SANOFI

Risk Based Approaches to Immunogenicity

EBF Training Day: Practical Aspects of Immunogenicity

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Immunogenicity
Clinical Consequences

Immunogenicity represents a major hurdle for the development of biotherapeutics as it can impair both efficacy and safety of the treatment

Immunogenicity as standalone information is not helpful but needs to be put into context with clinical consequences (“holistic picture“)

- EMA immunogenicity guideline (2017): “*The purpose of investigating immunogenicity of therapeutic proteins is to understand the clinical consequences; i.e. consequences for PK, PD, efficacy and safety*”

Impact on efficacy:

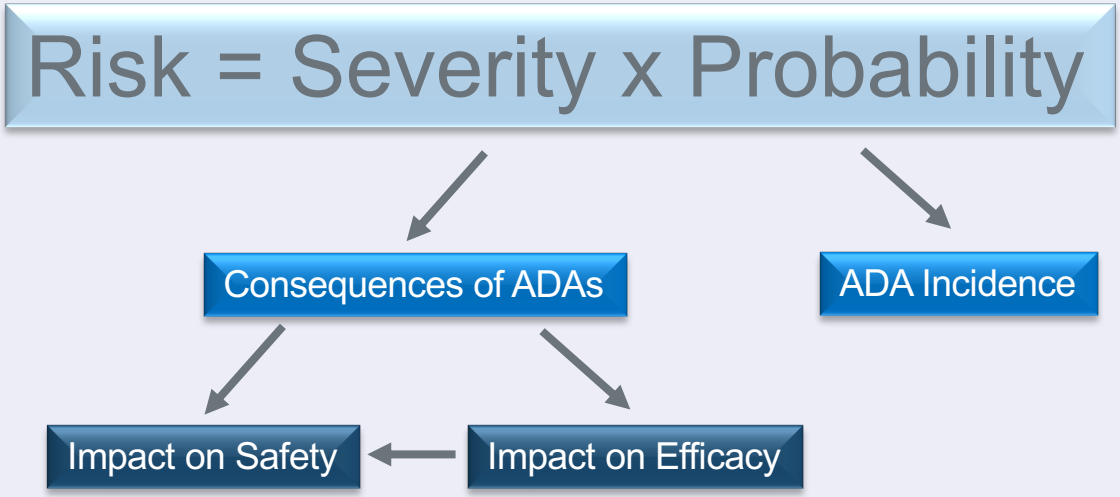
- Altered PK
  - ADAs increasing the clearance of a biotherapeutic => reduced efficacy
  - ADAs decreasing the clearance of a biotherapeutic => problematic for agonistic drugs => risk of exaggerated pharmacology
- Impaired target binding due to neutralizing antibodies

Impact on safety:

- Hypersensitivity reactions (prior sensitization with “foreign” sequences)
  - Anaphylaxis (type 1 hypersensitivity)
  - Deposition of immune complexes in tissues (type 3 hypersensitivity)
- Neutralization of endogenous counterpart (deficiency syndrome)

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

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

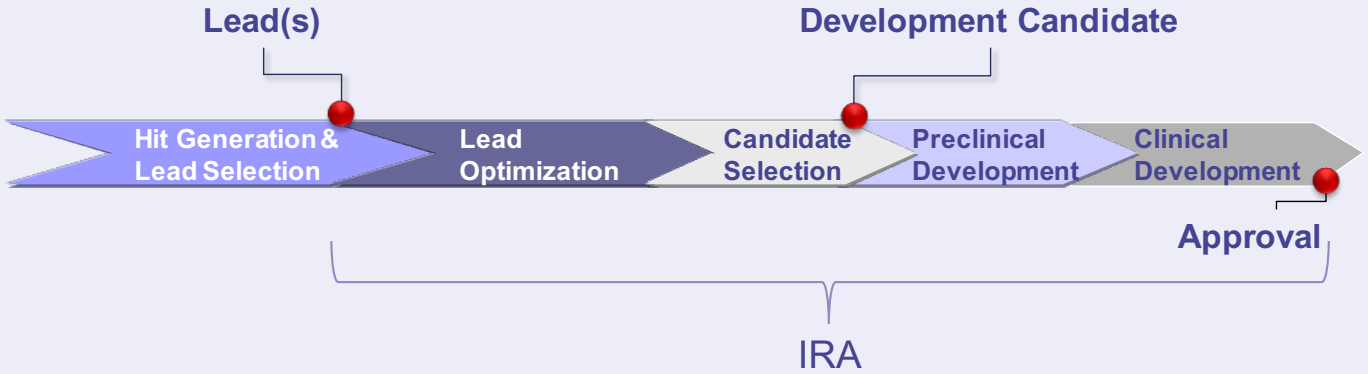
Moderate immunogenicity risk

Immunogenicity Risk Assessment

Process

Immunogenicity Risk Assessment is a living document

- It usually starts at lead selection
- It should be updated to accommodate additional information (at least at every major milestone)
- It should be part of an IND/IMPD
- It is part of the „integrated summary of immunogenicity“ in a BLA/MAA

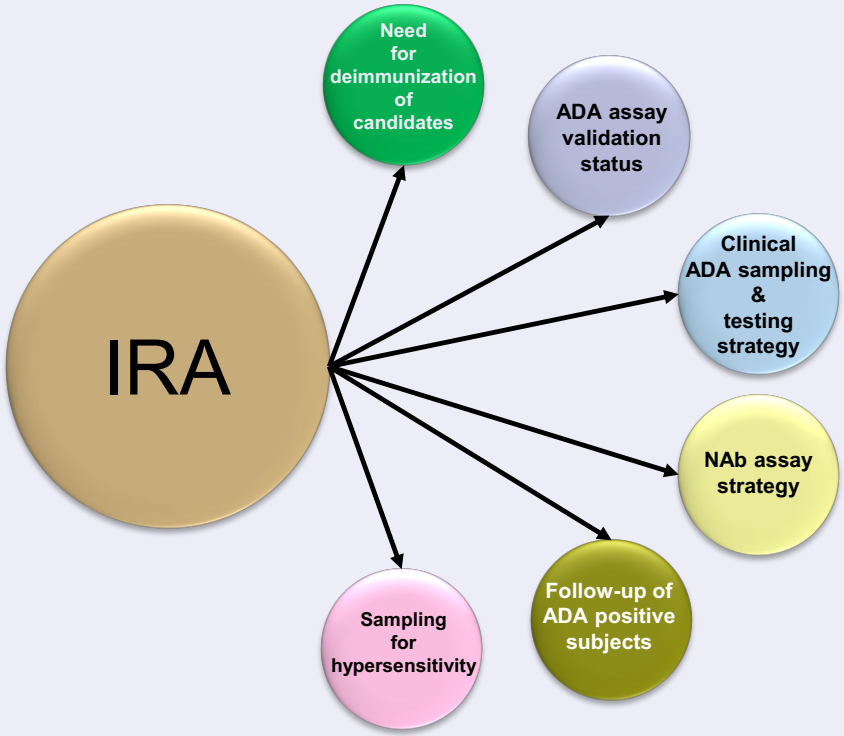


Immunogenicity Risk Assessment

Risk Based Approaches

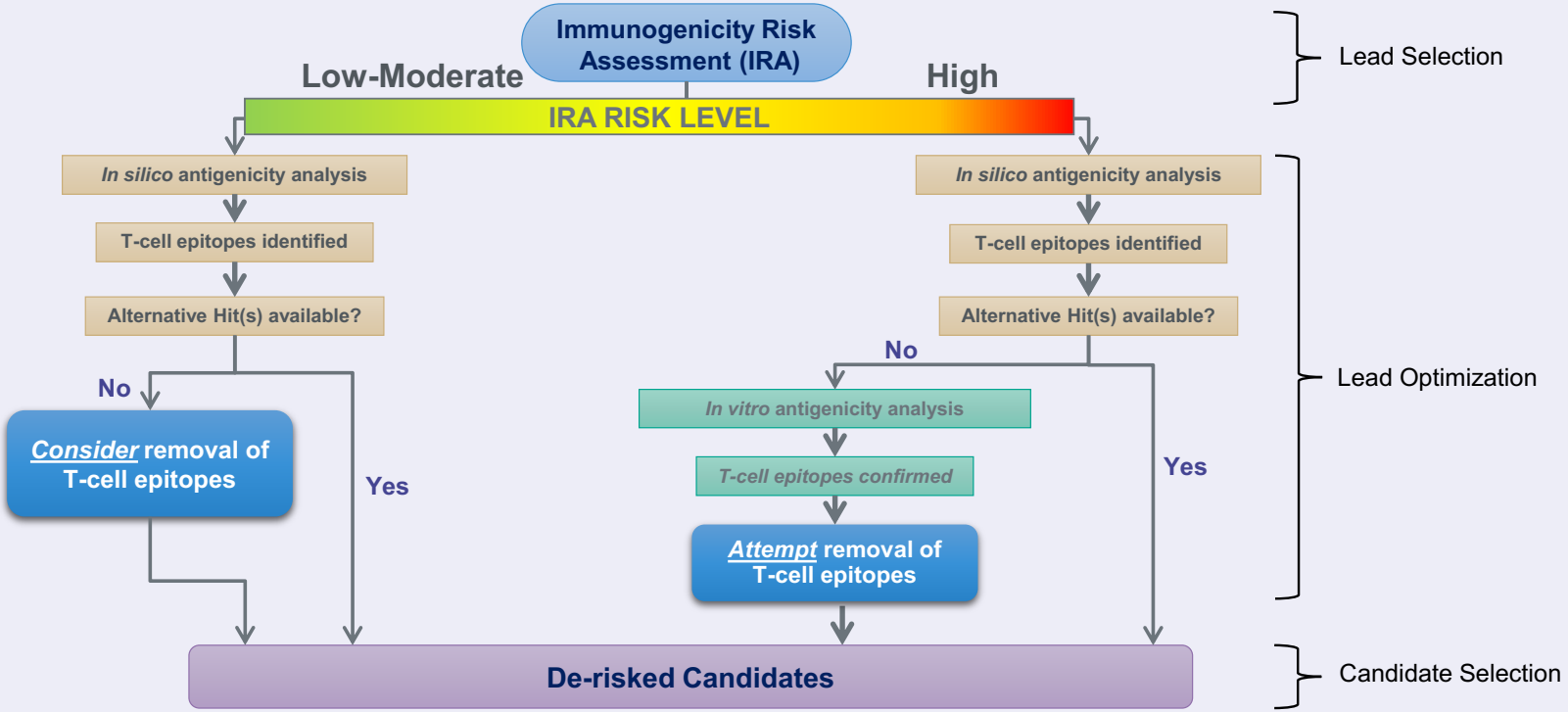
Ranking of Biologics according to their immunogenicity risk category enables:

- 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)

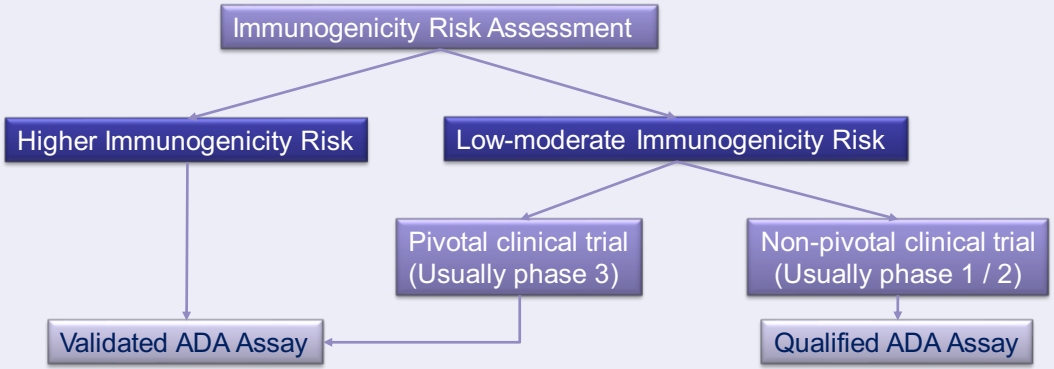
FDA

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

www.fda.gov 21

João A. Pedras-Vasconcelos; EIP Meeting Lisbon 2017



Risk Based Approach

Clinical ADA Sampling and Testing Strategy

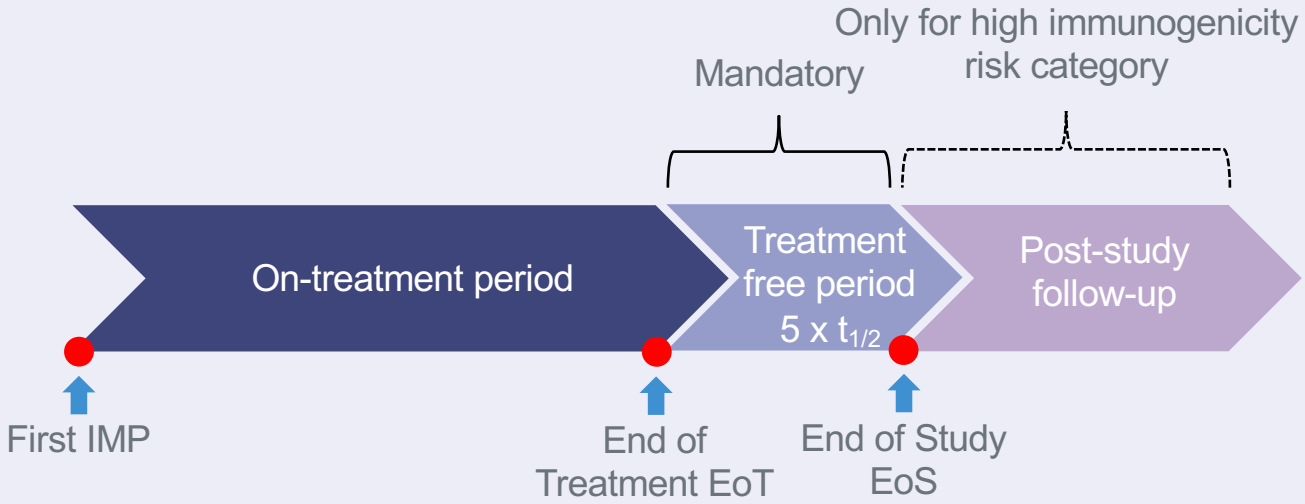
ADA Testing/Sampling Strategy for Low-Moderate Risk Therapeutic Proteins	ADA Testing/Sampling Strategy for High Risk Therapeutic Proteins
Frequency of Sampling Within Study	**Frequency of Sampling Within Study**
• Minimum/optimum sampling frequency to allow decent understanding of the ADA incidence and 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

Risk Based Approach

Post-Study Follow-Up of ADA Positive Subjects

In general, ADA samples should be obtained approximately five half-lives after last exposure (EoS)

In cases when the IRA suggests that ADAs could lead to serious consequences (e.g. hypersensitivity), additional follow-up samples beyond EoS should be drawn



Risk Based Approach

Ad Hoc Hypersensitivity Samples

FDA recommends the assessment of serum histamine, serum tryptase, and complement components or the detection of product-specific IgE antibodies following anaphylaxis

- These assays are extremely difficult to establish

Anaphylaxis (immediate type hypersensitivity) is mainly caused by

- Proteins of non-human origin, e.g. asparaginase
- Replacement human proteins in knock out phenotype
- Presence of host cell proteins (HCPs)

Anaphylaxis is extremely rare with “state of the art” fully human therapeutic proteins

Ad hoc samples ín case of hypersensitivity are not needed unless the IRA indicates

- Presence of non-human sequences or glycosylation pattern
- Replacement therapy with absent (or extremely low expressed) endogenous counterpart
- Previous hypersensitivity events with similar molecule (or class of molecule)

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Important risk factors for anaphylaxis

Summary

For all biotherapeutics regulatory authorities expect sponsors to perform and submit an immunogenicity risk assessment (IRA) to support the selected immunogenicity program

- Several product, process, posology and patient-related factors influence the immunogenicity of biotherapeutics and form the basis for risk assessment
- Focus is given to the potential severity of clinical consequences of immunogenicity rather than the probability of occurrence of ADA responses

Classification of biotherapeutics into immunogenicity risk categories allows application of tailored risk-based approaches to immunogenicity

- Deimmunization strategy
- Clinical ADA testing and sampling strategy
- Strategy for following-up of ADA positive subjects and for ad-hoc samples for hypersensitivity

It is indispensable to engage regulatory agencies early in the development program to discuss the selected immunogenicity strategy

THANKS!!!!!!