15th Open Symposium

The Bioanalytical Compass

Navigating to our True North

Past, present and future direction of EBF discussions and recommendations on immunogenicity

Robert Nelson, on behalf of the EBF

16-18 November 2022, Barcelona

A navigational aid to EBF discussions and recommendations on immunogenicity

The Past

“The past is a stepping stone, not a millstone.”

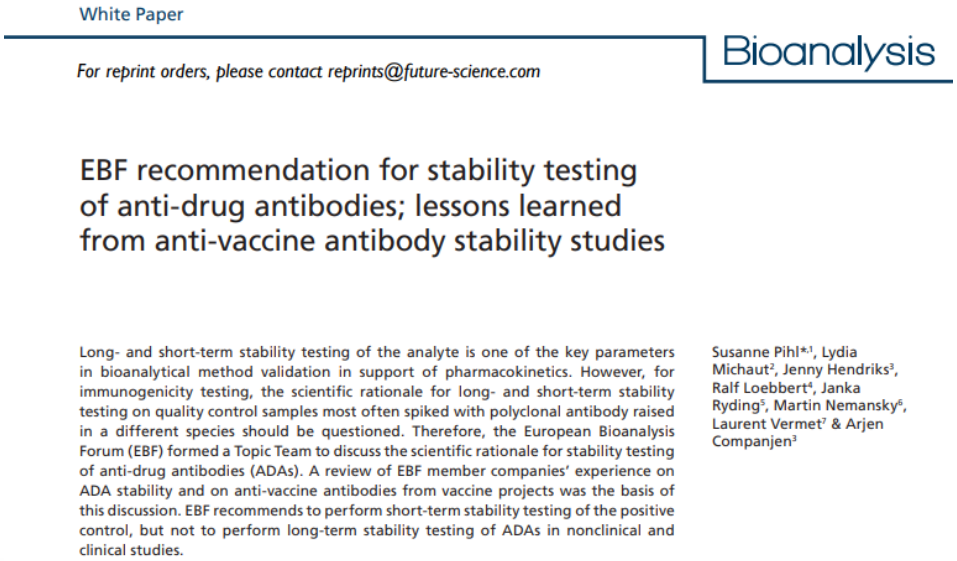
– Robert Plant

Past discussions on immunogenicity

- Previous EBF discussions:
  - Publication: “EBF recommendation for stability testing of anti-drug antibodies; lessons learned from anti-vaccine antibody stability studies”. Bioanalysis. 2014; 6(10):1409-13.
  - Focus Workshop: “Current analysis of immunogenicity – Best Practices and Regulatory Hurdles”, September 27-28, 2016.
  - Focus Workshop: “Today’s challenges and solutions in assessing immunogenicity in patients”, September 19-20, 2018.
  - Plus sessions in EBF Open Symposium, the EBF Strategy and Year End Members Meetings

EBF recommendation for stability testing of ADA

- Landmark publication providing **scientific rationale and evidence** that long-term stability (LTS) testing for anti-drug antibody (ADA) assays is unnecessary
  - Publication: https://doi.org/10.4155/bio.14.95



White Paper

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Bioanalysis

EBF recommendation for stability testing of anti-drug antibodies; lessons learned from anti-vaccine antibody stability studies

Long- and short-term stability testing of the analyte is one of the key parameters in bioanalytical method validation in support of pharmacokinetics. However, for immunogenicity testing, the scientific rationale for long- and short-term stability testing on quality control samples most often spiked with polyclonal antibody raised in a different species should be questioned. Therefore, the European Bioanalysis Forum (EBF) formed a Topic Team to discuss the scientific rationale for stability testing of anti-drug antibodies (ADAs). A review of EBF member companies' experience on ADA stability and on anti-vaccine antibodies from vaccine projects was the basis of this discussion. EBF recommends to perform short-term stability testing of the positive control, but not to perform long-term stability testing of ADAs in nonclinical and clinical studies.

Susanne Pihl*[1], Lydia Michaut[2], Jenny Hendriks[3], Ralf Loebbert[4], Janka Ryding[5], Martin Nemansky[6], Laurent Vermet[7] & Arjen Companjen[3]

2016 Focus Workshop

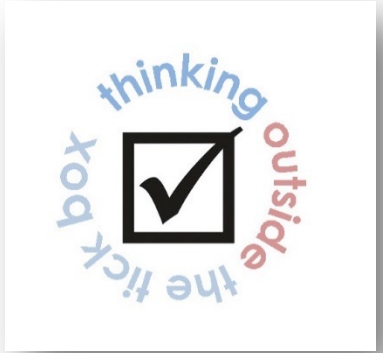
- Shortly after the publication of the EMA Draft Guideline on Immunogenicity assessment of biotechnology-derived therapeutic proteins (September 2015) and the FDA draft guidance for industry “Assay Development and Validation for Immunogenicity Testing of Therapeutic Protein Products” (April 2016)

- Topics included:
  - Challenges of drug tolerance and interferences
  - Alternatives for Neutralising antibody (NAb) assessment
  - Cut-point setting in ADA and NAb assays
  - Engagement with representative from FDA and EMA on current challenges

2016 Focus Workshop

Takeaway message:

- Immunogenicity assessment should be a balance of fulfilling regulatory expectations as they appear in the guidance documents and **applying sound scientific logic**
- Simply following guidance to the letter will not guarantee a successful drug registration
- Conversely, omitting certain parameters with scientific justification does not automatically mean rejection of the submission



- Workshop Agenda & Slides: https://e-b-f.eu/fw201609-slides/
- Publication: https://doi.org/10.4155/bio-2017-4971

2018 Focus Workshop

EBF Autumn Focus Workshop

Today's challenges and solutions in assessing immunogenicity in patients

- Topics included:
  - Harmonized approaches for immunogenicity method validation
    - Outlier exclusion, pre-existing ADA, drug tolerance
  - Progress in Clinical nAb assays
    - Integration of PK, PD and ADA
  - Clinical immunogenicity and the value for the patient and physician

- Workshop Agenda & Slides: https://e-b-f.eu/fw201809-slides/

2018 Focus Workshop

- Takeaway message:
  - We have come a long way
    - Harmonised approaches to ADA and NAb assay validation and reporting
    - Increased focus on the relevance of ADA rather than the incidence
  - Still a long way to go
    - When we focus on assay performance (sensitivity/drug tolerance), we can lose sight of whether the performance/data are **suitable for their intended use**
    - Need increased focus on risk assessment driving immunogenicity assessment approach and evaluation of clinical relevance of observed immunogenicity

The Present

“Yesterday is history, tomorrow is a mystery,
but today is a gift... that is why it is called the present.”

– Master Oogway, Kung Fu Panda

Recent discussions on immunogenicity

- Recent EBF immunogenicity focus areas:
  - Publication: “A strategic approach to nonclinical immunogenicity assessment: a recommendation from the European Bioanalysis Forum” Bioanalysis. 2021; 13(7):537-549.
  - Training Day: “Managing the Practical Aspects of Immunogenicity”, Cyberspace March 23-24, 2021
  - Focus Workshop: “Points to Consider on Cut Points”, Cyberspace April 28-29, 2022
    - https://e-b-f.eu/fw202201-slides/
    - Summary will be presented later in this session

Preclinical ADA

- Decision tree on approach to preclinical ADA testing

White Paper

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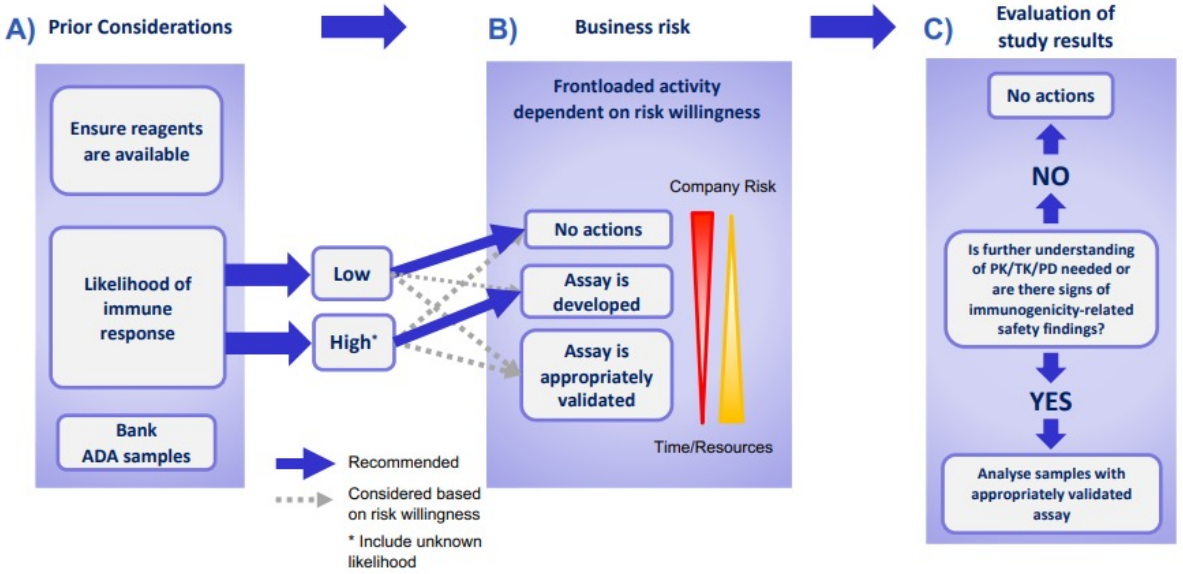
Bioanalysis

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] & Philip Timmerman[*,10]



Publication: https://doi.org/10.4155/bio-2021-0028

Preclinical ADA

- Streamlined approach to validation
  - Fit-for-purpose approach (≠ lower quality data)

Parameter	Minimal Number of Runs and Samples
Screening Cut Point (SCP)	2 runs of 30 individuals or 4 runs of 15 individuals
Sensitivity	1 run
Selection of Low Positive Control (LPC)	Tested as part of precision
Drug Tolerance	1 run
Precision	3 runs

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Presentation: https://e-b-f.eu/wp-content/uploads/2021/04/005.-Anna-Lauren-on-behalf-of-the-EBF.pdf

Training Day 2021

EBF Cyberconnect Events:
Training Day: Practical Aspects of Immunogenicity
23-24 March 2021

- Topics included:
  - Regulatory updates (China draft technical guideline published August 2020)
  - Preclinical immunogenicity assessment
  - Drug tolerance & target interference
  - Cut-points & outlier exclusion
  - Pre-existing ADA
  - Domain specificity
  - NAb assay approaches
  - Immunogenicity in Cell & Gene Therapy (CGT) development

- Workshop Agenda & Slides: https://e-b-f.eu/fw202101-slides/
- Paper: https://doi.org/10.4155/bio-2021-0200

Training Day 2021

- Newer focus areas:
  - Life cycle management
  - Risk-based approaches

- Takeaway messages:
  - CGT development is requiring us to look beyond the humoral (antibody) response, bringing additional technologies into the bioanalytical space (e.g. flow cytometry, ELISpot)
  - Classification of biotherapeutics into risk categories allows application of tailored risk-based approaches to immunogenicity
  - Have we lost sight of the relevance of what we are measuring and reporting?

Current EBF immunogenicity teams

- Neutralising antibody (NAb)
  - Presentations at EBF Symposia and workshops:
    - https://bcn.e-b-f.eu/wp-content/uploads/2020/12/227.-Anna-Lauren-on-behalf-of-the-EBF-Nab-team.pdf
    - https://e-b-f.eu/wp-content/uploads/2021/12/14.-Robert-Nelson-on-behalf-of-the-EBF-NAb-team.pdf
    - https://e-b-f.eu/wp-content/uploads/2022/06/04.-Nicoline-Videbaek-on-behalf-of-the-EBF.pdf
  - Currently preparing a manuscript summarising activities
- Immunogenicity Strategy
  - Adapting approach to the stage of development with the risk assessment
    - https://e-b-f.eu/wp-content/uploads/2022/01/Michaela-Golob-on-behalf-of-the-EBF.pdf
- Cell & Gene Therapy (CGT)
  - Approaches for immunogenicity assessment are a core discussion topic
    - https://autumnfocus.e-b-f.eu/wp-content/uploads/2020/10/Arno-Kromminga-EBF.pdf
    - https://e-b-f.eu/wp-content/uploads/2022/06/22.-Johannes-Stanta-on-behalf-of-the-BEF.pdf

The Future

"The future is not some place we are going, but one we are *creating*. The paths are not to be found, but *made*. And the activity of making them *changes* both the maker and the destination."

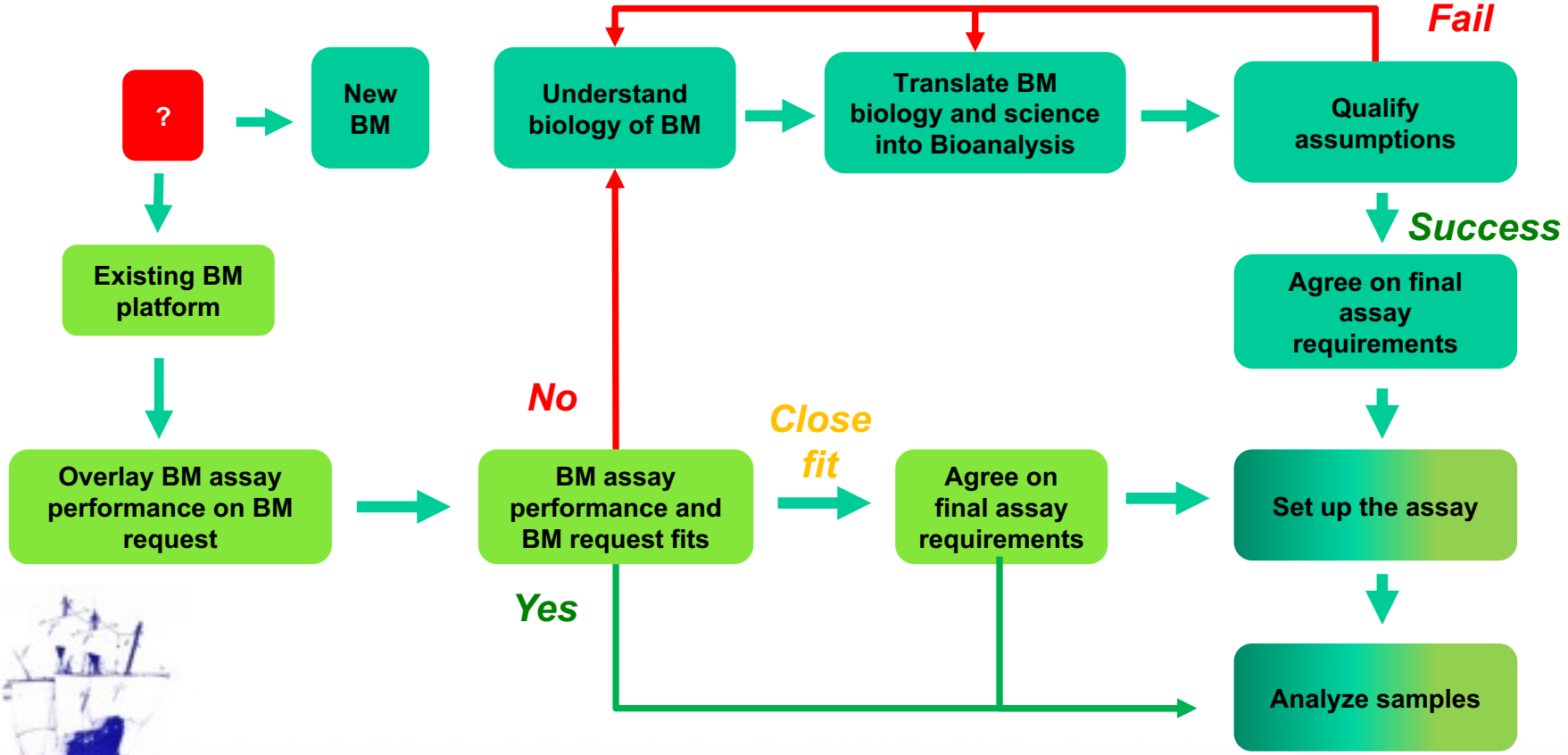
– John H. Schaar

Looking back to look forwards…

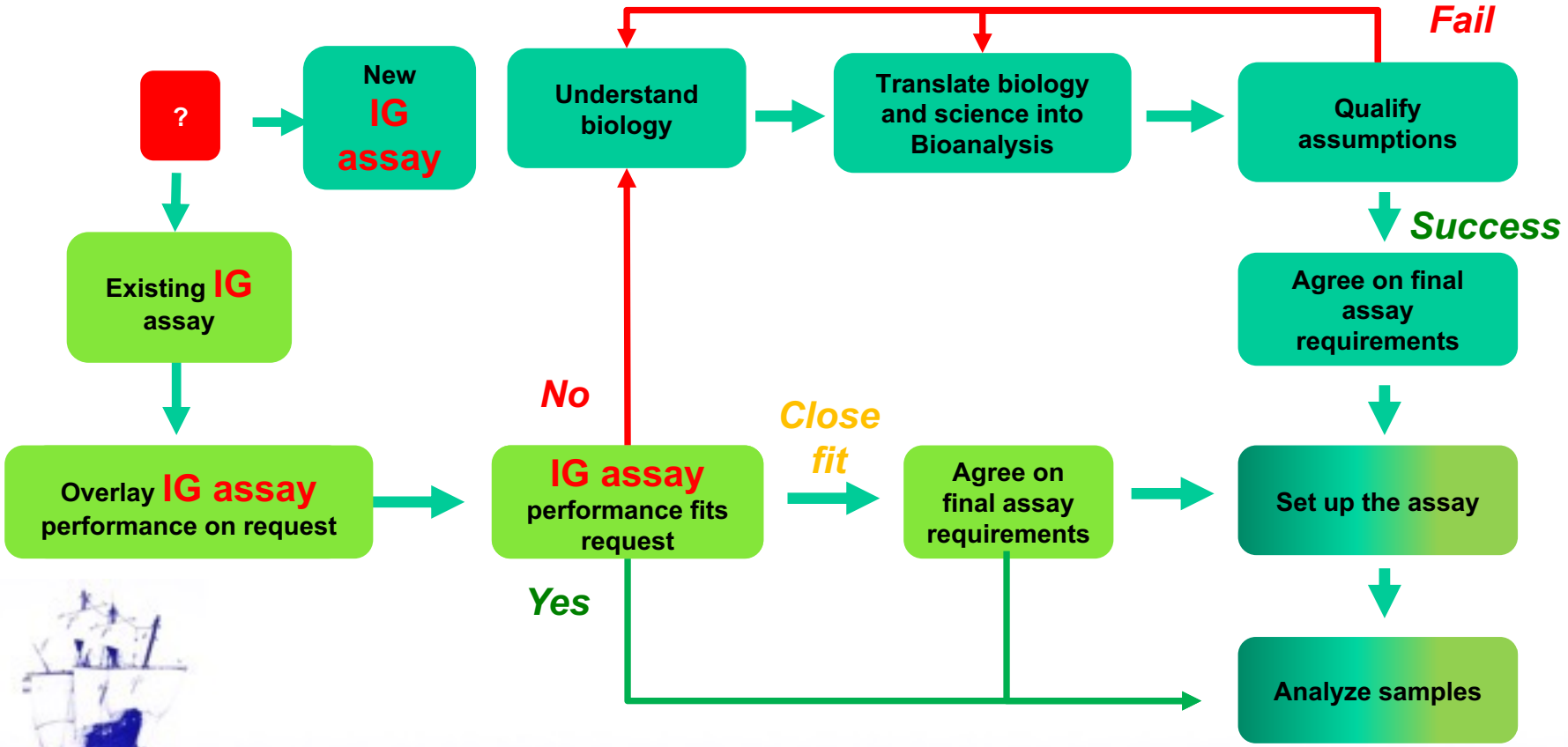
- Previous EBF discussions:
  - Focus Workshop: “New Modalities and Novel Concepts in Bioanalysis”, May 15-16, 2018: https://e-b-f.eu/fw201805-slides/
  - Session: New analytical challenges for immunogenicity testing
    - Multi-domain proteins (e.g., ADCs, fusion proteins, bispecifics, …)
    - Peptide drugs
    - Gene therapy vectors
    - Lipid nanoparticles (LNP) containing RNA
    - Cell therapies
    - (Oligonucleotides)
- We are seeing increasing numbers of these newer modalities, often requiring different and/or more complex immunogenicity testing strategies

Context-of-Use (biomarkers)

Timmerman et. al. 2012. EBF recommendation on method establishment and bioanalysis of biomarkers in support of drug development. Bioanalysis
Goodman et al. 2020. Update to the EBF recommendation on biomarkers assays; bringing context of use into practice. Bioanalysis



Context-of-Use (immunogenicity)



We want to hear from you

- If there are immunogenicity topics that you would like us to discuss within EBF, please let us know…

Acknowledgements

- EBF immunogenicity teams
- EBF Steering Committee and Project Governance Team leadership

- EBF meeting participants

Contact Information

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www.e-b-f.eu