A fit-for-purpose strategy for the risk-based immunogenicity testing of biotherapeutics – a European industry perspective

Cathelijne Kloks 7 February 2012

On behalf of EIP assay working group

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EIP assay working group

Composition & Focus:

- Representatives of various pharmaceutical & biotech companies in Europe
- Discuss & exchange experiences
- Provide feedback to regulatory authorities

- Last 2 years discussing translation of requirements from authorities & white paper advice into risk-based immunogenicity assessment
- Condensed into a summitted manuscript

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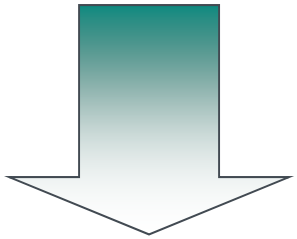
Reason

Guidance & white papers:

Risk assessment → case-by-case approach



HOW?

Immunogenicity testing for your drug

Select assays:

- ☑ Screening
- ☑ Confirmation
- ☑ Neutralization
- ☑ Quasi-quantification
- ☑ Isotyping
- ☑ IgM detection
- ☑ IgE detection
- ☑ Affinity determination
- ☑ Epitope mapping

Rationale:
To be on safe side for drug filing

But, this is…
Not risk-based nor patient safety driven

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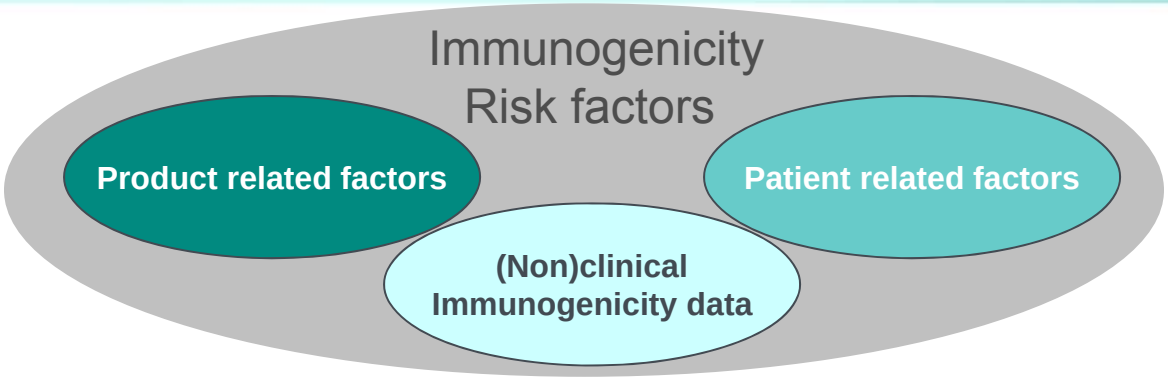
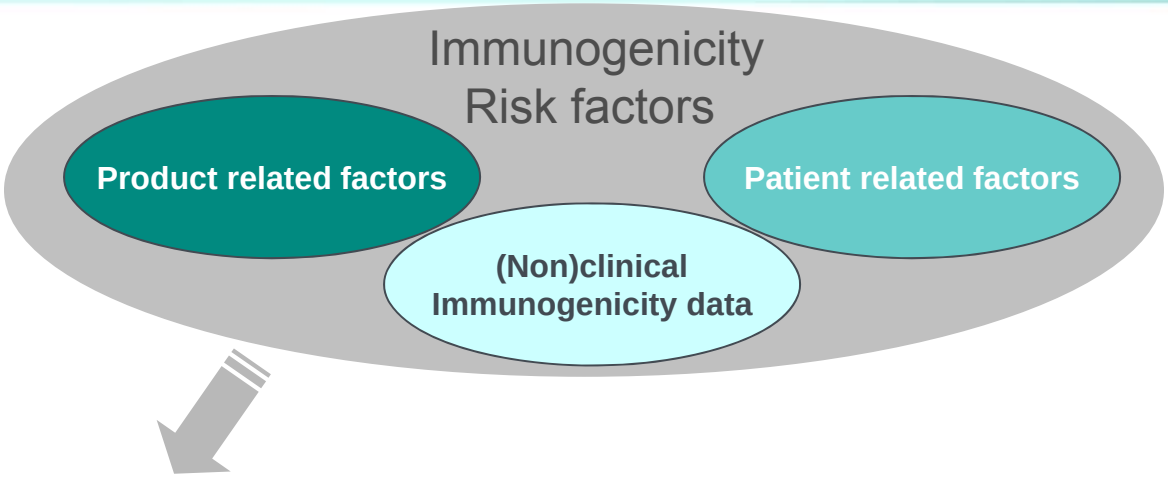
Risk assessment



Risk-assessment



Overall Risk

Qualitative risk assessment for final product

Probability x Severity

Low | **Medium** | **High**

Impact on drug development strategy
Impact on risk management plan
Integrated part of the dossier

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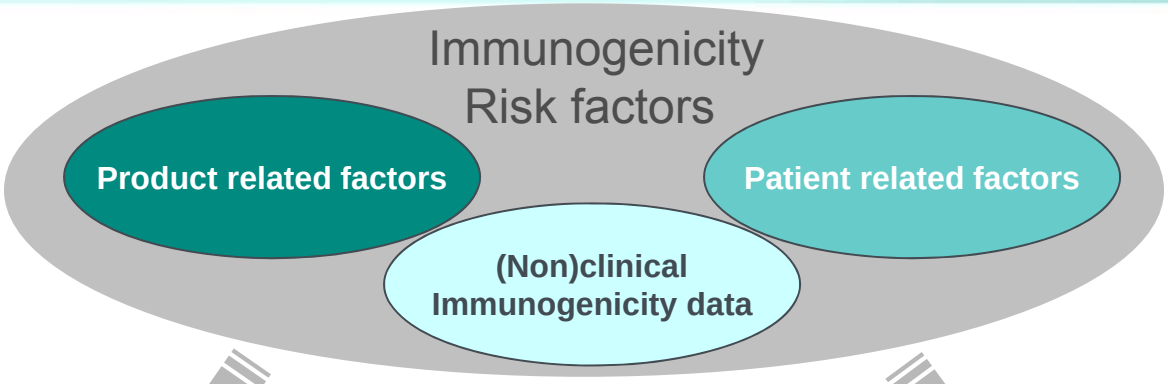
Risk-assessment



Note:
Clinical consequences: Safety AND efficacy effects

Overall Risk

Qualitative risk assessment for final product
Probability x Severity

Low | **Medium** | **High**

Impact on drug development strategy
Impact on risk management plan
Integrated part of the dossier

Immunogenicity Testing

Testing strategy design decision
Severe ADA mediated clinical consequences in patients anticipated?

No → **Category 1**

Yes → **Category 2**

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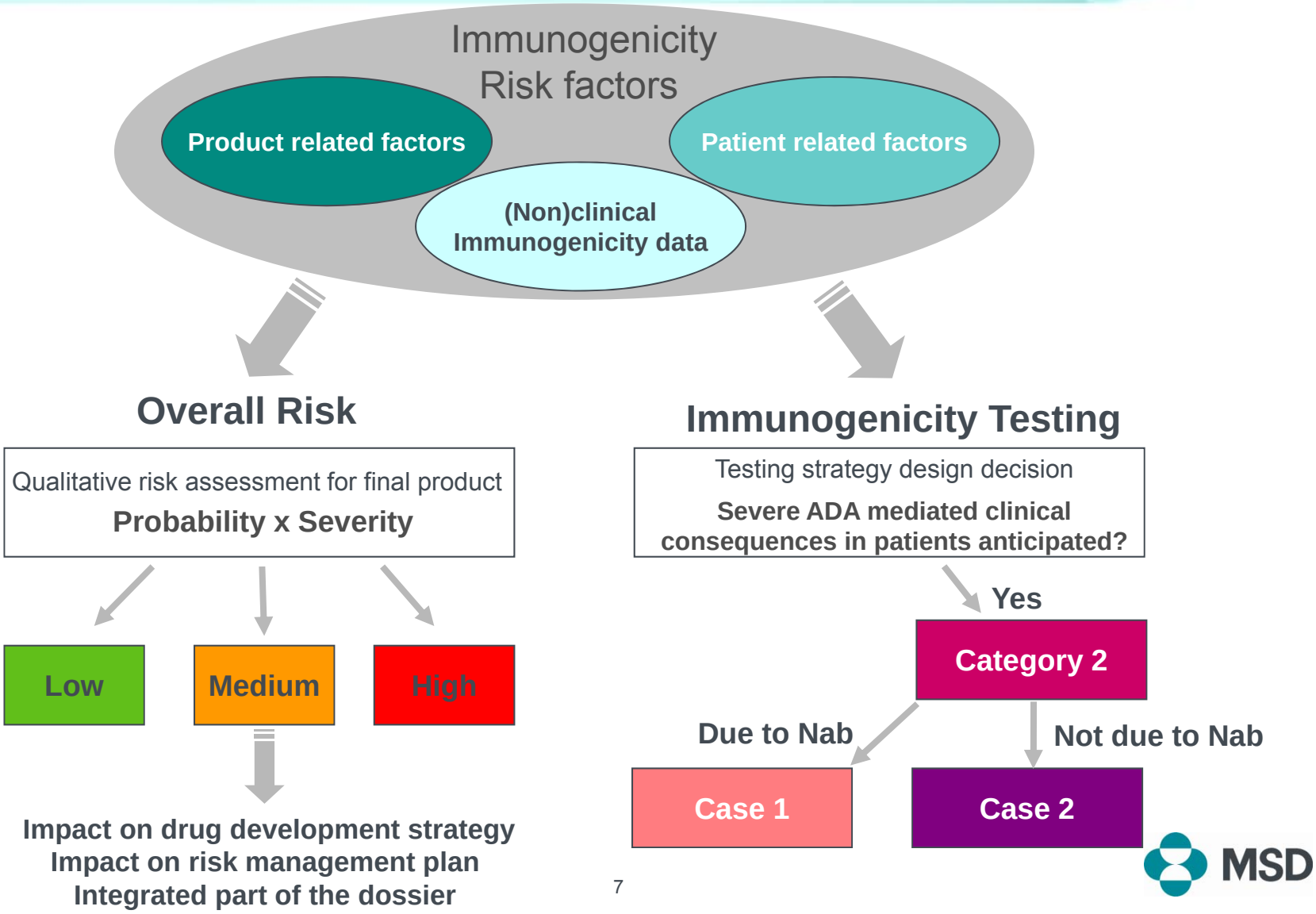
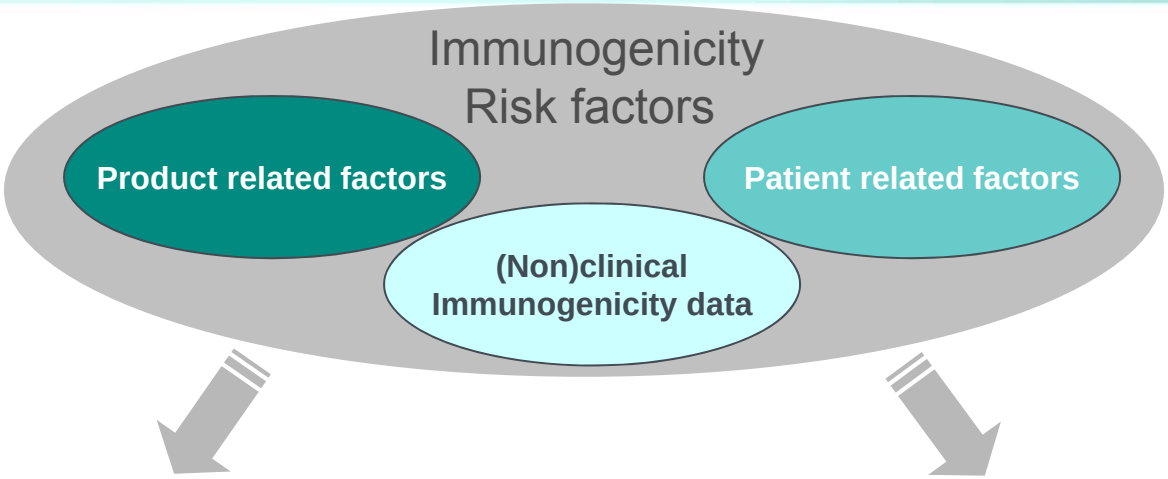
Risk-assessment



Risk-assessment



Adjustment of **both** overall risk assessment and immunogenicity testing in every development stage based on gathered data

Overall Risk

Qualitative risk assessment for final product

Probability x Severity

Low | **Medium** | **High**

Impact on drug development strategy
Impact on risk management plan
Integrated part of the dossier

Immunogenicity Testing

Testing strategy design decision

Severe ADA mediated clinical consequences in patients anticipated?

No | **Yes**

Category 1 | **Category 2**

Impact on clinical decision making
Impact on sampling schedule
Impact on assay format

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Examples of categories & cases

Category 1
Binding ADA without impact on safety & efficacy
Cases where harm by ADA can be prevented by concomitant medication
Category 2
Case 1 (severe clinical consequences due to Nabs)
Loss of efficacy leading to severe clinical consequences (e.g. life-threatening disease)
Neutralization of non-redundant endogenous counterpart (e.g. causing deficiency syndrome)
Case 2 (severe clinical consequences due to non-Nabs)
Overstimulation of endogenous mechanism due to drug molecules cross-linked by ADA (superagonists)
Potential for severe hypersensitivity reactions (based on (clinical) data))
Immune complex disease, vasculitis, serum sickness

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Proposal: One general testing strategy

- Applies for all sorts of biotherapeutics (mabs, conjugates, hormones, biosimilars etc.)
- For each development phase (each phase has different goal)
- Differentiated for category & case
- Defined:
  - Sampling
  - Timing of testing
  - Assay type ADA detection
  - Characterization ADA response
- Main driver: generate data on which clinical decision can be based
- Note: clinical decisions themselves out-of-scope for paper & presentation

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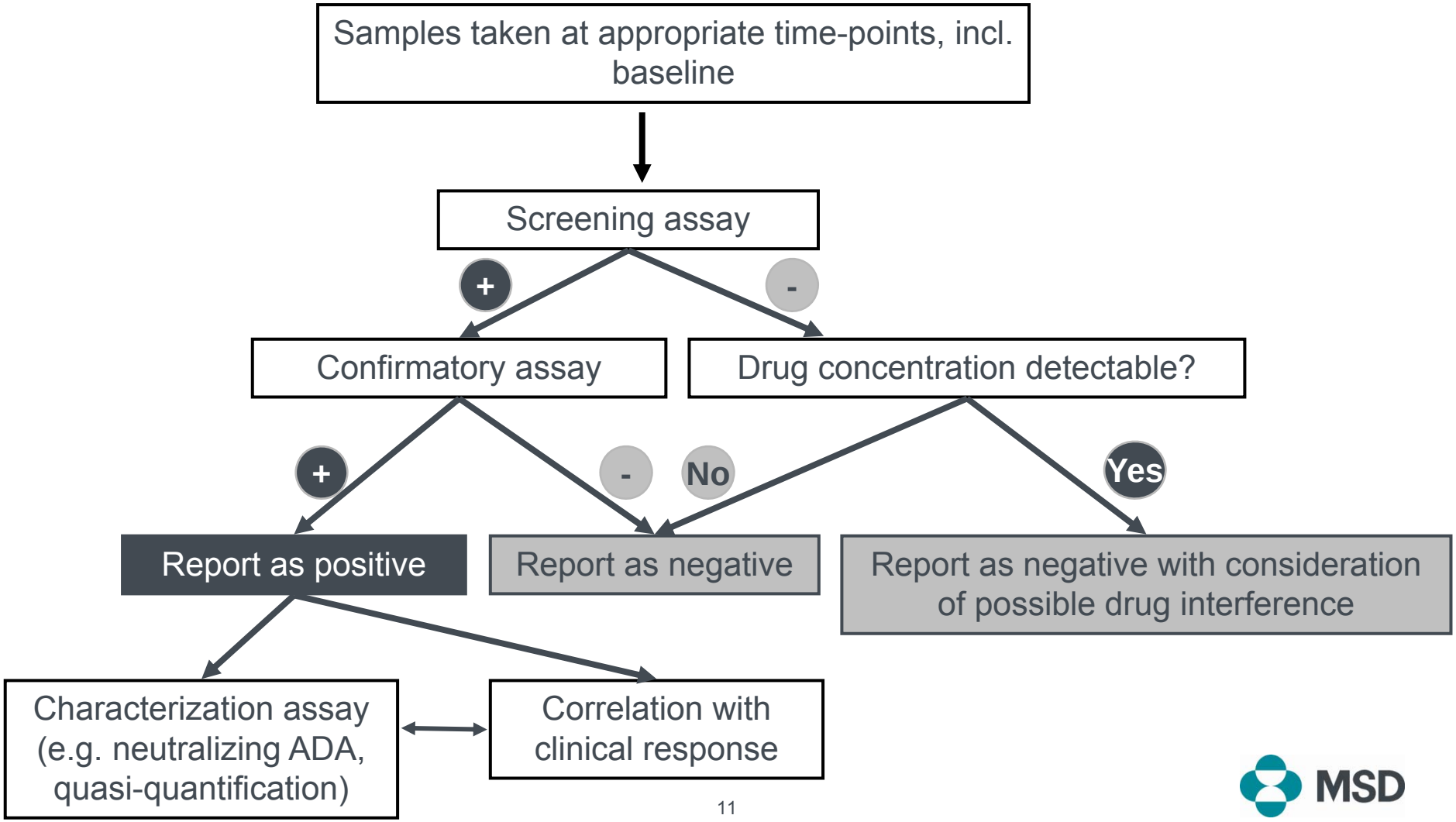
First: Testing strategy components



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Second: Development phases

Nonclinical	Toxicity
	Interpretation toxicity & TK/PD in animals
Phase I/IIa	Safety & Tolerability/POC
	Interpretation PK, Explanation clinical symptoms & ADA-related (S)AE
Phase IIb	Safety, dose selection & efficacy in patients
	Interpretation PK/PD Explanation clinical symptoms, ADA-related (S)AE Population-dependency of immunogenicity
Phase III	Safety & efficacy in large groups of patients
	Interpretation PK/efficacy Explanation clinical symptoms, ADA-related (S)AE Population-dependency of immunogenicity & low frequency ADA
Phase IV	Rare adverse events
	Explanation clinical observations, very low frequency ADA-related (S)EA

Third: Considerations made (1)

- **ICH S6:**
  - Sampling ≠ testing. Retrospective analysis accepted
  - Animal immunogenicity not predictive of human response, especially the frequency of immune responses
  - No humans at risk, check on exposure only → screen with CP at 99.9th percentile sufficient

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Third: Considerations made (2)

- Neutralization assay rationale
  - When to test: phase II onwards (then efficacy)
    - Unless….. There is a high risk for NAb with severe clinical consequences (category 2 case 1) and/or if the mode of action in animal is predictive for the mode of action in human
  - How to test:
    - Preferred PD: best reflection of in-vivo situation
    - Followed by CLB for antagonists
    - And CBA for agonists (but if CLB performance >> CBA, then CLB)

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Third: Considerations made (3)

- Added value of characterization assays discussed

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Considerations on characterization assays

- Further characterization assays

Quasi-quantification

isotyping

Anti-drug IgM

Anti-drug IgE

Affinity determination

Epitope mapping

- Immune responses are heterogeneous
- No adequate standard

- Provides indication of time-dependent development of immune response

Complementary (sponsor's discretion)

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Considerations on characterization assays

- Further characterization assays

Quasi-quantification

isotyping

Anti-drug IgM

Anti-drug IgE

Affinity determination

Epitope mapping

- Correlation to specific adverse events unclear
- Most screening assays allow detection of most isotypes

Complementary (theoretical understanding)

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Considerations on characterization assays

- Further characterization assays

Quasi-quantification

isotyping

Anti-drug IgM

Anti-drug IgE

Affinity determination

Epitope mapping

- Currently under discussion in community
- Clinical effect of low affinity IgM negligible in most cases
- Detection often not possible due to interference of high circulating drug levels at time of sampling (7 -14 days after treatment)

Not needed

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Considerations on characterization assays

- Further characterization assays

Quasi-quantification

isotyping

Anti-drug IgM

Anti-drug IgE

Affinity determination

Epitope mapping

- Some proteins have elevated risk for hypersensitivity reactions (due to product related or patient related factors)
- Based on risk assessment, patient history, use IgE detection (skin prick, IgE detection)

- Note: IgE detection need very sensitive assays (< 0.5 ng/mL)

Based on risk assessment

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Considerations on characterization assays

- Further characterization assays

Quasi-quantification

isotyping

Anti-drug IgM

Anti-drug IgE

Affinity determination

Epitope mapping

- No quantification possible → full kinetic analysis impossible
- It is not of importance whether clinical effect is caused by many low-affinity ADA or few high affinity ADA. Clinical observations (data) on patient safety and efficacy drive decision-making.

Not needed

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Considerations on characterization assays

- Further characterization assays

Quasi-quantification

isotyping

Anti-drug IgM

Anti-drug IgE

Affinity determination

Epitope mapping

- Impact for understanding clinical effects limited.
- For fusion proteins with (homologous) endogenous domains, it may be of interest (cross-reactivity)
- For Mabs: anti-Fc ADAs may impact Mab-functionalities

Fusion proteins with endogenous domains, anti-allo or anti-idio for mabs (sponsor's discretion)

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Considerations on characterization assays

- Further characterization assays

Quasi-quantification	→	Complementary (sponsor's discretion)
isotyping	→	Complementary (theoretical understanding)
Anti-drug IgM	→	Not needed
Anti-drug IgE	→	Based on risk assessment
Affinity determination	→	Not needed
Epitope mapping	→	Fusion proteins with endogenous domains, anti-allo or anti-ideo for mabs (sponsor's discretion)

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Testing strategy – Nonclinical

	Nonclinical	Phase I single dose	Phase I multiple dosing	Phase II and III
Sample collection	At least base line & end of study			
Sample testing	Event driven Batch-wise at end of study			
ADA assay format	Screen (99.9th)			
Neutralization	- If of added value PD/ CLB or CBA			
Characterization	-			

All categories & cases

Category 1

Category 2 Case 1 Case 2

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Testing strategy – Phase I single dose

	Nonclinical	Phase I single dose	Phase I multiple dosing	Phase II and III
Sample collection	At least base line & end of study	At least base line & end of study		
Sample testing	Event driven Batch-wise at end of study	Event driven (all) Batch-wise at end of study		
ADA assay format	Screen (99.9th)	Screen (95th) & confirmation	**Assay availability** Assay developed Not necessarily validated	
Neutralization	- If of added value PD/ CLB or CBA	- PD/ CLB or CBA		
Characterization	-	- If of added value		

All categories & cases | Category 1 | Category 2 | Case 1 | Case 2

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Testing strategy – Phase I multiple dose

	Nonclinical	Phase I single dose	Phase I multiple dosing	Phase II and III
Sample collection	At least base line & end of study	At least base line & end of study	Frequent	
Sample testing	Event driven Batch-wise at end of study	Event driven all Batch-wise at end of study	At least baseline & end of study all Batch wise at end of study Timely	**Timely:** Based on expected clinical symptoms, data ready for next dose
ADA assay format	Screen (99.9th)	Screen & confirmation	Screen & confirmation	
Neutralization	- If of added value PD/ CLB or CBA	- PD/ CLB or CBA	- PD/ CLB or CBA	
Characterization	-	- If of added value	If of added value Select relevant assays	

All categories & cases | Category 1 | Category 2 | Case 1 | Case 2

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Testing strategy – Phase II onwards

	Non clinical	Phase I single dose	Phase I multiple dosing	Phase II and III
Sample collection	At least base line & end of study	At least base line & end of study	Frequent	Frequent
Sample testing	Event driven Batch-wise at end of study	Event driven all Batch-wise at end of study	At least baseline & end of study all Batch wise at end of study Timely	At least baseline & end of study all Batch wise at end of study Timely
ADA assay format	Screen (99.9th)	Screen & confirmation	Screen & confirmation	Screen & confirmation
Neutralization	- If of added value PD/ CLB or CBA	- PD/ CLB or CBA	- PD/ CLB or CBA	PD/ If of added value CLB or CBA
Characterization	-	- If of added value	If of added value Select relevant assays	If of added value Select relevant assays

All categories & cases | Category 1 | Category 2 | Case 1 | Case 2

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Testing strategy - Overview

	Non clinical	Phase I single dose	Phase I multiple dosing	Phase II and III
Sample collection	At least base line & end of study	At least base line & end of study	Frequent	Frequent
Sample testing	Event driven Batch-wise at end of study	Event driven all Batch-wise at end of study	At least baseline & end of study all Batch wise at end of study Timely	At least baseline & end of study all Batch wise at end of study Timely
ADA assay format	Screen (99.9th)	Screen & confirmation	Screen & confirmation	Screen & confirmation
Neutralization	- If of added value PD/ CLB or CBA	- PD/ CLB or CBA	- PD/ CLB or CBA	PD/ If of added value CLB or CBA
Characterization	-	- If of added value	If of added value Select relevant assays	If of added value Select relevant assays

All categories & cases | Category 1 | Category 2 | Case 1 | Case 2

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Summary

- It is advised to consult appropriate authorities
- Severity of anticipated clinical effects driver for testing design
- Development phase dependent testing
- Generate those data that aid clinical decision making
- Details of testing strategy:
  - Non-clinical studies: screen with CP at 99.9th percentile
  - Sample frequency, timing of measurements~need & risk
  - Neutralization assays:
    - Phase II onwards (except for case 1)
    - Assay Preference 1) PD 2) CLB for antagonists 3) CBA for agonists
  - Further characterization in most cases not manditory

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Awknowledgements

- Contributing assay working group members:

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