14th EBF Open Symposium-
Immunogenicity Strategies

How immunogenicity risk assessment can translate into an immunogenicity testing strategy

25th Nov 2021 / Yvonne Katterle

Agenda

- **Immunogenicity Risk Assessment**
  - Introduction
  - Risk Identification
  - Risk Analysis and Evaluation
- **Immunogenicity Risk Management**
  - Sampling Strategy
  - Bioanalytical Testing Strategy
  - Example High Risk Molecule
- Conclusion

Immunogenicity Risk Assessment

Introduction

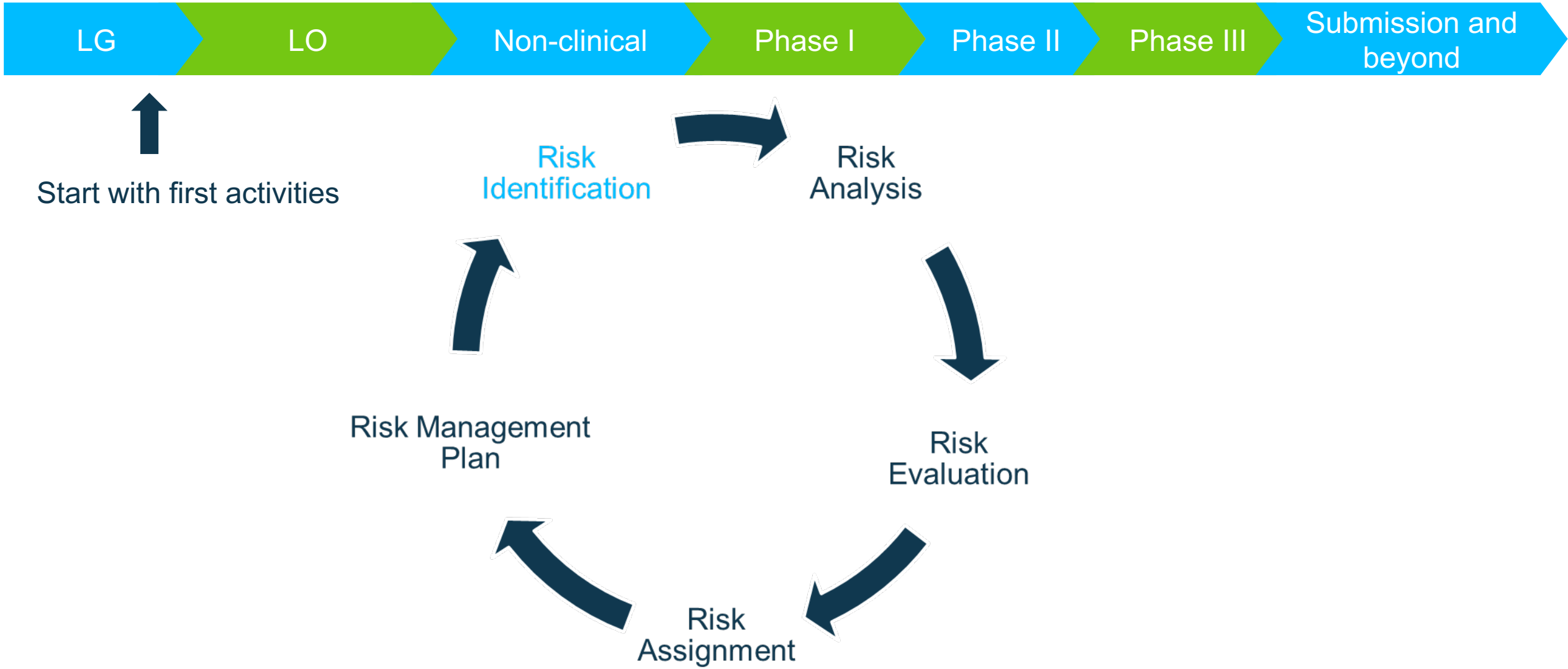
Immunogenicity Risk Assessment

Introduction

- Immunogenicity Risk ≠ Project Risk
  - consequences of an immune reaction can range from ADA without any clinical significance to severe life-threatening conditions
  - assigning an immunogenicity risk to a product ensures appropriate risk mitigation and management of patient's safety
- Immunogenicity risk assessment is a systematic approach
  - identification, analysis, evaluation, control, review, communication and management of potential immunogenicity risks
  - multidisciplinary task involving experts from research, CMC, quality, preclinical and clinical as well as safety and regulatory functions
  - Iterative process throughout the life-time of the product from research to market access, where risk levels might change with project progression

Immunogenicity Risk Assessment

Iterative Process

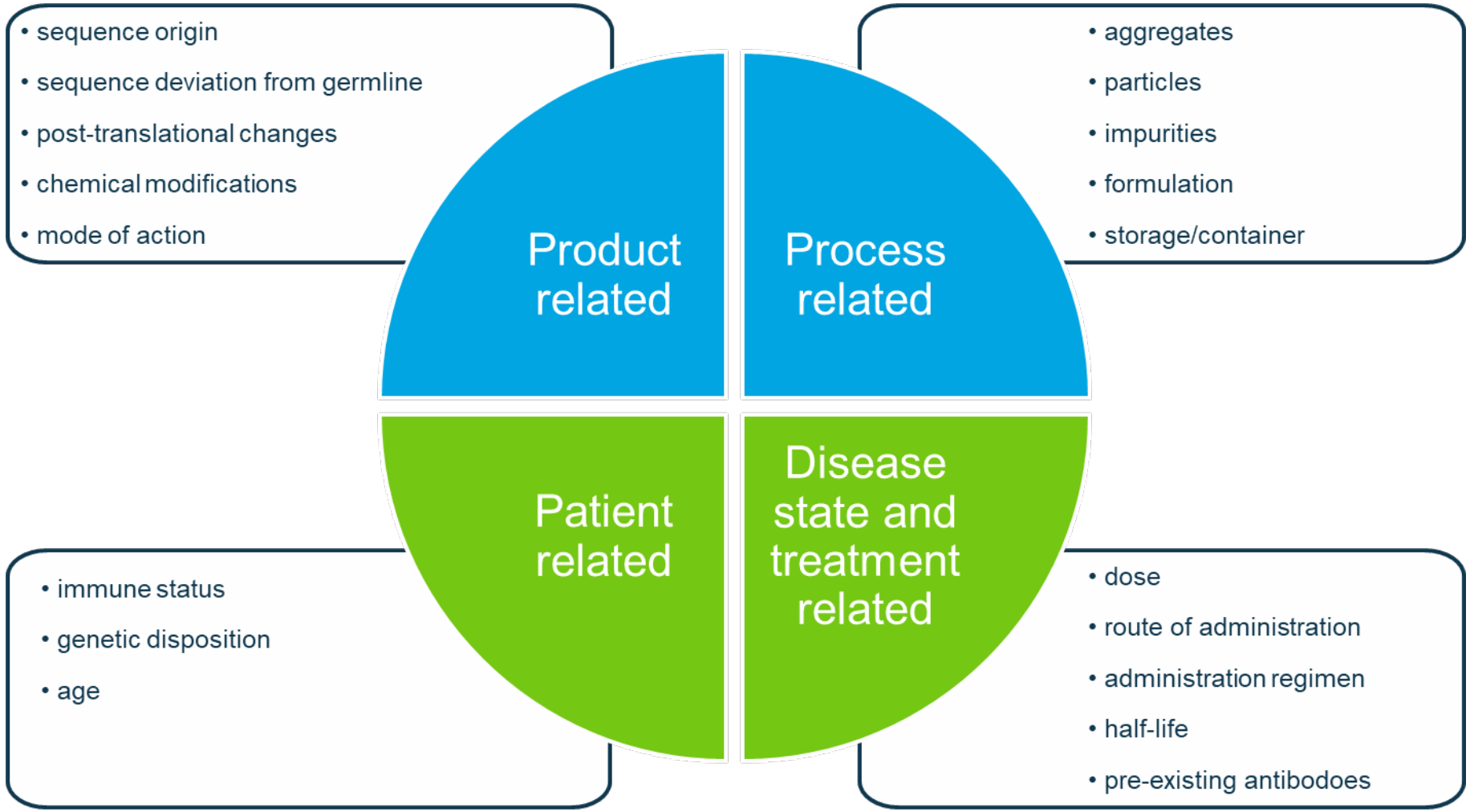


Immunogenicity Risk Assessment

Risk Identification

Immunogenicity Risk Identification

Risk Factors



Immunogenicity Risk Identification

Potential Clinical Consequences

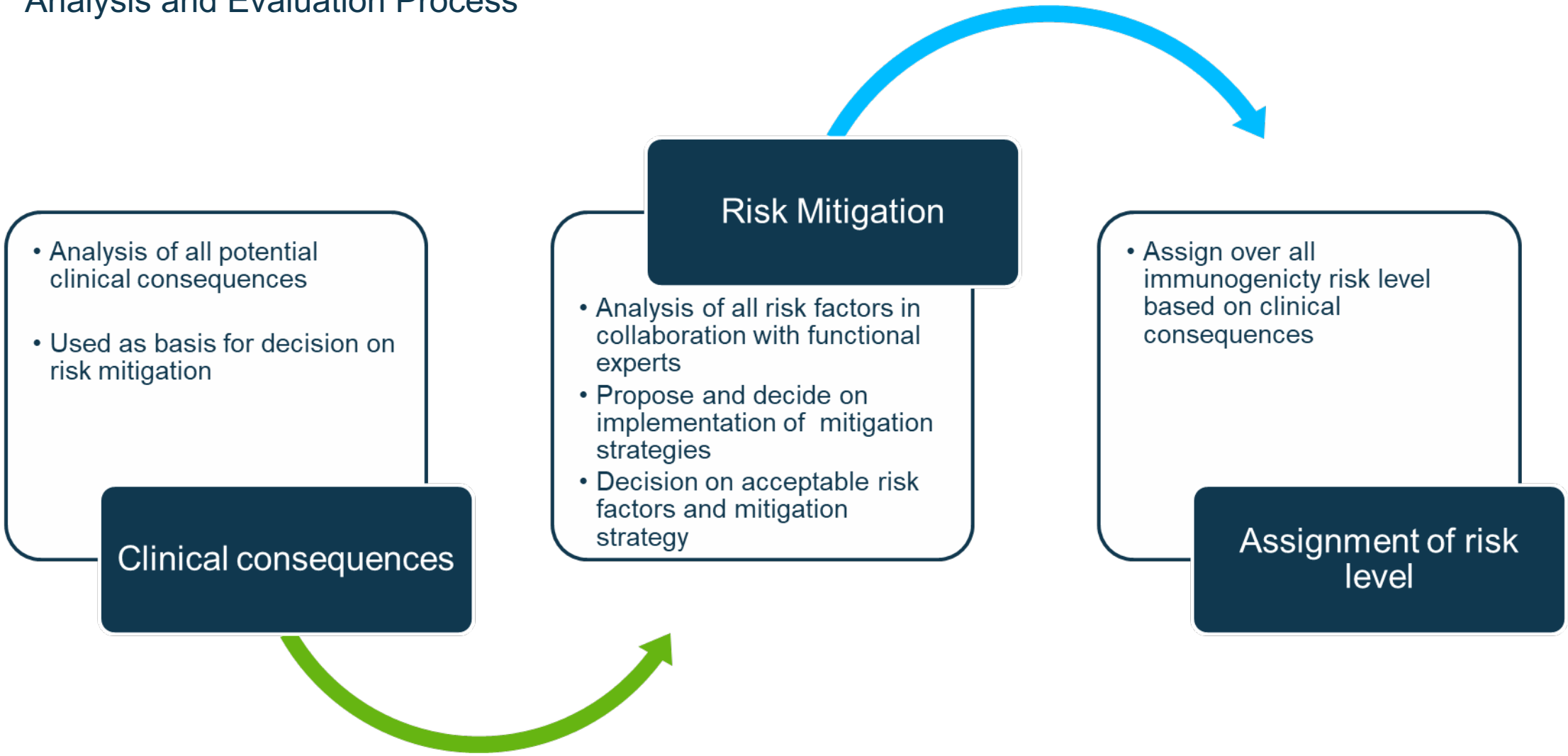
- No impact on PK-PD, efficacy or safety
- Change in PK-PD relationship, target engagement
- Loss of efficacy
- Immune related adverse events
  - Cytokine release
  - Hypersensitivity or allergy
  - Unintended mode of action via ADA-drug complexes
- Cross reactivity of ADA to endogenous protein

Immunogenicity Risk Assessment

Risk Analysis and Evaluation

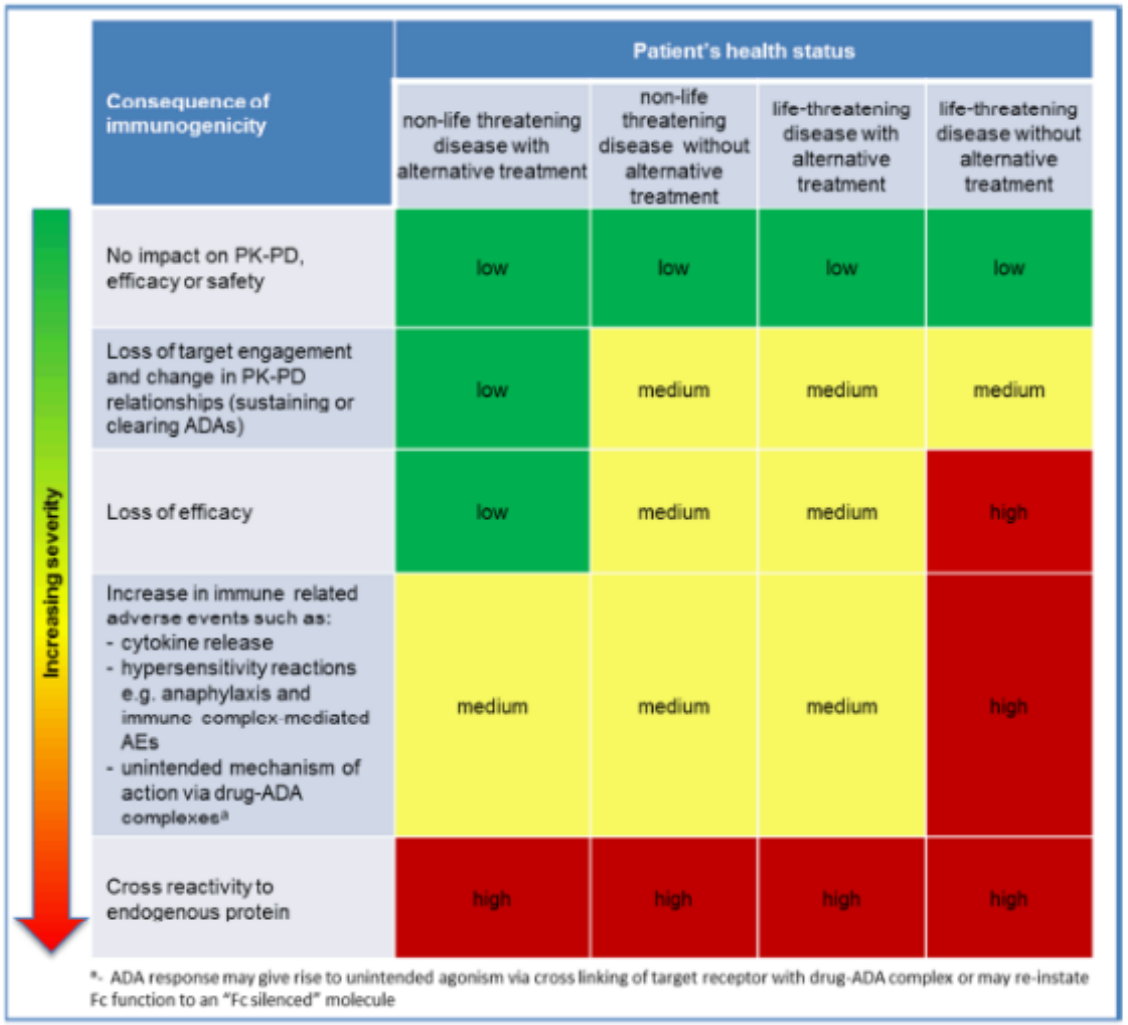
Immunogenicity Risk Analysis and Evaluation

Analysis and Evaluation Process



Immunogenicity Risk Assessment

Assignment of Risk Level



Consequence of immunogenicity	Patient's health status			
	non-life threatening disease with alternative treatment	non-life threatening disease without alternative treatment	life-threatening disease with alternative treatment	life-threatening disease without alternative treatment
No impact on PK-PD, efficacy or safety	low	low	low	low
Loss of target engagement and change in PK-PD relationships (sustaining or clearing ADAs)	low	medium	medium	medium
Loss of efficacy	low	medium	medium	high
Increase in immune related adverse events such as: - cytokine release - hypersensitivity reactions e.g. anaphylaxis and immune complex-mediated AEs - unintended mechanism of action via drug-ADA complexes[a]	medium	medium	medium	high
Cross reactivity to endogenous protein	high	high	high	high

Increasing severity

*- ADA response may give rise to unintended agonism via cross linking of target receptor with drug-ADA complex or may re-instate Fc function to an "Fc silenced" molecule

- Assignment of the immunogenicity risk level should mainly be based on the patient's health status and the anticipated or observed clinical consequences
  - Although all product and patient related factors have been considered it is difficult to determine a score or threshold to directly assess the impact of each factor to the overall risk
- The overall immunogenicity risk level may change during product development, e.g. when ADA incidences have been established during development

Immunogenicity Risk Management

Immunogenicity Risk Management Plan

Immunogenicity Risk Management Plan

Content

- Summarize any recommended mitigation actions
- Specify the immunogenicity testing strategy
  - Based on the assigned over immunogenicity risk

Sampling strategy

- Pre- and post exposure samples
- Timing of ADA sample collection (low drug levels, ability to detect transient and persistent immune responses, establish relationship to exposure/PK)
- Unscheduled sampling in case of suspected immune-related adverse events

Bioanalytical testing strategy

- Appropriate assays for PK and ADA to be developed
- Consider PD and Biomarker Assays as well
- Timing of sample analysis (batch-wise or real time)
- Further characterization of the immune response

Immunogenicity Risk Management

Bioanalytical Testing Strategy

Immunogenicity Testing Strategy

Based on Risk Assignment

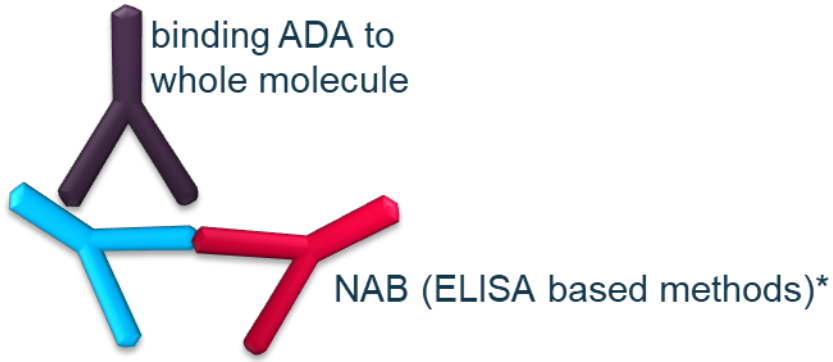
Immunogenicity Risk Level	Molecule Type	Project Development Stage		
		Preclinical	Phase I	Phase II, III, IV
low	standard	basic	basic	basic
	complex	basic	basic	extended
medium	standard/complex	basic	basic/extended	extended
high	standard/complex	basic/extended	extended	extended

Adaptation of the Testing Strategy may become necessary once first data are available

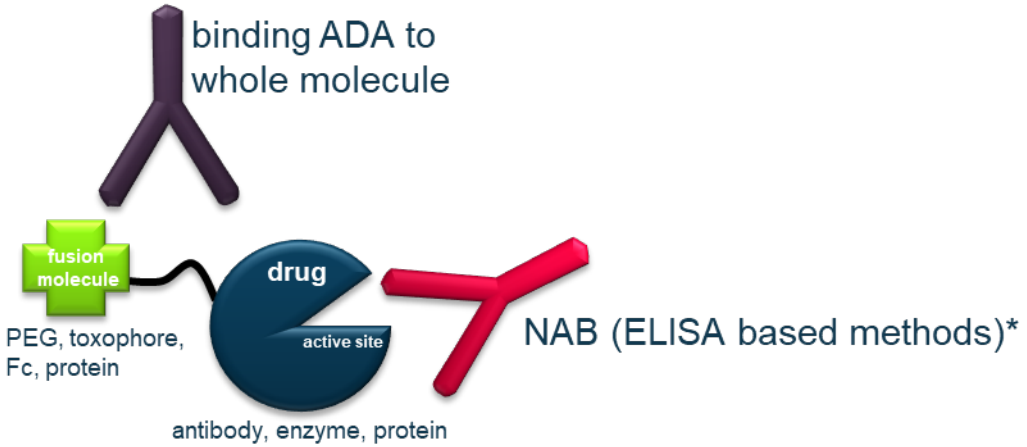
Immunogenicity Testing Strategy

Basic Approach

- Standard molecule
  - e.g. Monoclonal antibody or protein



- Complex molecule
  - e.g. fusion protein



*only in clinical studies

Immunogenicity Testing Strategy

Extended Approach

- Standard molecule
  - e.g. Monoclonal antibody or protein
    - Risk based:

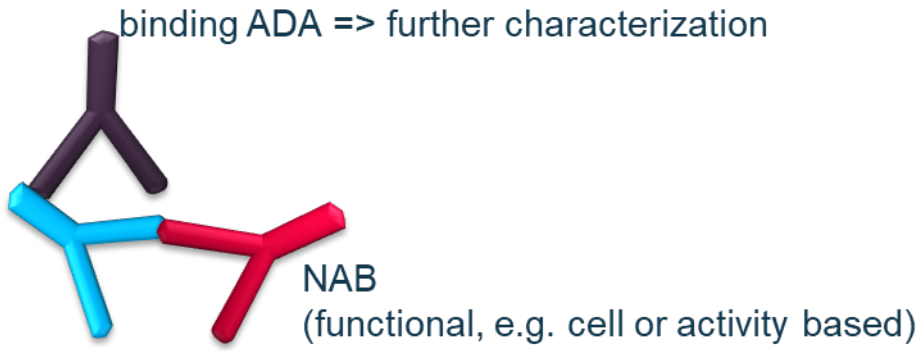
      Real time monitoring

      For replacement therapies: cross reactivity to endogenous counterpart

      Epitope mapping

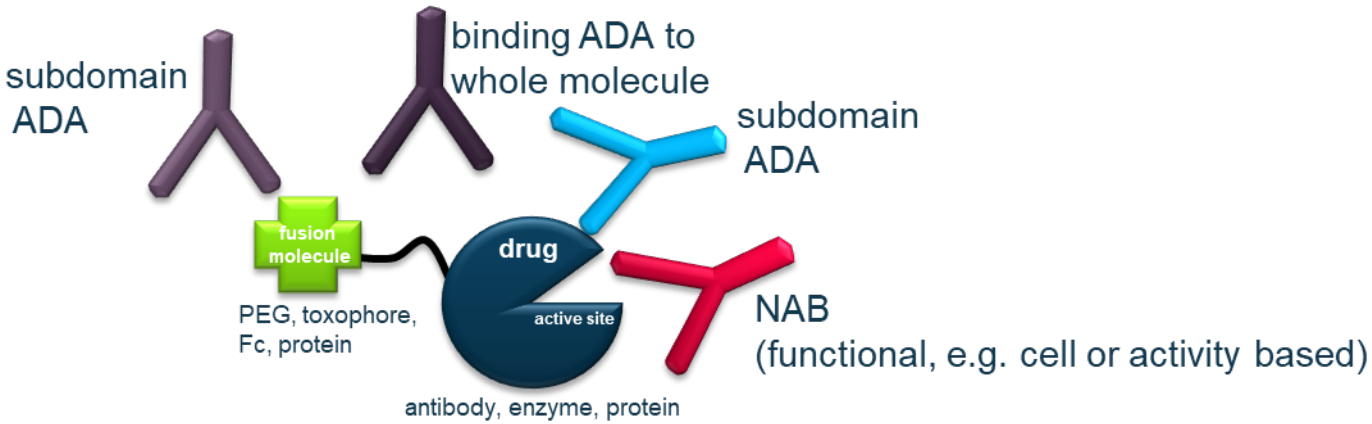
      IgM antibodies

      IgE antibodies



- Complex molecule
  - e.g. fusion protein
    - Risk based:

      As above plus subdomain analysis



Immunogenicity Testing Strategy

Example High Risk Project

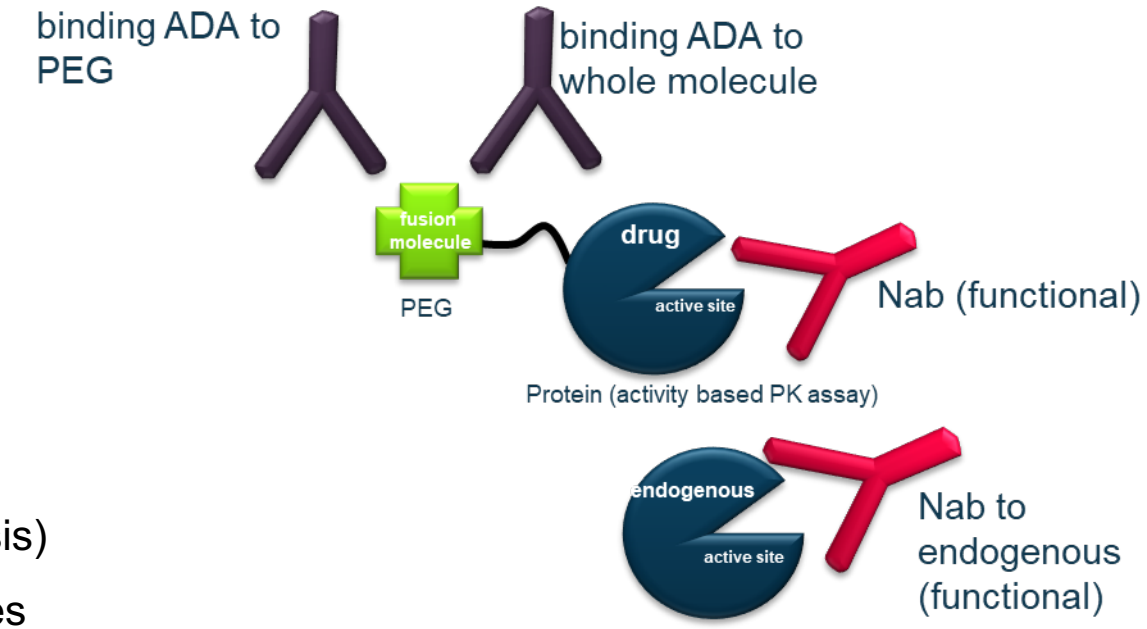
- Complex molecule
  - replacement therapy, pegylated
    - Planned risk-based testing strategy:

Real time monitoring for

cross reactivity to endogenous counterpart (NAB)

ADA to whole molecule and PEG (subdomain analysis)

Product specific NAB in case of ADA positive samples



Immunogenicity Testing Strategy

Example High Risk Project

// Adapted testing strategy (based on observed clinical consequences):

After some cases of loss of efficacy and hypersensitivity in special patient population:

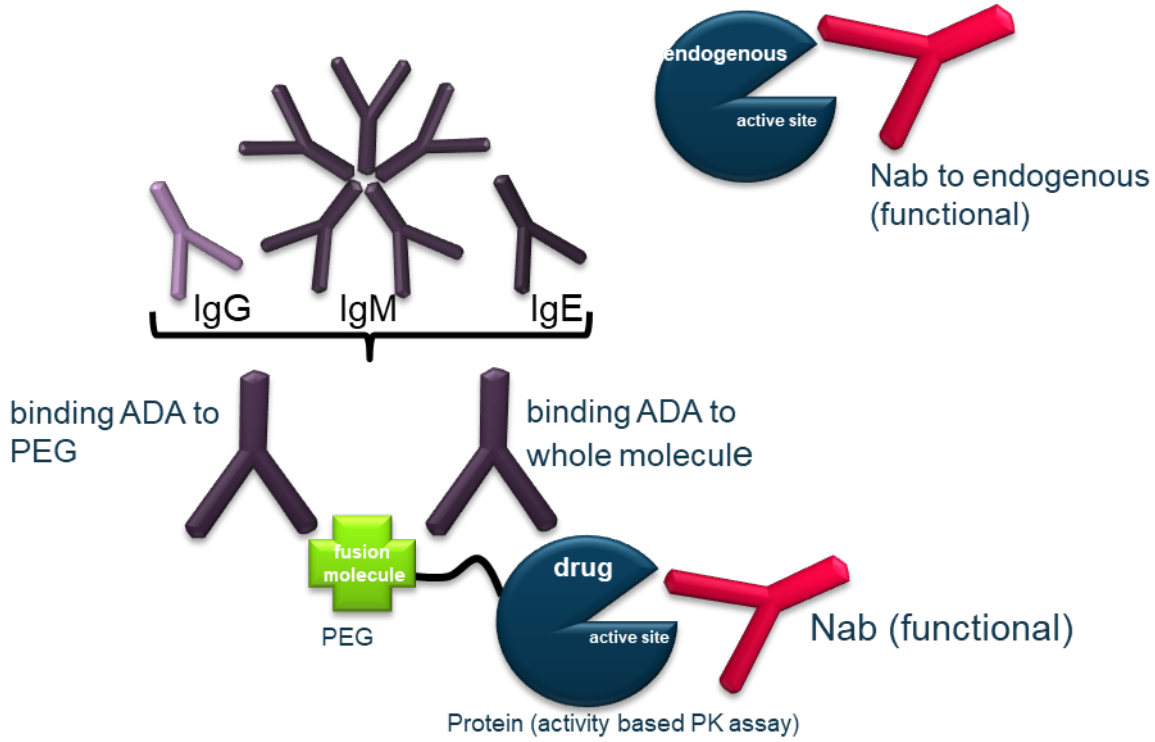
Sampling in extension cohort more frequently during first exposure days

IgM antibodies against PEG => optimized confirmatory step to increase sensitivity

Evaluation of hypersensitivity reactions:

IgE antibodies

HCP antibodies



Conclusion

- Immunogenicity Risk Assessment starts early during development of Biologics
- Product, process, patient and treatment related risk factors need to be identified and addressed by appropriate mitigation strategies
- During the development process the overall immunogenicity risk can change depending on successful mitigation actions or availability of clinical data
- A general immunogenicity testing strategy can roughly be developed based on the risk assignment but may need to be adapted
  - to specific product and project needs
  - after observed clinical consequences

Acknowledgements

// Bayer Immunogenicity Alignment Team

// Cross functional team giving advice on how to perform Immunogenicity Risk Assessment and Management (Best Practice Document)

// Bayer Bioanalytics Team

Thank you!

Bye-Bye