Immunogenicity strategies across programs: risk-based approaches and challenges

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EBF Open Symposium - November 2021

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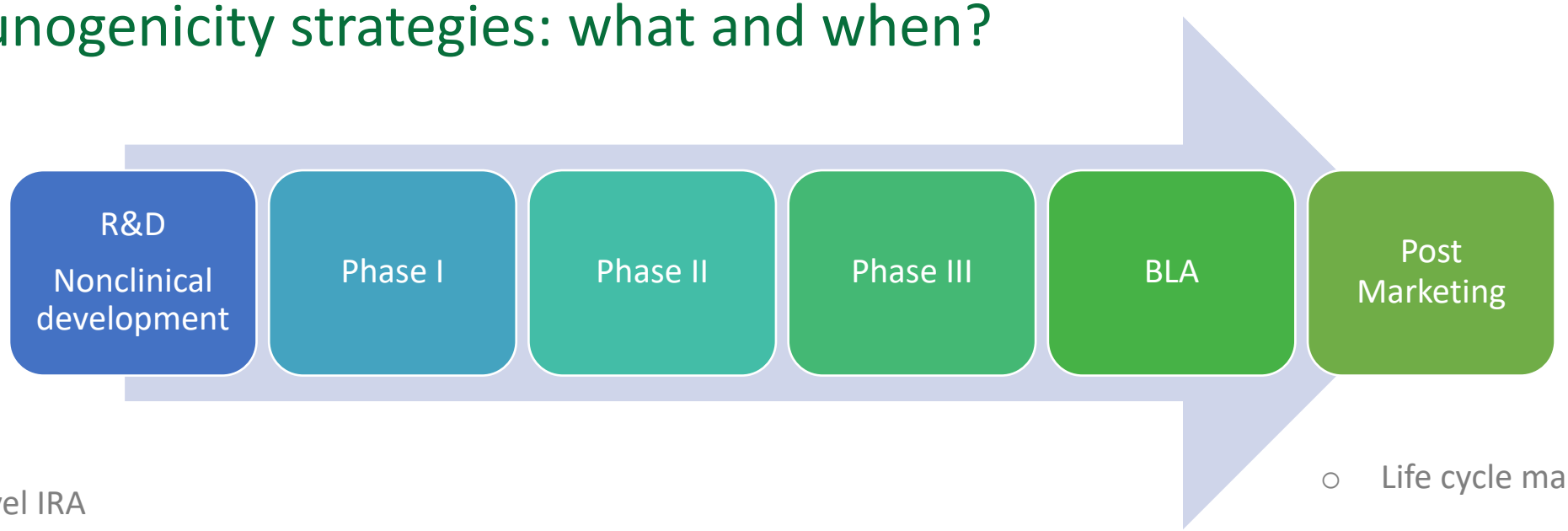
Outline

- Introduction
- Case study 1:
  - Nonclinical ADA testing in relation to current EBF recommendation
- Case study 2:
  - From immunogenicity risk assessment to clinical immunogenicity strategy

Immunogenicity strategies: what and when?



- High level IRA
- T cell epitope prediction
- Lean nonclinical bioanalytical strategy **Case study 1**
- Non-GLP/GLP bioanalysis and data transfer

- In-depth IRA
- Bioanalytical strategy **Case study 2**
- PK/PD/ADA/NAb development, transfer, validation and troubleshooting
- Critical reagent management
- Oversight outsourced assays and GxP bioanalysis
- Clinical immunogenicity data reporting and interpretation
- Regulatory submissions: IB, IND, BLA, ISI
- Interactions with Health Authorities

- Life cycle management

Case study 1:
Nonclinical ADA testing in relation to current EBF recommendation

Nonclinical ADA testing:

EBF recommendation

- Decision tree: minimal strategic approach of when and what to include for nonclinical immunogenicity assessments
- Minimum set of validation parameters
- Lean sample analysis strategy

A strategic approach to nonclinical immunogenicity assessment: a recommendation from the European Bioanalysis Forum

Anna Laurén[1,2], Joanne Goodman[2], Jonas Blaes[3], John Cook[4], Kyra J Cowan[5], Madeleine Dahlbäck[6], Joanna Grudzinska-Goebel[6], Deborah McManus[7], Robert Nelson[8], Susanne Pihl[9] & Philip Timmerman*[1,10]

Bioanalysis. 2021 Apr;13(7):537-549

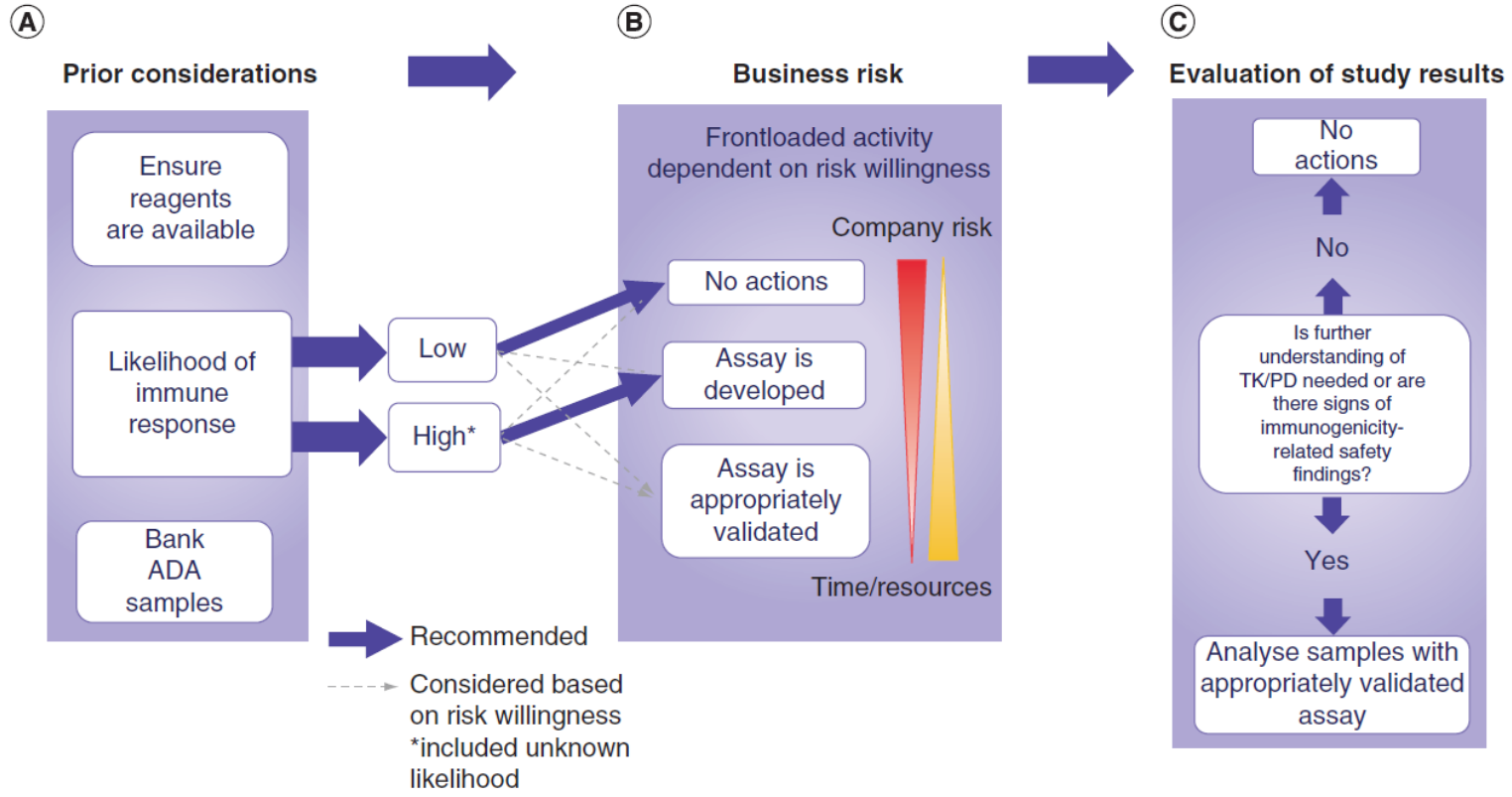


Figure 1. Decision tree for the strategic considerations of nonclinical anti-drug antibody assessment.

Nonclinical ADA testing:

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- Monoclonal antibody compound
- Low immunogenicity in DRF; no PD marker
- In support of the GLP tox studies:
  - In-house ADA assay development
  - Method validation is outsourced
    → Less flexible in terms of timelines; Slot reservation needed
    → Method transfer can be time-consuming

→ Default method transfer and validation to limit business risk of delaying the project in case ADA evaluation would be required
But lean method validation approach

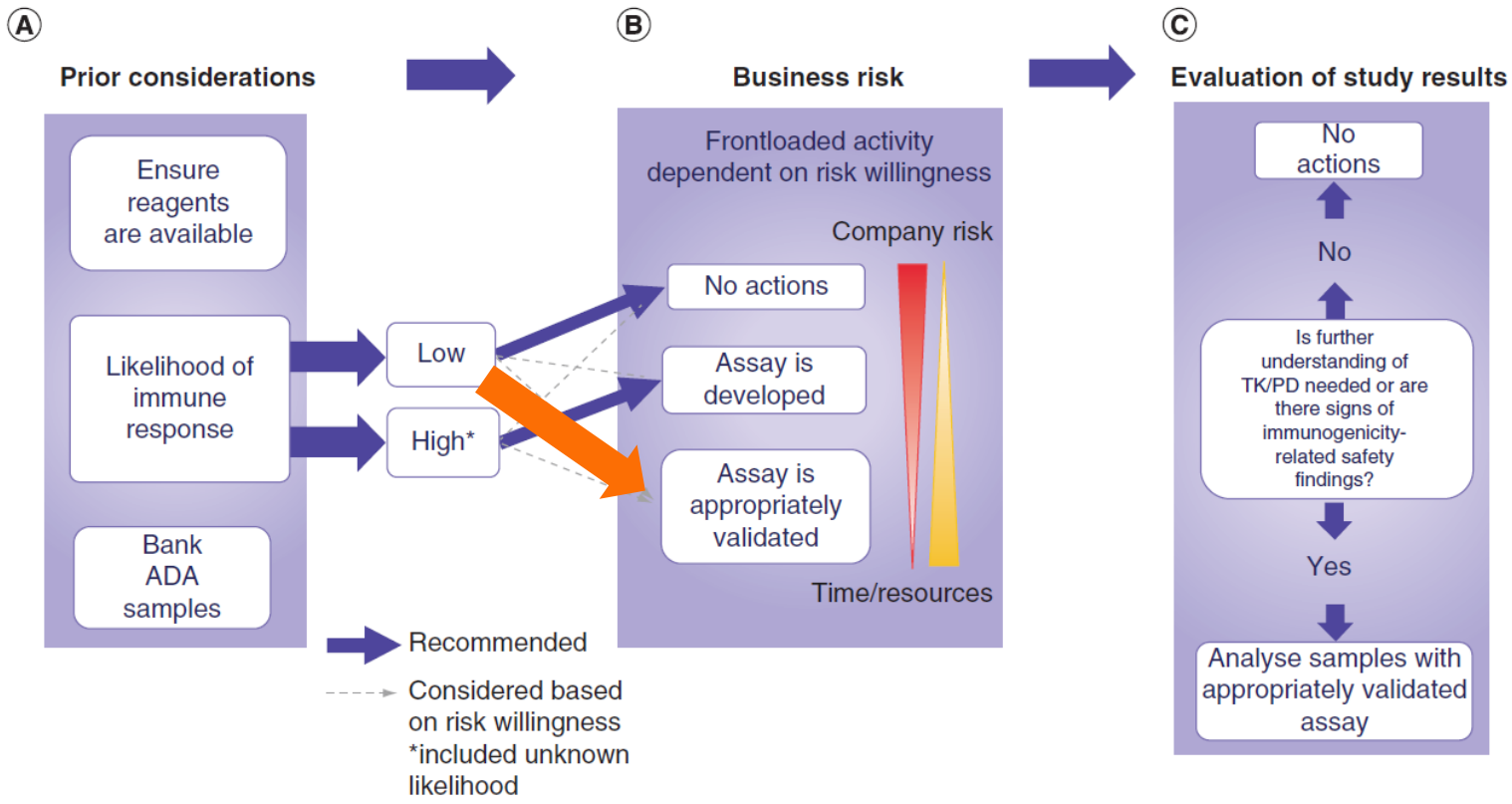

Figure 1. Decision tree for the strategic considerations of nonclinical anti-drug antibody assessment.

Nonclinical ADA testing:

EBF recommendation

Lean method validation approach for nonclinical immunogenicity assessment

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Table 2. Overview of recommended anti-drug antibody validation parameters for nonclinical immunogenicity assessment.

Parameter	Minimal number of runs and samples	Comment
SCP	Two runs of 30 individuals or Four runs of 15 individuals	Minimum 60 data-points from individual samples. May be generated from multiple analysts. 0.1–1% FPR and no confirmatory assay
Sensitivity	One run	At least 1000 ng/ml ≥SCP. No need for statistical analysis
Selection of LPC	Tested as part of precision	LPC is predefined during assay development and confirmed during validation. The concentration is selected at a reasonable range close to sensitivity (e.g., 2–3x to the signal of SCP)
Drug tolerance	One run	At LPC (or for more sensitive methods at least at 1000 ng/ml positive control) in presence of appropriate drug concentrations should remain positive
Precision	Three runs	Ensure that the LPC and the HPC, if used, is tested ≥SCP and NC is <SCP in each run Acceptance criteria defined *a priori*

HPC: High positive control; LPC: Low positive control; NP: Negative control; SCP: Screening cut point.

Nonclinical ADA testing:

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Lean method validation approach for nonclinical immunogenicity assessment

- Outsourced method validation
- ADA screening assay only
- Validation parameters:
  - Screening cut-point setting (n = 4 runs):
    - 25-30 individuals in duplicate
    - 0.1% FPR
  - Selection of LPC:
    - At +/- 2 x NC signal
  - Sensitivity (n = 4 runs or n = 1 run if cannot be combined with CP runs)
  - Precision
    - inter-assay (n = 4 runs)
    - intra-assay (n = 1 run)
  - Drug tolerance (n = 1 run)
  - Selectivity and hook effect are assessed only during method development

Run	Analyst	Validation parameter	Acceptance criteria
Run 1 - 4	1 and 2	Screening cut-point determination Sensitivity LPC selection Inter-assay precision	• Report cut-point factor at 0.1% FPR • Report results at 50%, 95% and 99% CI • < 1000 ng/mL • LPC and HPC: CV < 20%; precision of scoring
Run 5	1 or 2	Intra-assay precision Drug tolerance	• LPC and HPC: CV < 20%; precision of scoring • LPC and 1000 ng/mL PC

5 runs versus 18 runs in historical studies

Nonclinical ADA testing:

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CHALLENGE

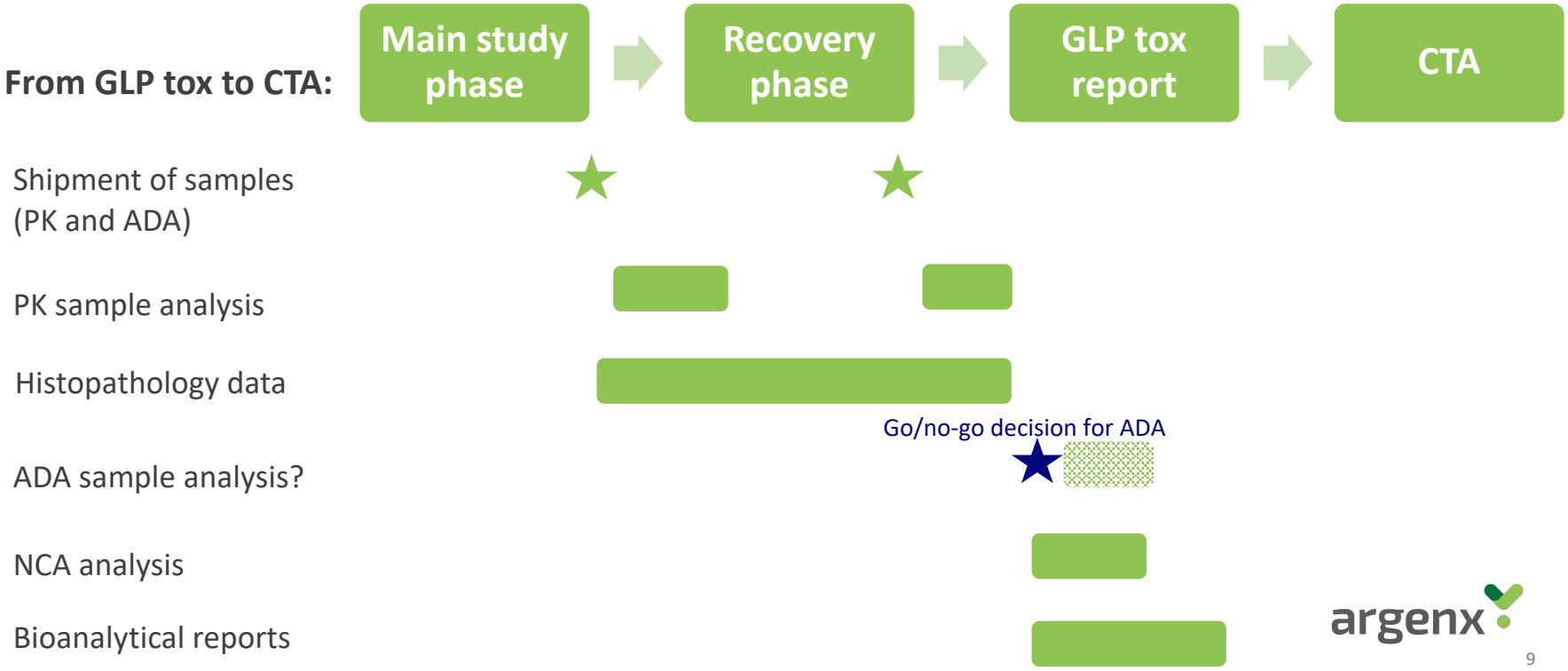
- Tight timelines to CTA
- Reduced flexibility due to outsourced sample analysis

MITIGATION

- Accurate planning required
- Default ADA sample shipments to CRO
- Agree with vendors to implement go/no-go decision in the contracts

Sample analysis approach for nonclinical ADA testing

- Appropriate sampling
- The addendum to ICH S6 recommends that immunogenicity should be examined where there is:
  - evidence of altered pharmacodynamic activity;
  - unexpected changes in exposure in the absence of a pharmacodynamic marker or
  - evidence of immune-mediated reactions



Case study 2:
From immunogenicity risk assessment to clinical immunogenicity strategy

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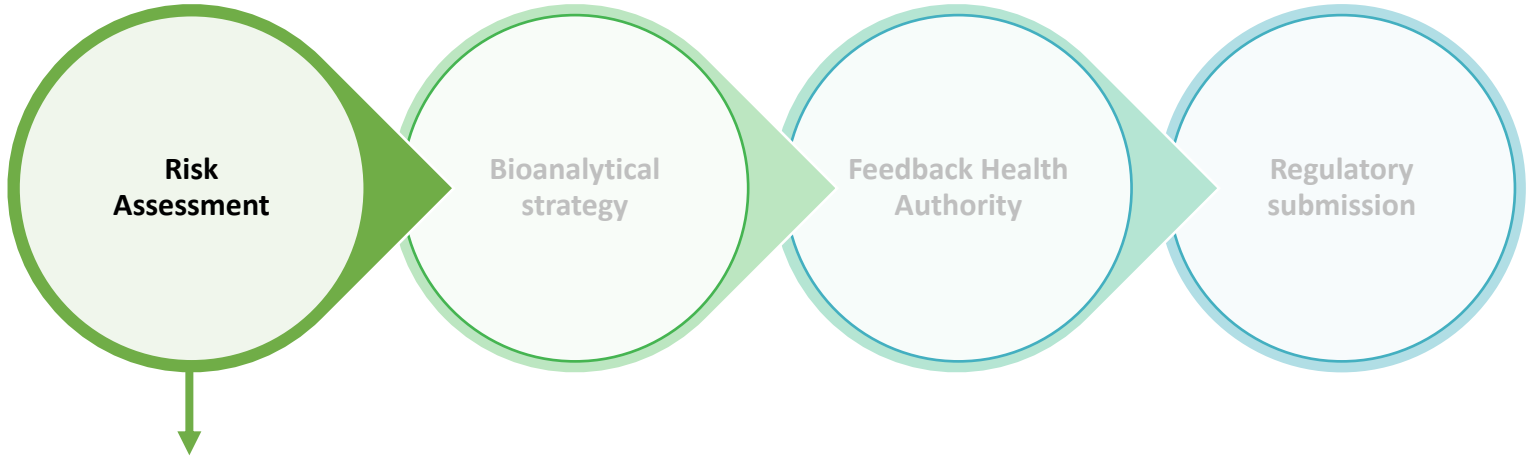
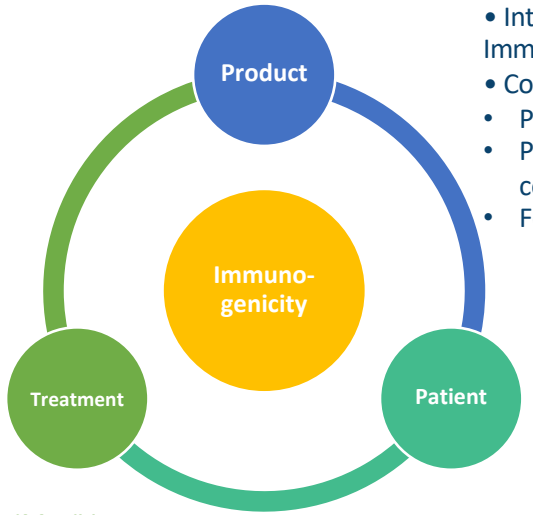


- Monoclonal antibody compound
- Prior to IND, an **immunogenicity risk assessment** was performed:
  - Product-, patient- and disease-, and treatment-related risk factors that can affect immunogenicity were considered
  - An *in silico* prediction of potential T-cell epitopes arising from the variable heavy-variable light (VH-VL) region was performed

  → Based on the available risk factors, the overall immunogenicity risk for the lead candidate was considered **low**

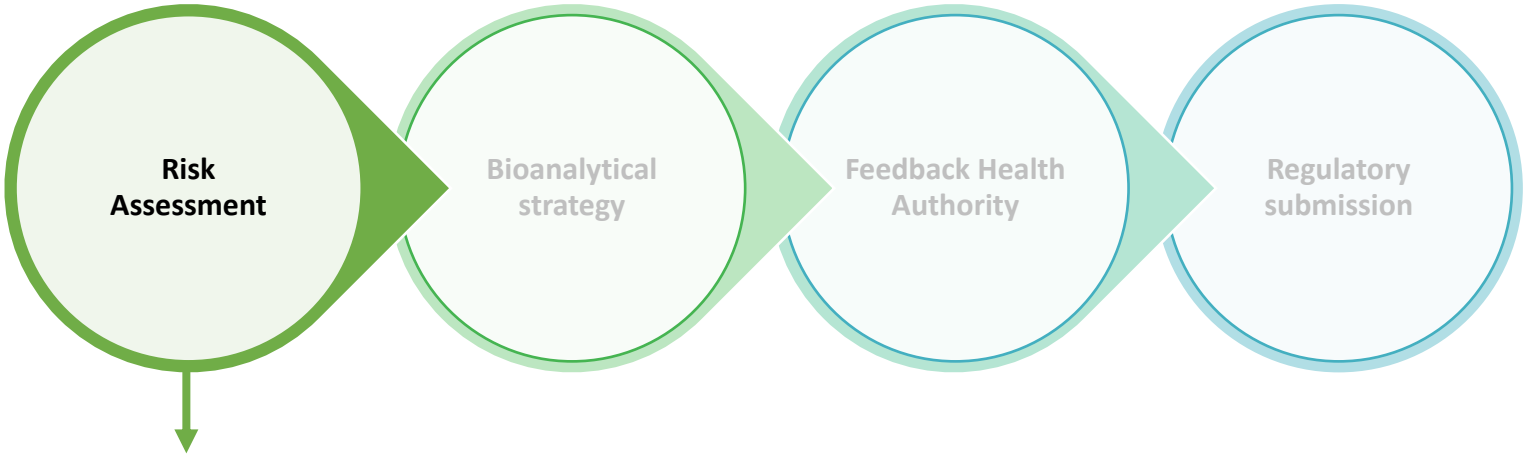


- Intrinsic factors (Antigenicity, Immunomodulatory properties)
- Control of product quality:
  - Product-related variants
  - Process-related Impurities (host cell proteins, etc)
  - Formulation, container closure

- Genetics (HLA)
- Immune status
- Disease state
- Pre-existing immunity

- SC > IM > IV
- Dose, frequency and duration
- Concomitant medication

Case study 2: From immunogenicity risk assessment to clinical immunogenicity strategy



- Common approach defined for immunogenicity risk assessment:
- Initiate risk assessment during Discovery phase
- Start T-cell epitope prediction prior to final lead selection
  - Risk-based approach for in silico versus in vitro strategy:
    - Perform high level immunogenicity risk assessment (IRA) early on
      - Only in silico for low risk molecules to enable ranking of pre-leads
      - More elaborate testing for higher risk molecules
  - Consider de-immunization along the sequence optimization process

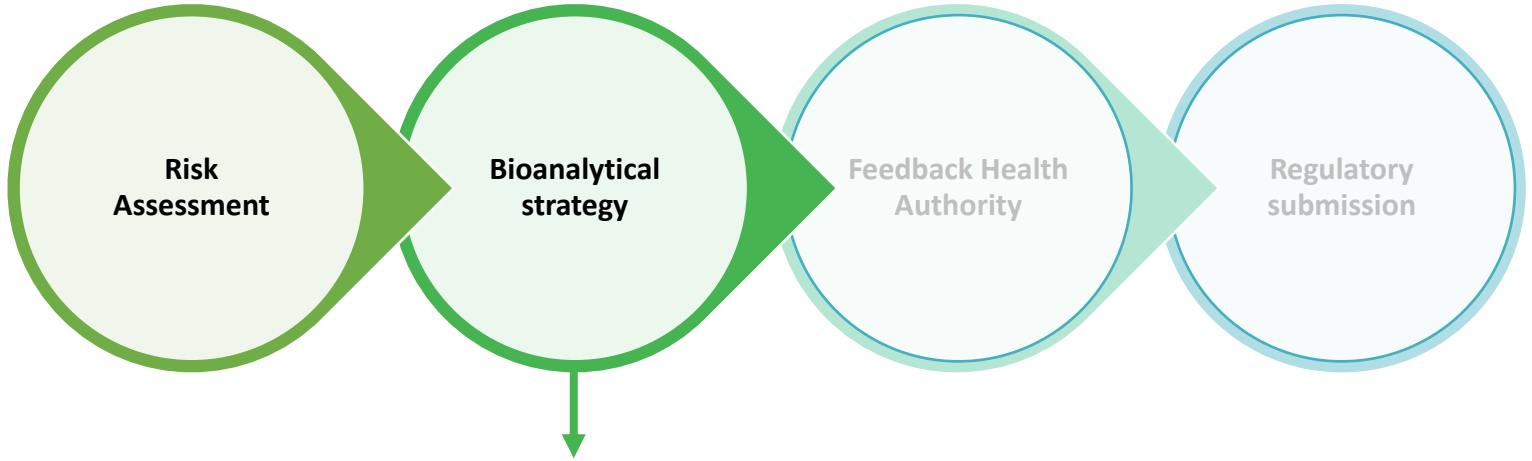
CHALLENGE

- No internal procedure on roles and responsibilities and timing of IRA in place

MITIGATION

- Activities started up for setting up a guidance/procedure

Case study 2: From immunogenicity risk assessment to clinical immunogenicity strategy



- **Clinical assays**
  - PK assay
    - Total PK assay to evaluate exposure
  - PD assays
    - Free and total target assay to evaluate target engagement
    - Downstream PD assay to evaluate functional activity
  - ADA assay
    - Tiered approach: screening – confirmatory – titration assay
    - High drug-and target tolerance required → acid pre-treatment
    - Implementation as of Phase 1 using validated ADA assay

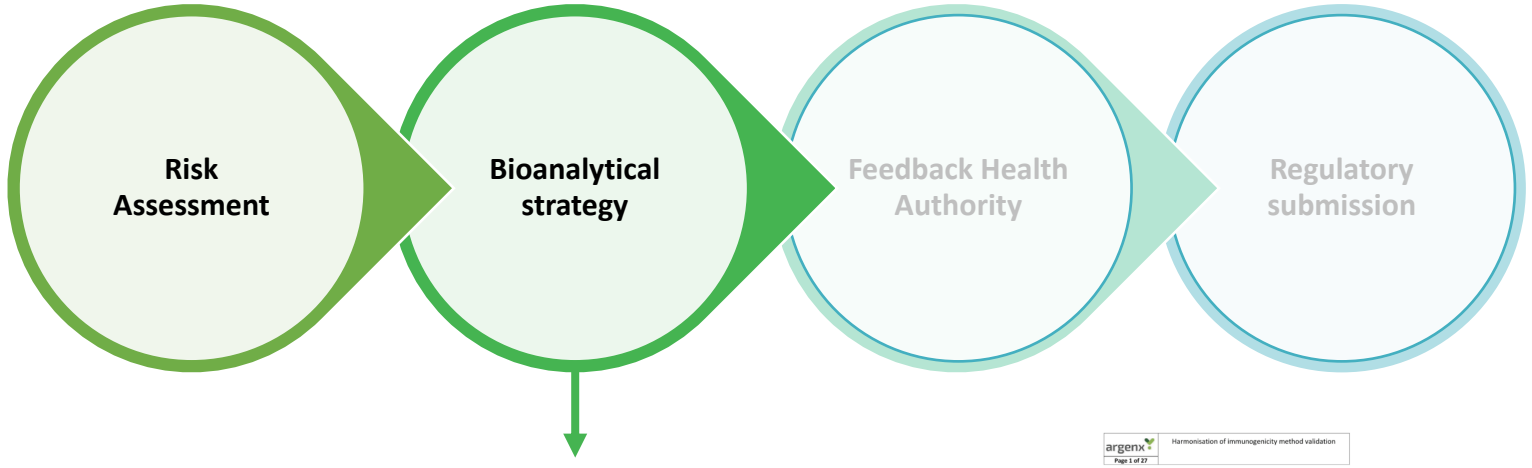
CHALLENGE

- Potential 'pipeline in a product' compound→ validate method at different vendors: harmonization of validation and CP setting required

MITIGATION

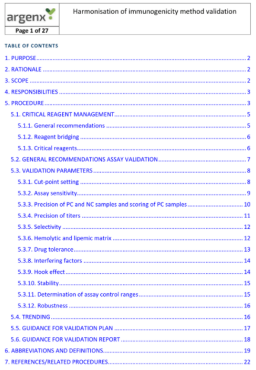
- Internal procedures in place to harmonize ADA method validations
- CP setting done in-house by Statistician (SAS script)

Case study 2: From immunogenicity risk assessment to clinical immunogenicity strategy



- Harmonization of outsourced method validations at external vendors

- Harmonization of ADA CP setting in regulated studies across vendors
  - In-house CP setting via validated SAS script
  - Process described in a guidance
  - Excel input file
  - SAS programmed output file
  - 2-pager summary report


argenx Harmonisation of immunogenicity method validation

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CHALLENGE

- Potential ‘pipeline in a product’ compound→ validate method at different vendors: harmonization of ADA validation and CP setting required

MITIGATION

- Internal procedures in place to harmonize method ADA validations
- CP setting done in-house by Statistician (SAS script)

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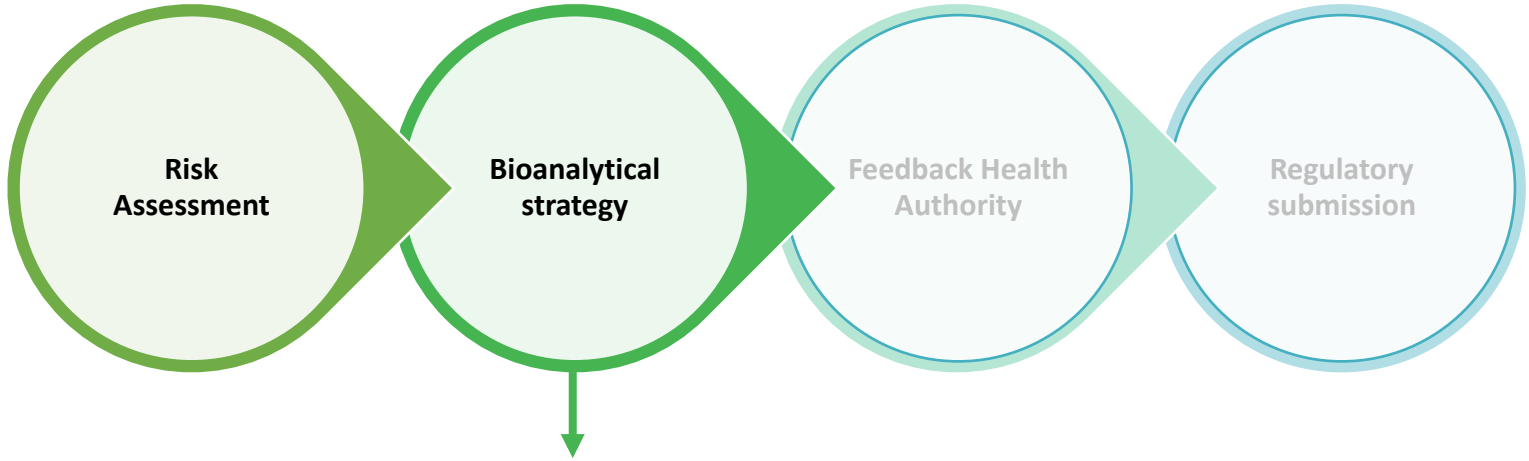
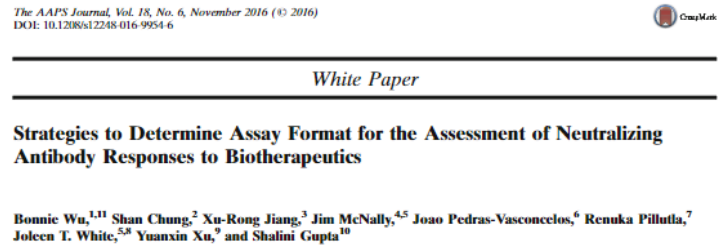



The AAPS Journal, Vol. 18, No. 6, November 2016 (© 2016)
DOI: 10.1208/s12248-016-9954-6

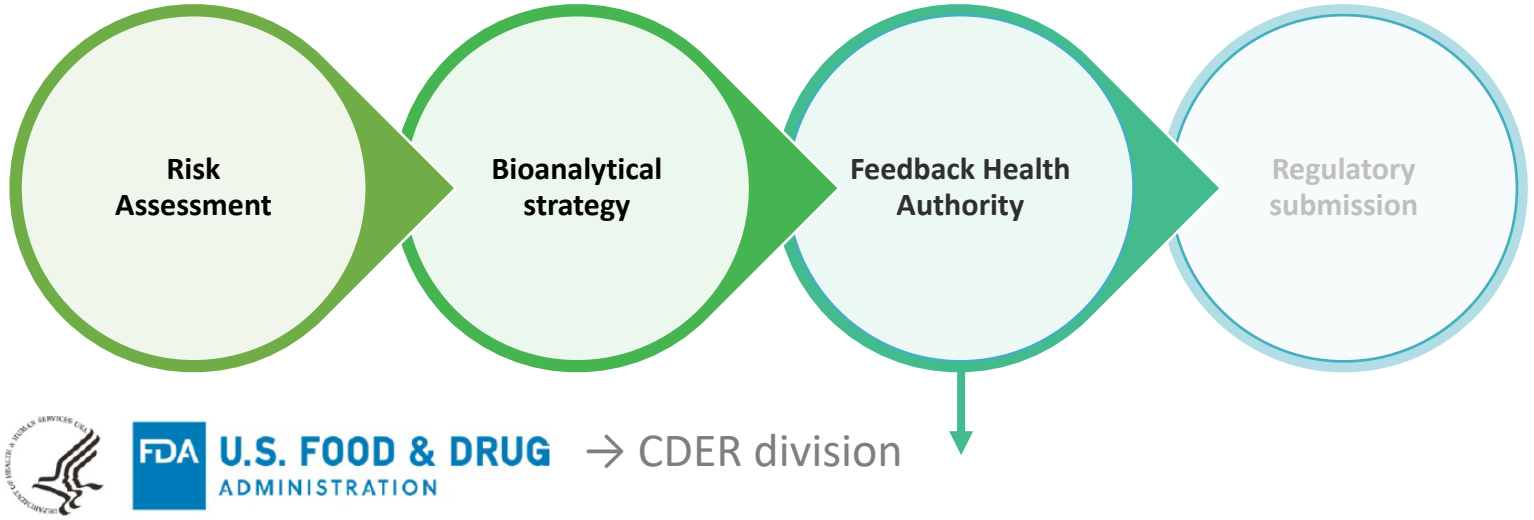
White Paper

Strategies to Determine Assay Format for the Assessment of Neutralizing Antibody Responses to Biotherapeutics

Bonnie Wu,[1,11] Shan Chung,[2] Xu-Rong Jiang,[3] Jim McNally,[4,5] Joao Pedras-Vasconcelos,[6] Renuka Pillutla,[7] Joleen T. White,[5,8] Yuanxin Xu,[9] and Shalini Gupta[10]

- **Clinical assays**
  - Neutralizing Ab assay
    - Based on MoA of compound (antagonistic molecule; soluble target) and risk assessment:
    - An indirect competitive ligand binding assay
      - Inhibition of ligand-target binding by drug → reflects the drug's biological function
      - NAbs, if present, reverse this inhibition of ligand-target by drug and lead to a restored assay signal
  - NAb assay development work starts at start of the Phase 2 study
  - Banking of Phase 2 study samples; only analyze in case of inconclusive PK/PD results
  - NAb assay sample analysis as from pivotal studies

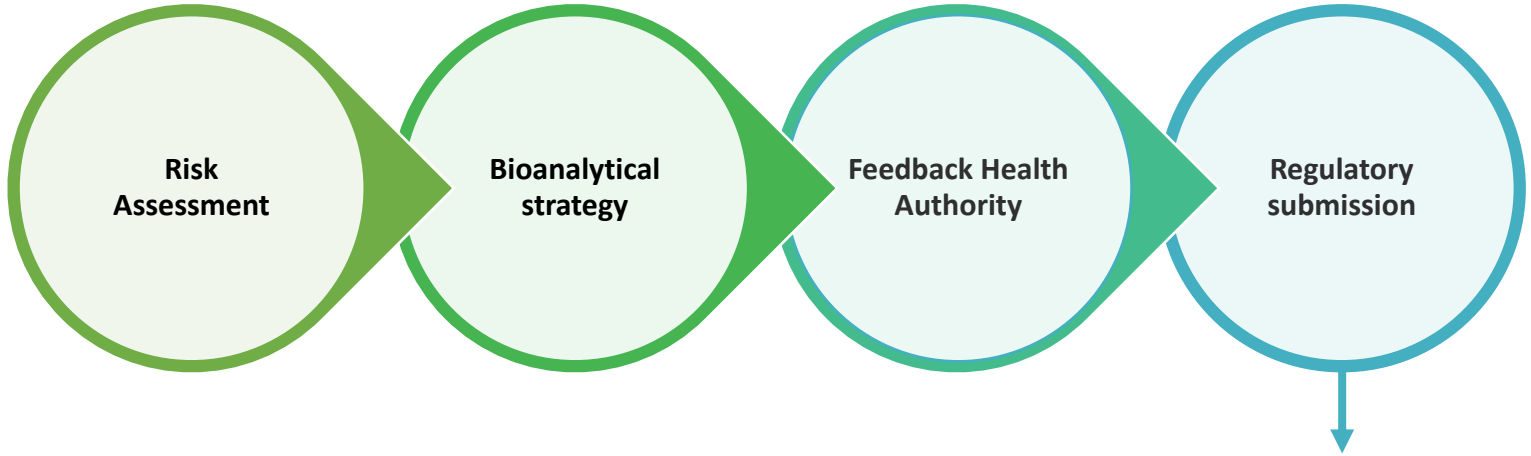
Case study 2: From immunogenicity risk assessment to clinical immunogenicity strategy



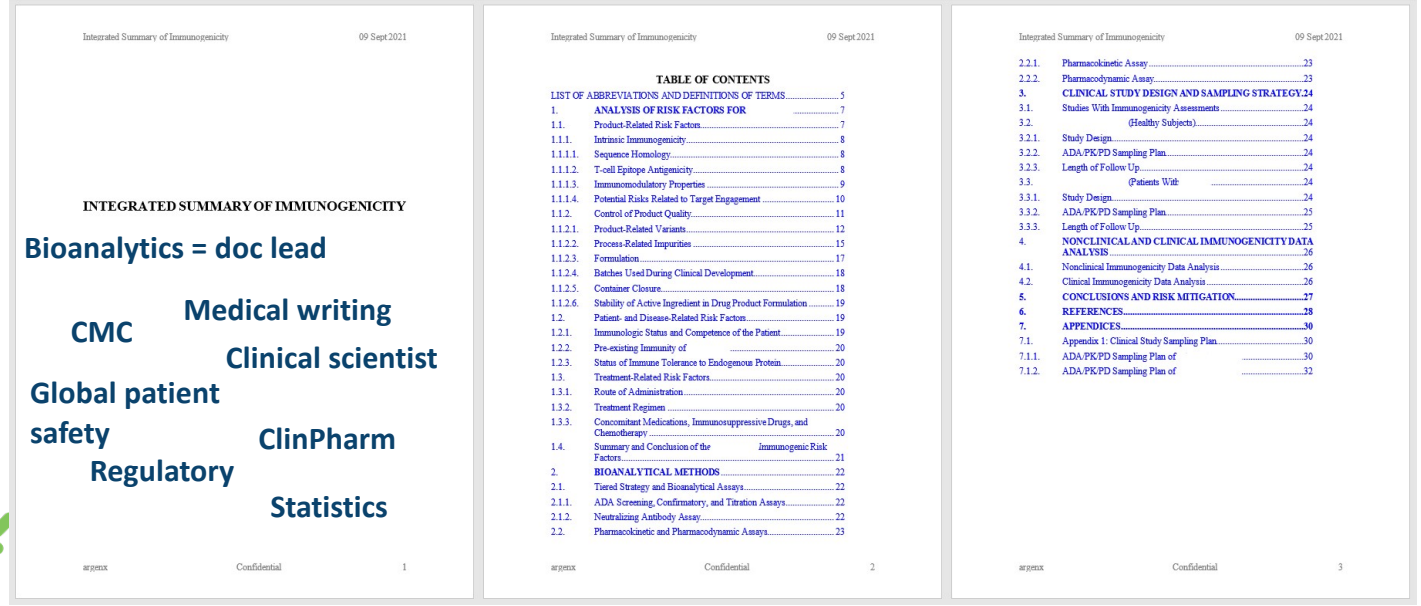
- *<u>Question Pre-IND:</u> Does the agency agree with the sponsor's proposed testing strategy for measuring binding and neutralizing anti-drug antibodies (ADAs) as an integral part of the immunogenicity risk assessment?*
  - An indirect competitive ligand binding assay is proposed as NAb assay format (based on MoA and IRA)
  - ADA assay with acid pre-treatment step

- *<u>Response:</u>*
  - In general, **your proposed immunogenicity testing strategy appears reasonable**. However, the adequacy of your testing strategy **will depend on the quality of data to support assay validation**.
  - ADA may be lost during acid dissociation step → evaluate recovery of ADA as part of assay validation

Case study 2: From immunogenicity risk assessment to clinical immunogenicity strategy



- IND submission including an ISI Summary document with all available information



1. ANALYSIS OF RISK FACTORS FOR THE DRUG
2. BIOANALYTICAL METHODS
3. CLINICAL STUDY DESIGN AND SAMPLING STRATEGY
4. NONCLINICAL AND CLINICAL IMMUNOGENICITY DATA ANALYSIS
5. CONCLUSIONS AND RISK MITIGATION
6. REFERENCES
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TOC inspired by Chamberlain 2019 paper and FDA 2019 guidance

Thank You