of ADAs using screening- and confirmatory assays • ADA titer for confirmed positive samples • Neutralizing capacity of confirmed positive samples at phase 3 the latest • Validated assays only required for pivotal clinical trials	• Detection of ADAs using screening- and confirmatory assays • ADA titer for confirmed positive samples • Neutralizing capacity of confirmed positive samples from phase 1 onwards • Fully validated assays already required for phase 1
Sample Testing	**Sample Testing**
• Retrospective analysis at the end of the trial is deemed sufficient	• Consider “real time” analysis of ADA samples

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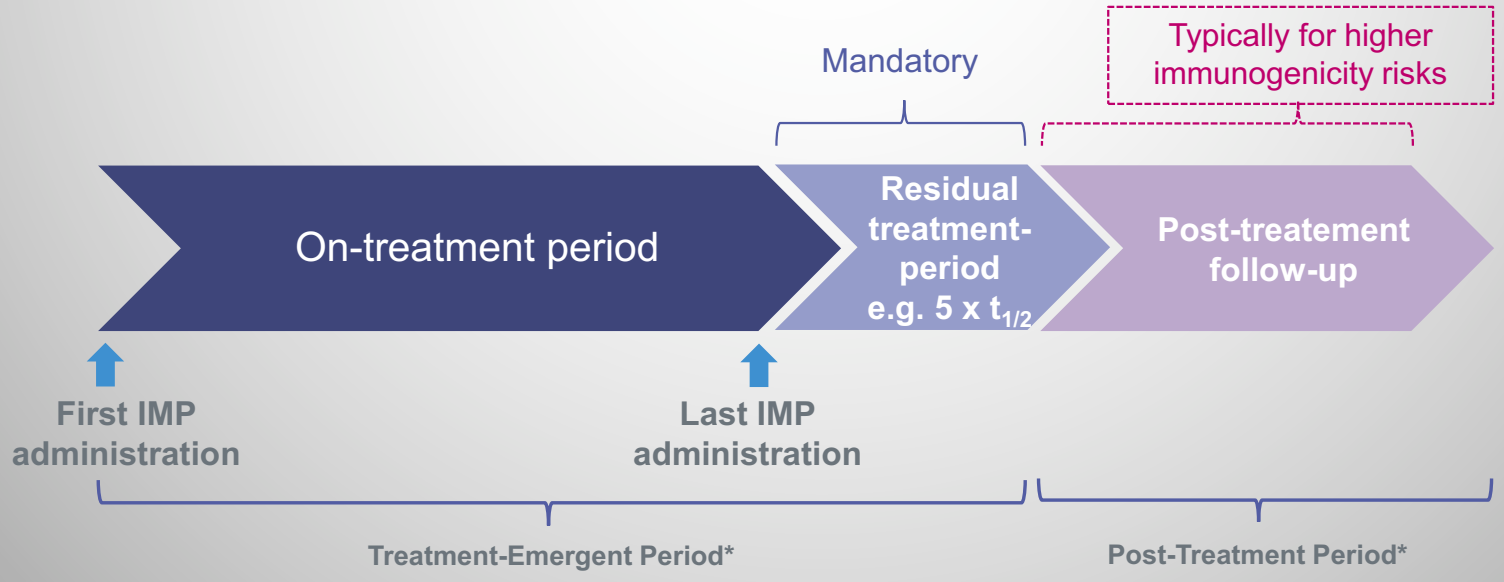
Risk-Based Approaches

Post-Study Follow-Up of ADA Positive Subjects

- **In most cases (low-moderate risk based on the IRA and/or previous clinical experience),** the last ADA sample should be drawn at the end of the treatment emergent period approximately 30 days or five half-lives (for products with long half-lives) after last exposure
- **In some cases (higher risk based on the IRA and/or previous clinical experience),** ADAs could lead to serious consequences and adverse events. In such cases, post-treatment follow-up for ADA positive subjects with immunogenicity-related AEs should be considered.



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Risk-Based Approaches

Ad-Hoc Hypersensitivity Samples

- Ad hoc samples in case of hypersensitivity **are needed if such an adverse event was experienced previously** in clinical trials.
- In the absence of previous clinical experience ad hoc samples in case of hypersensitivity **should be considered when specific safety risk(s) are identified in the IRA**, e.g.:
  - Presence of non-human sequences or glycosylation pattern
  - Replacement therapy with absent (or extremely low expressed) endogenous counterpart
  - Products of non-human origin, e.g. aprotinin, asparaginase
- FDA recommends the assessment of serum histamine, serum tryptase, and complement components or the detection of product-specific IgE antibodies following anaphylaxis
- These assays may provide potential mechanism of action for the basis of an adverse event but are difficult to establish and deserve specific sampling requirements

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------- **Important risk factors for hypersensitivity**