EBF

14th EBF Open Symposium

Science – Our Universal Language

Immunogenicity Strategies: cross-industry, cross-functional approaches to understand immunogenicity potential from discovery through launch

Michaela Golob, on behalf of the EBF

24-26 November 2021, Barcelona

Current ADA strategy team

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Yvonne Katterle	Bayer

Life cycle of Biologics (NBEs)

What bioanalytical scientists support at what stage

Discovery

Concept

- Discovery PK analysis
- In-silico
- Assessment of Immuno-genicity Risk and Mitigation

- DMPK strategy from Discovery to Ph1
- Set-up bioanalytical strategy
- PK, PK/PD, TK assessment
- Immunogenicity evaluation

- Clinical strategy
- Clinical bioanalytical strategy & assays
- Clinical PK
- Immunogenicity risk management and mitigation
- Clinical Protocol
- Clinical Study Report (CSR)
- Statistical Analysis Plan (SAP)

- Approval & Post-Approval strategy
- Late Bioanalytical support

Initial Development Plan (IDP)

Participating to dossier writing:

Integrated Risk Assessment (IRA)

Integrated Summary Immunogenicity (ISI)

IB, IMPD/IND, BLA/MAA

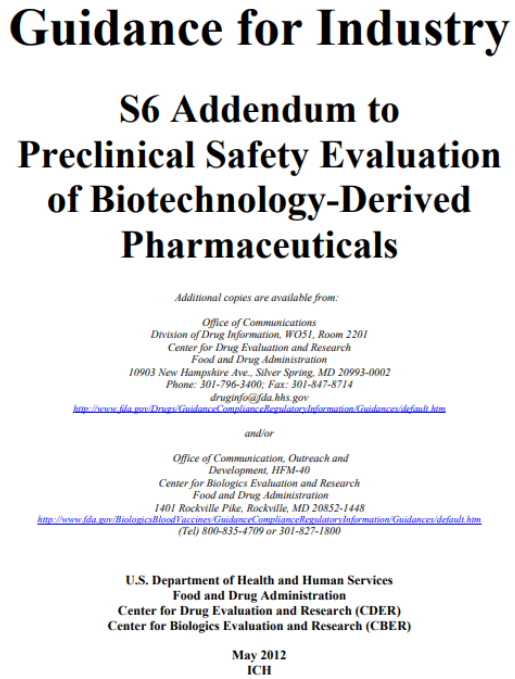
Interaction with health authorities

Immunogenicity strategy – key points

Continued support of bioanalysis from discovery to post-approval requires a multidisciplinary approach

- Immunogenicity strategy set-up
- Cross-functional collaboration: Development teams, preclinical teams, clinical teams, review boards
- Risk assessment (IRA)
- Immunogenicity assay strategy based on risk assessment and MoA
- ADA/Nab method development, validation incl. cut-point analysis and trouble-shooting
- Life cycle managements of methods
- CMC support, including CQAs for Immunogenicity
- GLP (if conducted) and GCP sample analysis
- Study design, Immunogenicity assessment, data interpretation, reporting
- ISI; SAP; IB; IMPD/IND; BLA/MAA support
- Safety monitoring support

Non-clinical Immunogenicity testing strategy



Guidance for Industry

S6 Addendum to Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals

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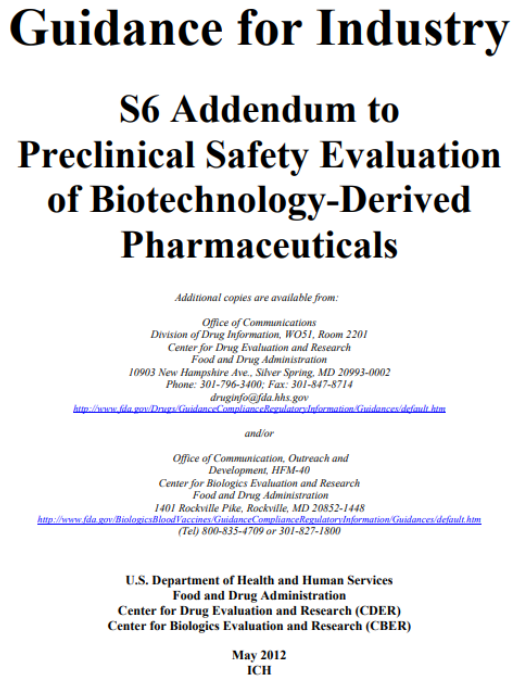
May 2012
ICH

ICH S6 addendum => need for ADA evaluation in non-clinical studies when there is evidence for

- altered PD
- unexpected changes in exposure in absence of a PD marker
- Immune-mediated reactions

- General regulatory position on ADA testing => "Risk based and Fit-for-Purpose"

Non-clinical Immunogenicity testing strategy



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White Paper

For reprint orders, please contact: reprints@future-science.com

Bioanalysis

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

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

In majority of new drug projects:

- No confirmatory assay needed
- No titration needed => S/N ratio is an option
- Titre assay may be valuable when you do not have an assay with good drug tolerance
- Neutralization assay is not needed

(Published online March 2021)

Clinical Immunogenicity testing strategy

Sampling

- ADA sampling schedule & frequency based on evaluated risk from IRA
- Match ADA sample time point with a PK sample
- Unless risk suggests otherwise, NAb usually requested by Health Auth. from Ph3 onwards
- Aliquot numbers depend on potential use
- Immunogenicity safety including follow-up of positive patients in certain high-risk situations

Unified cut-point approach across disease states

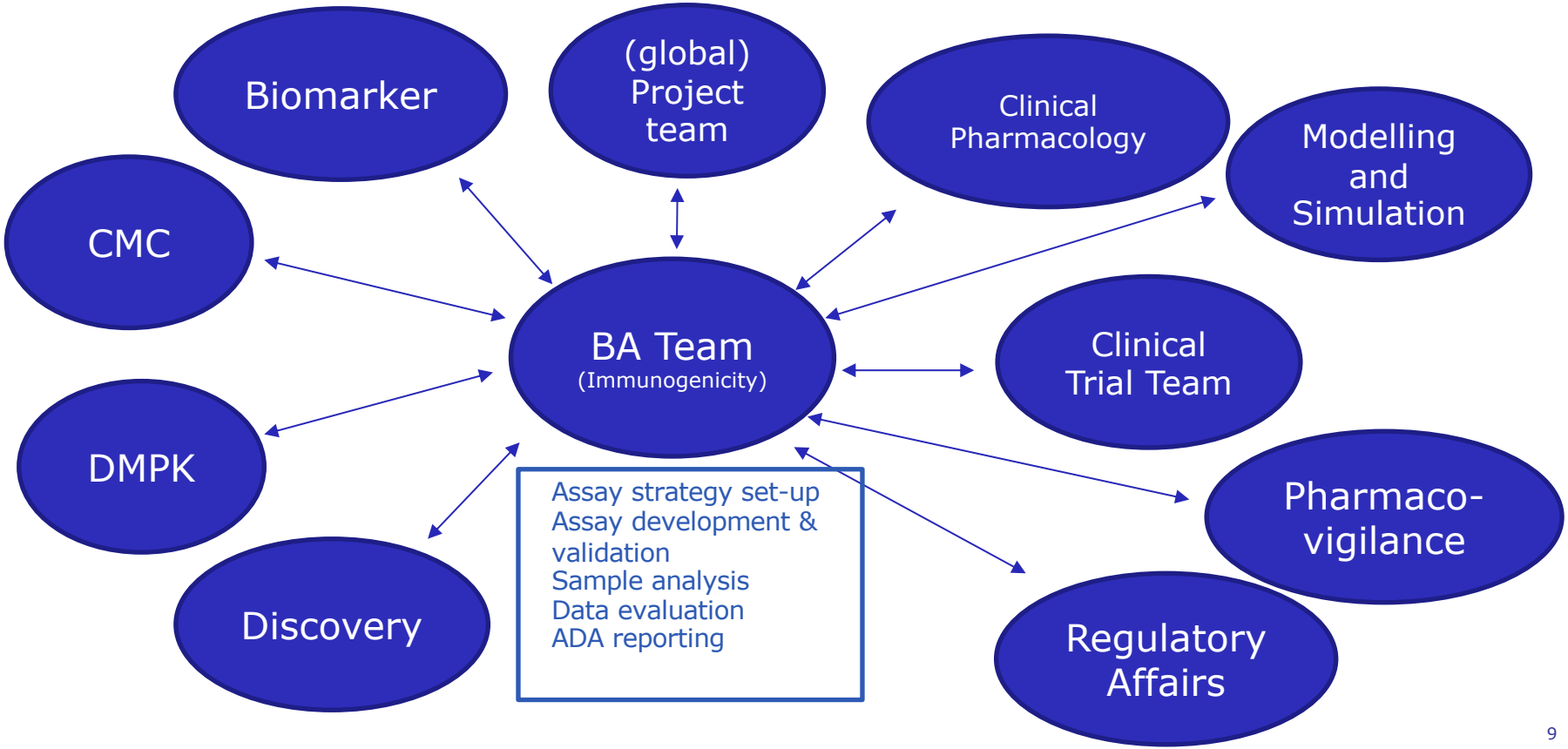
Retention of samples

- Due to FDA change in not classifying an assay as validated until they have
- reviewed, for pivotal studies retain samples 1-2 years after submission (may depend on modality type)

Informed Consent

- templated language important - secondary use of samples

BA & cross-functional collaboration



Immunogenicity Risk Assessment (IRA)

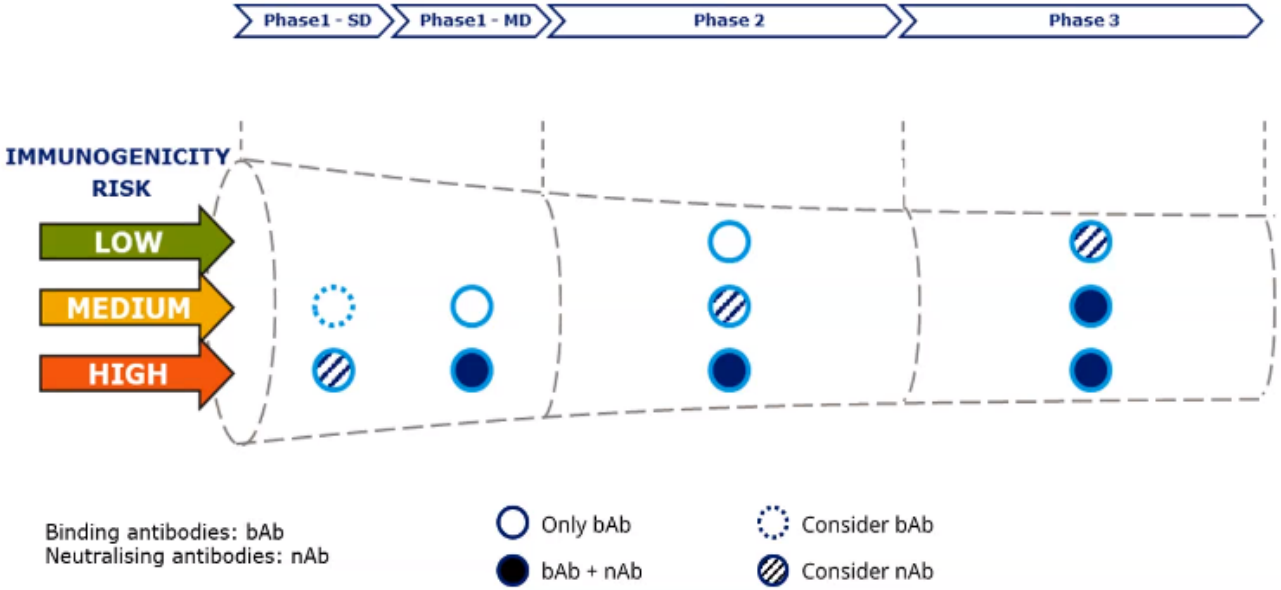
- Document requested by FDA & EMA
- Pre-requisite for immunogenicity testing strategy
- Integrative part of clinical study design
- Reflected in the Label information

Key risks for clinical impact (not necessarily just ADA incidence)

- Risk of IgE-mediated hypersensitivity reactions, incl. anaphylaxis
- Risk of delayed immune complex-mediated hypersensitivity reactions
- Induction of cross-react with endogenous counterpart
- Neutralisation of drug and/or neutralization of endogenous counterpart
- Reduced target engagement and efficacy response
- Altered PK
- Long-term clinical impact

Risk-assessment linked to testing strategy

A company proposal:



Binding ADAs (can consist of sustaining ADAs, clearing ADAs, neutralizing ADAs or ADAs with no effect)
Neutralising ADAs (subpopulation of binding ADAs)

Immunogenicity Plan/Strategy

- Company specific internal document describing the project specific plan for immunogenicity evaluation
- Support overall project strategy and be aligned with other team plans
- Living document to be updated along the project development stages

Key topics to be covered:

- Risk assessment
- Action plan how to manage/mitigate potential safety risks
- Assay strategy – what assays to be used when
- Sampling and analysis plan for non-clinical and clinical studies
- Considerations when to update the Integrated Summary of Immunogenicity (ISI)
- Plans for regulatory interactions

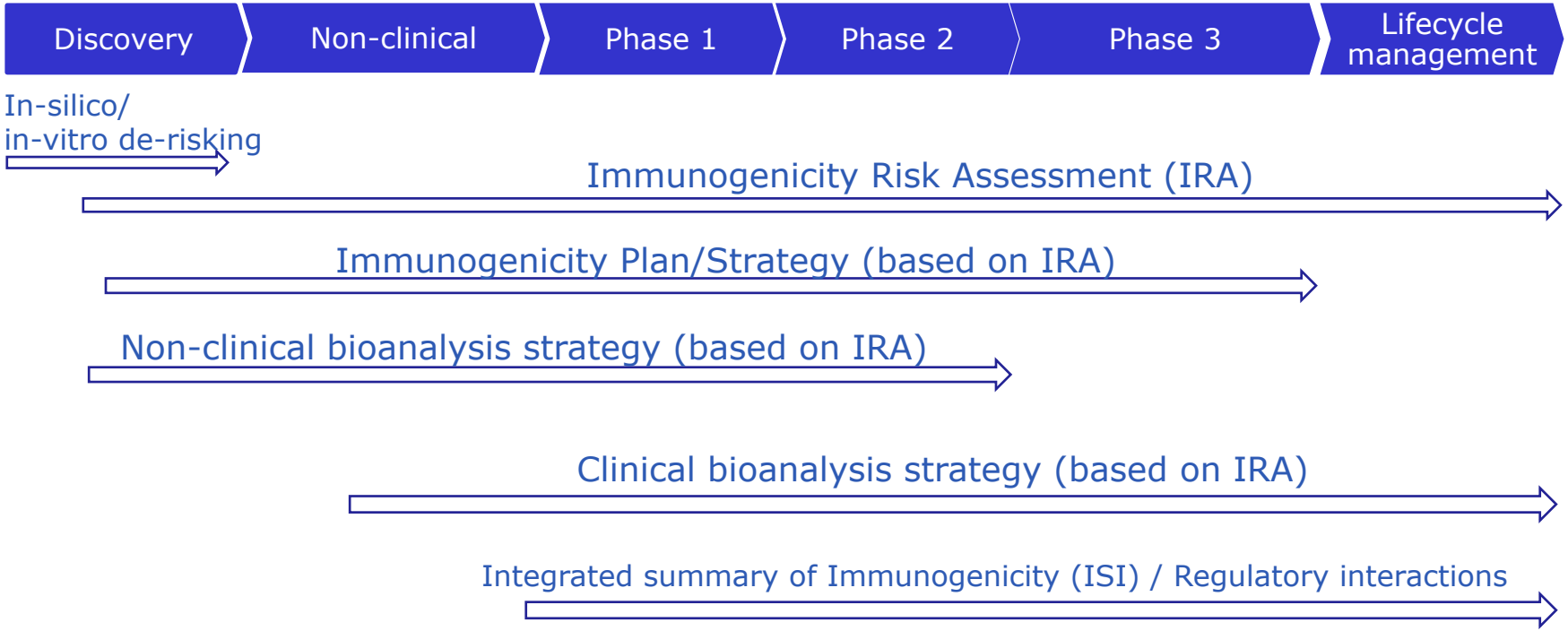
Integrated Summary of Immunogenicity (ISI)

- Requested by FDA & EMA
- Document integrating all aspects of immunogenicity from development program for easy review by regulatory authorities' (e.g. scientific advice, end-of-ph2 meeting)
- Initial version ready for IND
- Updated along with clinical development
- Full version required for BLA/MAA submission

Key topics to be covered :

- Adapted to the stage of development with the risk assessment being the core component
- Analysis of immunogenicity risk factors for the compound (identify risk, evaluation and mitigation)
- Tiered testing strategy and assay validation summary
- Clinical immunogenicity data analysis
- Overall conclusion for clinical immunogenicity evaluation and risk mitigation
- Assess need for statistical analysis plan
- Identify tables and listings needed for data review (CSR & ISI)

Building an Immunogenicity strategy – when we do what



Acknowledgements

ADA strategy team members

EBF Interest Group Macromolecules (IGM)

EBF community

Contact Information

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