EBF

16th Open Symposium

Science Winning the Race

EBF Feedback on Immunogenicity: When to Accelerate and When to Apply the Brakes!

Jo Goodman, on behalf of the EBF

15-17 November 2023, Barcelona

Continuing the Past EBF Discussions on Immunogenicity

- Previous EBF discussions:
  - "Current analysis of immunogenicity – Best Practices and Regulatory Hurdles", September 27-28, 2016: https://e-b-f.eu/fw201609-slides/
  - FW Paper: https://pubmed.ncbi.nlm.nih.gov/29345496/
  - "Today's challenges and solutions in assessing immunogenicity in patients", September 19-20, 2018: https://e-b-f.eu/fw201809-slides/
  - "Training Day: managing the Practical Aspects of Immunogenicity", Cyberspace March 23-24, 2021: https://e-b-f.eu/fw202101-slides/
  - Recommendations and discussion points on immunogenicity, biomarkers, automation/technology and protein–MS from the 2021 European Bioanalysis Forum Focus Workshops: https://www.future-science.com/doi/10.4155/bio-2021-0200
  - A strategic approach to nonclinical immunogenicity assessment: a recommendation from the European Bioanalysis Forum: https://www.future-science.com/doi/full/10.4155/bio-2021-0028
  - Plus, sessions in Barcelona and the EBF Strategy and Year End Members Meetings

2023 saw Continued Momentum for Immunogenicity Discussions

11:10 12:50 Session 3: ADA - Strategy - (Parallel) - Jupiter
Session Chair: Jo Goodman, AstraZeneca, on behalf of the EBF

11:10 11:30 ***EBF team presentation***
Jo Goodman, on behalf of the EBF

11:30 11:50 ***Daniel Kramer, Sanofi, on behalf of the European Immunogenicity Platform (EIP)***
EIP Overview and Cross-Validation of Immunogenicity Assays

11:50 12:10 ***Hanna Widmaier, Nuvisan***
Cut-Point Limbo - low cut-points and their challenges

12:10 12:30 ***Claire Seal, invoX Pharma***
Case Study of a Neutralising Antibody Assay for FS118, an anti-PD-L1/LAG-3 Bispecific, Tetravalent Antibody

12:30 12:50 ***Nick White, AstraZeneca***
To analyse or not to analyse; that is the question? Changing the Immunogenicity Testing Strategy: Should it be Mandatory, or would a Risk-based Approach be More Appropriate?

11:20 13:00 Pitlane 2: Drug Tolerance case studies unravelled (15 min pitch/case studies) - (Parallel)
In Jin Mao/Petronals/Liberty
Session Chair: Jo Goodman, AstraZeneca on behalf of the EBF

11:20 11:25 ***Martin Rieger, MorphoSys AG***
Case study: Regulatory interaction with regards to DT on a mAb

11:25 11:40 ***Morten Funch Carlsen, LEO Pharma***
Life Cycle Management of ADA and NAb Assays During Clinical Development of a Monoclonal Antibody with Focus on Drug Tolerance Improvement – Nice to Have or Must Have?

11:40 11:55 ***Laura Geary, Resolian***
Improving assay performance when complex sample pre-treatment is required – a CRO perspective

11:55 12:10 ***Daniel Dyer, Labcorp Drug Development***
Experience of a CRO: Drug Tolerance Case Studies

12:10 12:25 ***Arno Kromminga, BioNTech***
ADA Drug Tolerance – Why and when?

12:25 13:00 ***And now...unravel***
Panel discussion of the 5 case studies presented

16:20 18:00 Session 7: Drug Tolerance - Technology - (Parallel) - Jupiter
Session Chair: Kyra Cowan, Merck KGaA, on behalf of the EBF

16:20 16:40 ***Jean-Christophe Genin, F. Hoffmann-La Roche***
Let the Biology guide our choices - Case study : Decoding immunogenicity assay performance for reliable ADA data delivery

16:40 17:00 ***Foka Venema, Ardena***
Adequate neutralization steps are essential for the development of sensitive, robust and highly drug tolerant anti-drug antibody screening and confirmatory assays

17:00 17:20 ***Gregor Jordan, Roche Diagnostics***
Improving drug tolerance: "An assay perspective"

17:20 17:40 ***Lill Liao, Frontage Laboratories***
Strategies for Improving Drug Tolerance in Immunogenicity Assay

17:40 18:00 ***Orbwin Van de Vyver, Sanofi***
PandA-monium: are we too tolerant in ADA method development?

14:00 15:40 Session 13: ADA Technology - (Parallel) - Jupiter
Session Chair: Michaela Golob, Nuvisan, on behalf of the EBF

14:00 14:20 ***Valeria Castagna, Merck KGaA***
Generic ADA Assay: how to speed up early phase and preclinical immunogenicity testing.

14:20 14:40 ***Sijranke Post, Ardena***
The challenges to overcome when developing a synthetic peptide Anti-Drug Antibody assay

14:40 15:00 ***Christopher Tiedje, BioAgilytix***
Application of Different Approaches to ADA Domain Specificity Characterization

15:00 15:20 ***Anna Vlachodimou, Genmab***
Novel approach of immunogenicity testing in support of multi-specific antibody drugs

15:20 15:40 ***Anne-Jan Dijkhuis, QPS***
Challenges during ADA assay development

9:00 10:00 Session 17: Cut Points & Singlicate/Duplicate - (Parallel) - Jupiter
Session Chair: Michaela Golob, Nuvisan, on behalf of the EBF

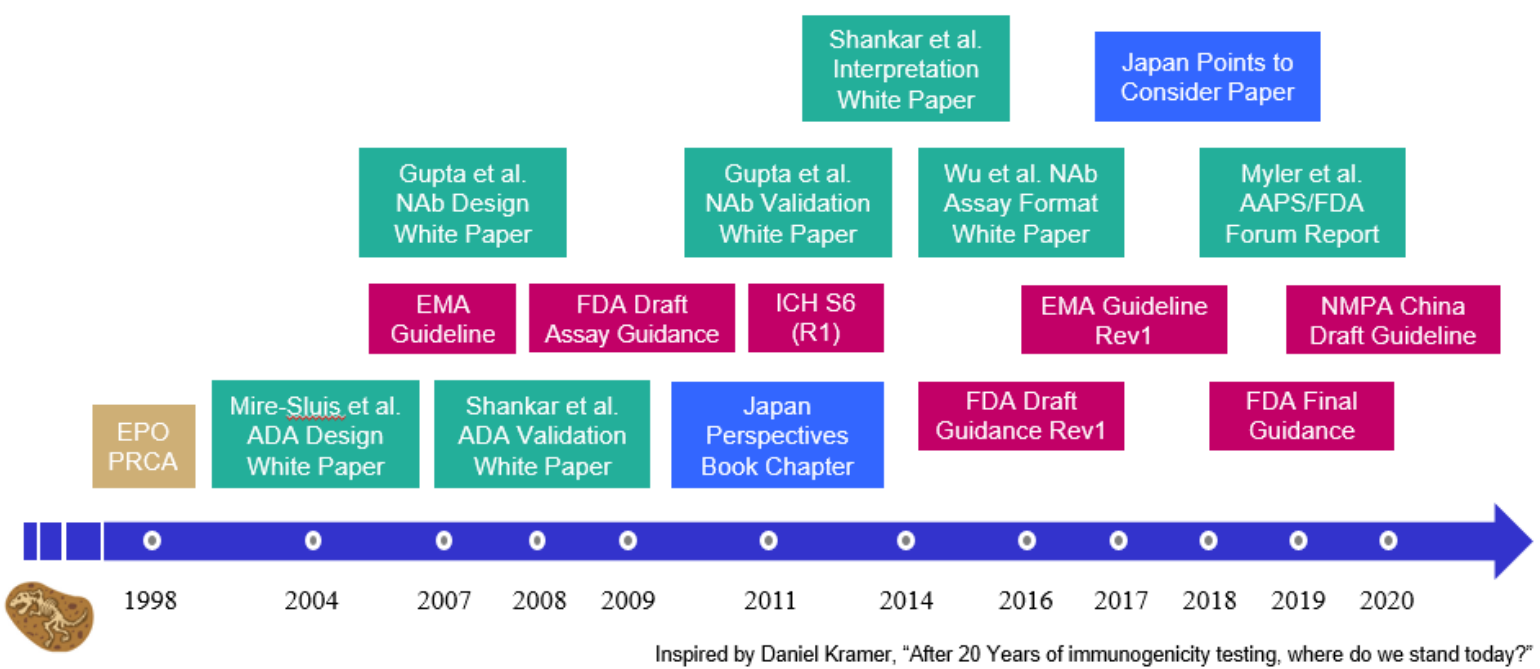
9:00 9:20 ***Jacomijn Dijksterhuis, ICON***
Singlicate analysis applied to pharmacokinetic ligand binding assays: case studies from a CRO perspective

9:20 9:40 ***Issa Jyamubandi, Resolian***
A generic singlicate immunogenicity method to detect anti-PEG antibodies: Pre and post dose of pegylated therapies

9:40 10:00 ***James Lawrence, Invox Pharma***
It's all relative, an alternative to the cutpoint approach to Pre-clinical immunogenicity assessment

The Immunogenicity Journey and Why We Needed a Focus Workshop?

Looking in the Rear-view Mirror on the Journey Thus Far



EPO: Erythropoietin
PRCA - Pure red-cell aplasia

Inspired by Daniel Kramer, "After 20 Years of immunogenicity testing, where do we stand today?"
EBF Focus Workshop, Lisbon, September 19-20, 2018
https://e-b-f.eu/fw201809-slides/

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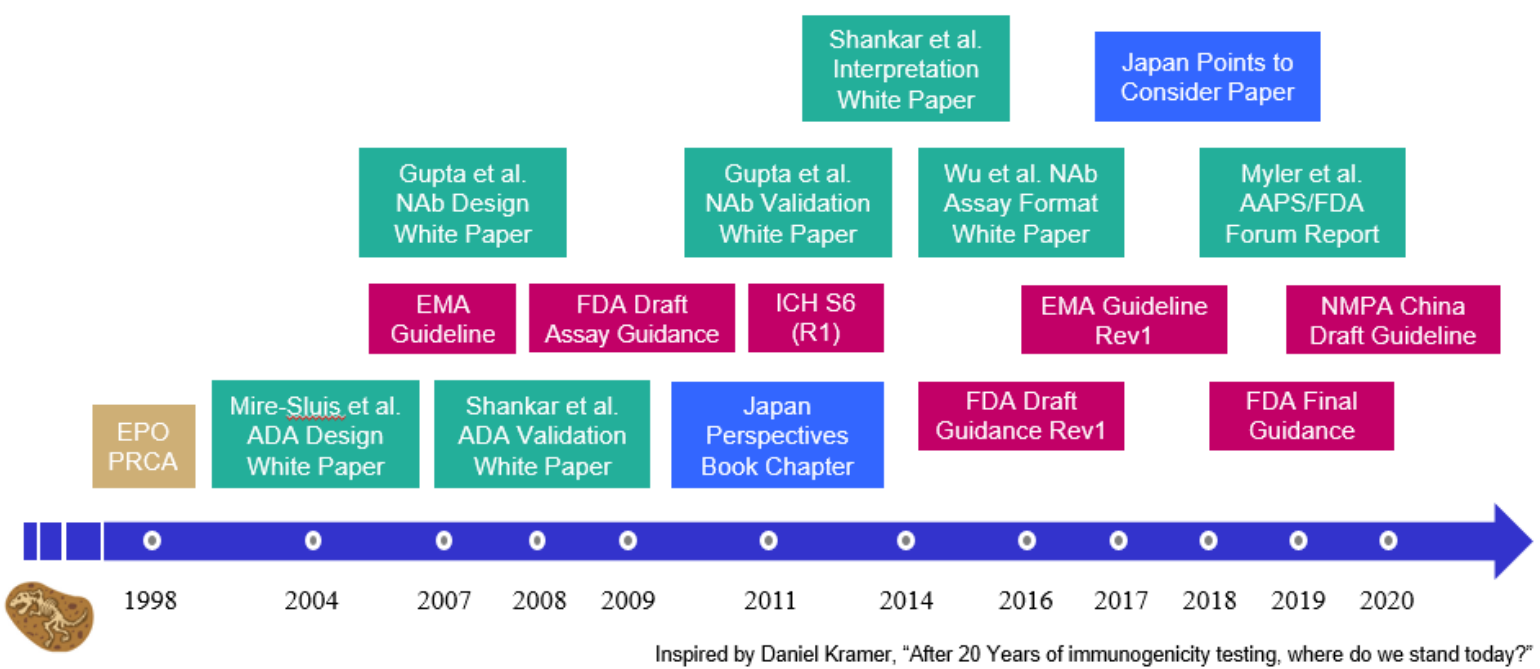

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Looking in the Rear-view Mirror on the Journey Thus Far

Shankar et al. Interpretation

Japan Points to

- After 20+ years much of what we are doing still follows the EPO case
- Guidance was written mainly to deal with these high-risk cases and sensitively detect and characterise responses
- Yet we increased experience and knowledge
- Is the approach still serving patients or is there a better way?

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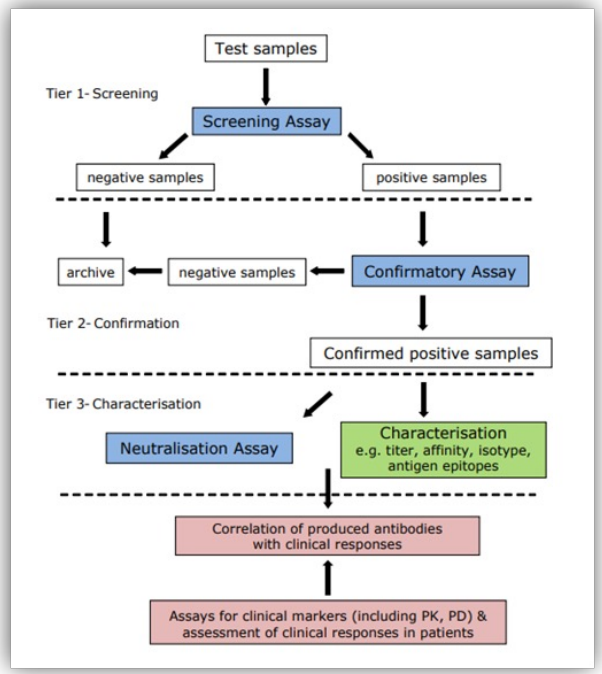
Challenging the Current Paradigm for ADA Testing



- Intended purpose was clinical immunogenicity assessment
- Created when the absence of data necessitated caution

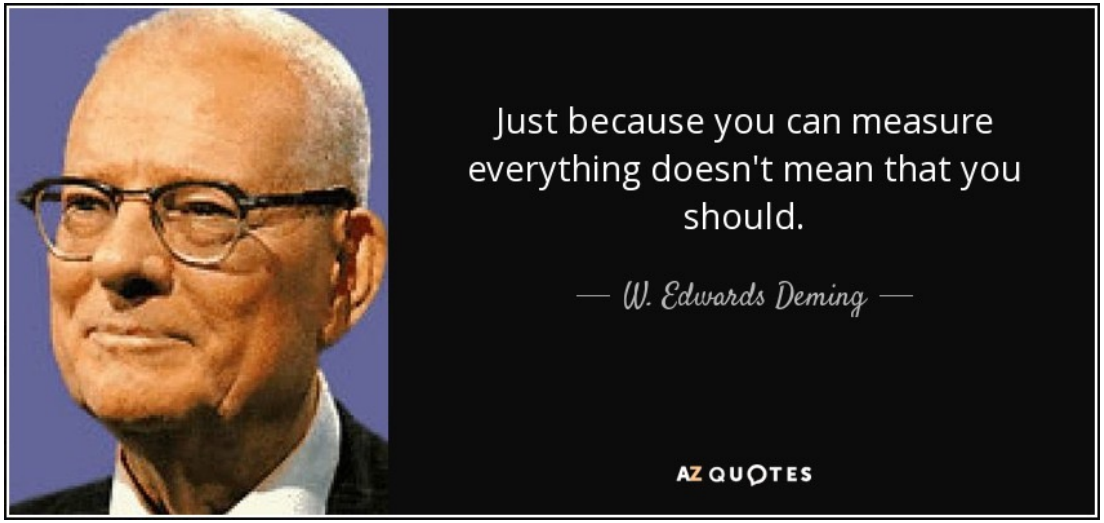
- But now we know that screening, confirmatory and titer tiers are **non-orthogonal assays**
- Human proteins in animals = a likely immune response and **nonclinical responses do not translate to the clinic**
- **3 tiers = heavy burden** on sample volumes and multiple aliquots that need storage (sometimes until HA review)
- **Is this approach still adding value and is it always needed?**

18 May 2017 EMEA/CHMP/BMWP/14327/2006 Rev 1 Committee for Medicinal Products for Human Use (CHMP)

Impact and Cost Should Not be Underestimated

- By applying the “tick box” and the misapplication/over-use of the 3-tiered testing paradigm we have created ….
  - Assays that are **highly sensitive**
  - Low cut points **measuring analytical noise**
  - **Scope creep into non-clinical studies** even in the presence of guidance such as ICH S6(R1)
  - High **incidence** of detection **that does not correlate with clinical impact**
  - **Heavy burden of testing** consuming time, money and resources
  - **Over application of excessive characterisation** (e.g. domain specificity, applying nAb as a default for all programs even when nAb can be detected by other means)
  - **Ultimately not bringing value to patients** or using a patient centric approach

Even a Famous Statistician Once Said ….



- Measuring everything doesn't mean that we pick up more clinically impactful responses or we increase patient safety
- What could we be doing that adds more value rather than using resources just because we can?

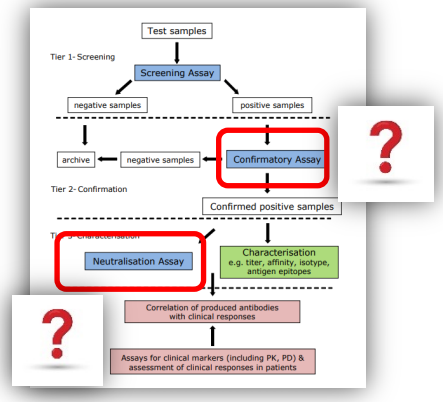
Context of Use (COU) Applies to All Assays!

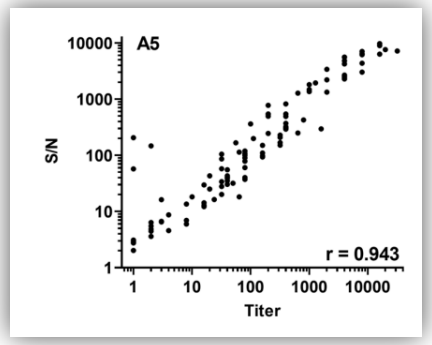
- COU is the purpose of the assays and the decisions being made with the data
  - Right assay to generate the right data for the right decision
  - Understand the ability and the limitations of the assay(s)
  - Use of the data and decisions being made
  - Communication and education of stakeholders

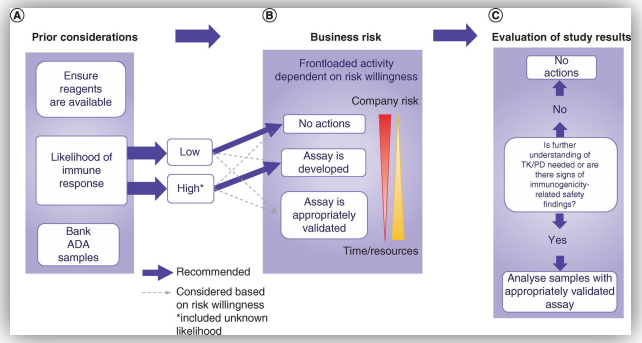
- Familiarity with COU has grown in the biomarker space but it applies to all assays

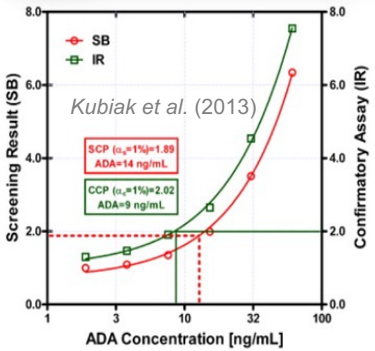
- But in fact, **immunogenicity assays are really biomarker assays**
  - *"A defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or biological responses to exposure or intervention, including therapeutic interventions"*
    - BEST (**B**iomarkers, **E**ndpoint**S**, and other **T**ools) definition

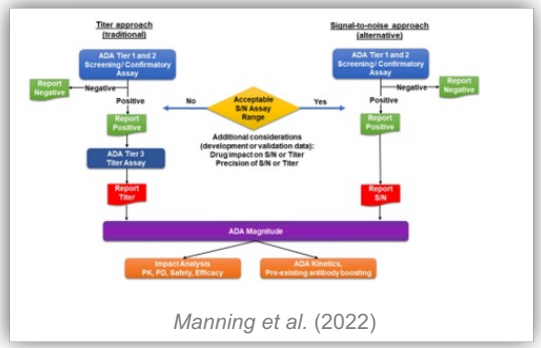
Evolution as Knowledge and Understanding Increases, New Ways of Thinking Emerge

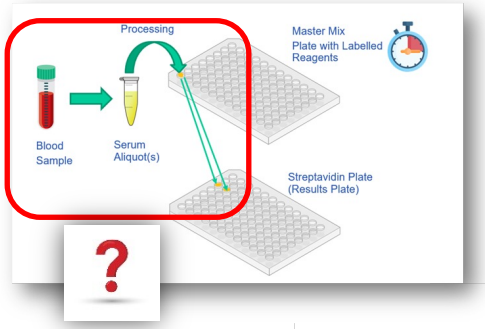




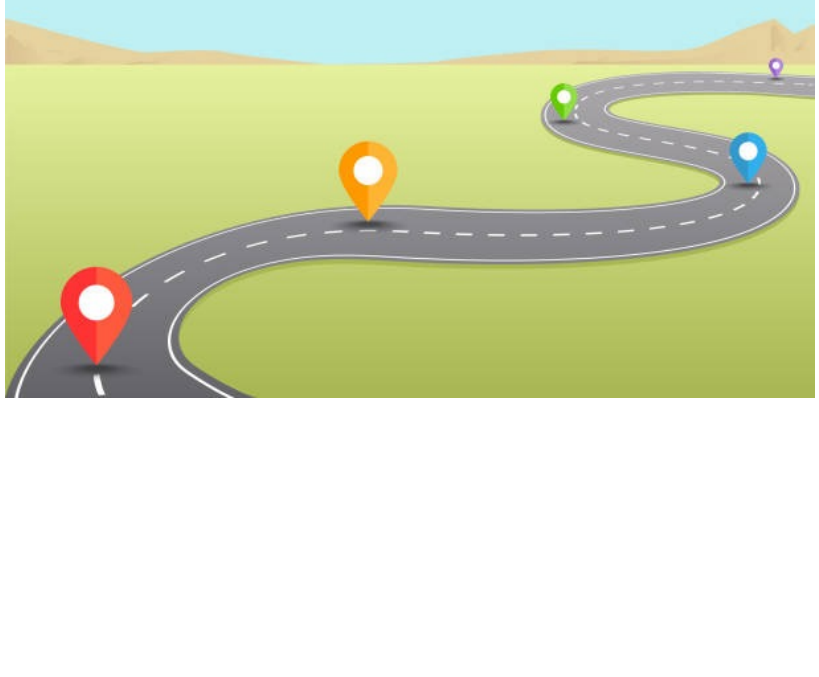








Where Do We Want to Go and What Should be the EBF Recommendations?



EBF Focus Workshop Outputs

- Pharma, biotech, and CROs, plus invited speaker from CDER
- 18 Case Studies showcasing the industry challenging the current paradigm:
  - AstraZeneca, Immunologix, Pfizer, Novartis, Regeneron, Sandoz, Charles River Laboratories, Fresenius Kabi, CheckImmune, Roche, Novo Nordisk, Nuvisan, Sanquin, Ardena, Sanofi, Celerion, BioAgilytix, Labcorp

- Slides from this workshop will be posted on the EBF website
- The recommendations will be published in a paper

Roundtable Discussions to Draft EBF Recommendations

- At the Focus Workshop the following topics were discussed

1. *Tiered paradigm*
2. *S:N as an alternative for titer*
3. *Characterisation (e.g., multi-domain, nAb, etc.)*
4. *Singlicate analysis*
5. *Drug tolerance*
6. *Measurement of placebo samples in clinical testing*

1. Tiered paradigm

a. Do you feel that the confirmatory tier is not serving us well, or do you like this from an operational standpoint?
b. In what cases would you move to a higher FPR (e.g. 1%) and only use screening prior to titre?
c. When do you consider the confirmatory tier is absolutely necessary?
d. What would be the EBF recommendation: ……..

2. S:N as an alternative for titre

a. Are you already applying?
b. What are the blockers or concerns?
c. What would be the EBF recommendation: ……..

3. Characterisation (e.g. multi-domain, nAb etc.)

a. Is it needed in all cases and how are you the data?
b. Does the stage of drug development change your approach?
c. When would you not assess?
d. What would be the EBF recommendation: ……..

4. Regarding singlicate analysis – we perform one sample preparation – are we just testing pipetting?

a. Are you already applying singlicate analysis for ADA, or considering the application of singlicate analysis or against singlicate analysis?
b. What do you see as the benefits and savings for singlicate analysis (e.g., cost, resources, time etc.)?
c. What tiers (or is it all tiers) of analysis do you feel would be most beneficial?
d. Do you see this differently for nAb, if so why, what are the blockers?
e. What would be the EBF recommendation: ……..

5. Drug tolerance

a. What concentrations do you consider to be appropriate (e.g., around relative sensitivity of assay and a few concentrations above, C_{trough} of drug etc.)
b. Which tiers are you performing drug tolerance in?
c. How do we move back to scientific approaches rather than a tick box for drug tolerance requirements
d. What would be the EBF recommendation: ……..

6. Measurement of placebo samples in clinical testing

a. Do you measure placebo samples in clinical trials
b. Does it change based on stage of drug development
c. What would be the EBF recommendation: ……..

Topic 1: Tiered Paradigm – Recommendation Slide

- **Inclusion of confirmatory assessment should be performed based upon risk of test article, rather than being mandatory**
- Justification to omit the confirmatory tier must be data driven:
  - Strong validation; specificity curves, inclusion of disease state matrix assessment
  - Inclusion of confirmatory alongside a 1% FPR screen should be considered for early phase clinical studies
- Omission of the confirmatory assay considered low risk due to recognised stability of ADA (if required assay can be performed at later date)
- Importantly, the omission of confirmatory tier must not jeopardise patient treatment (patient stratification/selection based upon NSB)

Topic 2: S/N as an Alternative for Titer – Recommendation Slide

- Adopt S/N in studies, preclinical and Phase 1, to share and build confidence with stakeholders, and consistently use it
  - There is ‘enough data’ shared and published to justify the approach
- Plan to discuss and justify your approach with health authorities
  - Be prepared to make HA justify why they need you to generate the additional dataset, if you have already provided assessment of incidence and magnitude that correlates PK, PD, and other clinical endpoints
- Keep samples in suitable storage conditions – you can always go back and titer if the health authorities require titer analysis

Topic 3: Characterisation (e.g., multi-domain, nAb, etc.) – Recommendation Slide

- Inclusion of additional characterisation assessments must be linked to a risk-based justification for the study or bring future development benefit and safety for patients
  - Safety and benefit to the patient is paramount when making these decisions

- Alternate, less resource-intensive approaches should be considered and implemented where possible for higher benefit for patients
  - If deemed necessary, consider early development and characterisation of reagents

Topic 4: Singlicate Analysis – Are we just testing pipetting? – Recommendation Slide

- Nowhere in regulatory guidance does it state that a sample must be analysed in more than one replicate
  - Generally, the reality = splitting the sample after an initial singlicate
- Provides operational benefits that does not impact data quality especially when combined with other approaches (S/N etc.)
- Green/sustainability considerations: less sample needed, storage (banked samples), CO_2
- Remember immunogenicity data does not sit alone – integrated interpretation with clinical impact, PK, PD, safety

Topic 5: Drug Tolerance (DT) – Recommendation Slide

- Whenever possible, consider your sampling time points, and choose appropriate drug levels for testing, depending on your study (at risk of not observing the kinetics)
- Ctrough is suggested, not Cmax: What drug tolerance is relevant for your study?
  - Aim for DT at the interested drug levels, considering the PK of the drug
- Assess DT in screening assay only, unless warranted for confirmatory assay (never titer)
- 100 ng/mL only suggested, other levels should be study related – if hyper-sensitive, not necessary to determine at LPC
  - Suggest testing in development, at 250, 500 etc.
  - Notably: DT of PC does not necessarily translate to actual samples – PC is a surrogate and is not representative of samples
  - Test just one DT run in validation, in singlicate
- Talking to the health authorities in advance at early stages

Topic 6: Measurement of Placebo Samples in Clinical Testing – Recommendation Slide

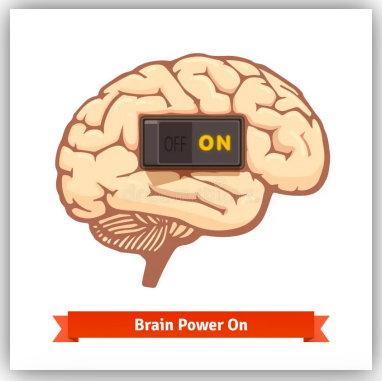
- Do not analyse placebo samples as the default – it does not normally add value (there are always exceptions)
- If you are pressured into analysing placebo samples then it should be done using selected timepoints in early studies, not in Phase 3

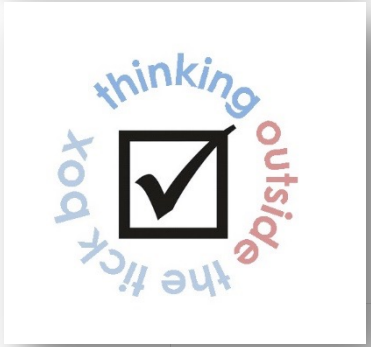
In summary

- Immunogenicity assessment **should not** be a tick box
  - Regulatory guidance lags behind what industry is seeing
  - Guidance takes time and data to change
  - The landscape is ever changing and so are the biotherapeutics being assessed
  - Guidance may not appropriate in all situations

- Immunogenicity evaluations **should** be driven by scientific rationale
  - Be prepared to have a conversation with regulators about your program
  - Not all drug programs are created equal!
  - What adds value rather than what we can do
  - Doing what is right for the patient

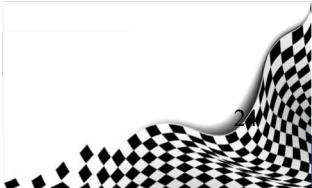
- **<u>If there is no scientific rationale, then it is not science</u>**





Acknowledgements

- EBF ADA Teams
- EBF Steering Committee and Chair
- Focus Workshop Presenters and Delegates



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