Thursday 21-Sep-2023

9:00	**9:10**	**Welcome**
9:10	**11:00**	**Session 1: Setting the Scene - the Current Landscape**
9:10	9:35	*Jo Goodman, on behalf of the EBF* Why this meeting? & Increasing the value of science in ADA testing
9:35	10:00	*Lauren Stevenson, Immunologix Laboratories* A 21st century paradigm: Immunogenicity assays are biomarker assays
10:00	10:25	*Daniel Baltrukonis, Pfizer* All We Need Is Screen; When Confirmatory and Titer Tiers Are Not Necessary in Clinical ADA Assays
10:25	10:45	Q&A
10:45	**11:00**	**Prepare for Session 4: Introduction to the Round Tables** A prepared mind: introduction to and intended deliverable of the themes the afternoon round table questions
11:00	**11:30**	**Coffee break**

EBF

Autumn Focus Workshop

Increasing the Value of Science in Immunogenicity Testing

Jo Goodman, on behalf of EBF

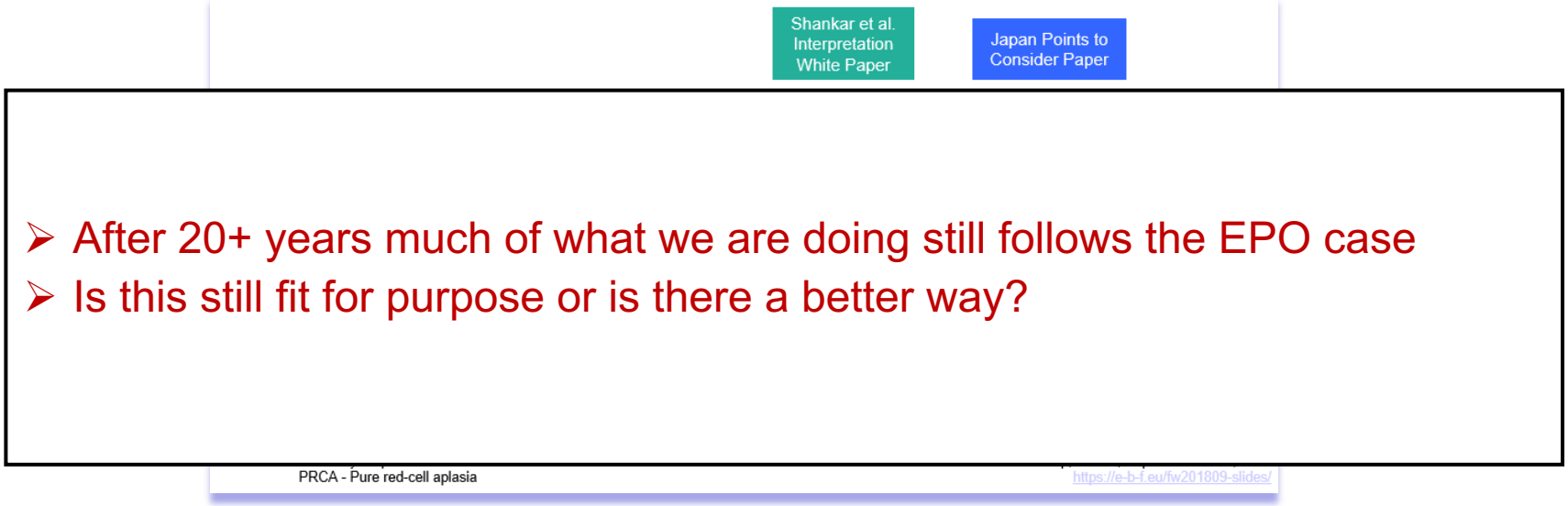
21-22 September 2023 – Malaga, Spain

The immunogenicity journey and why this meeting?

Continuing the past EBF discussions on immunogenicity

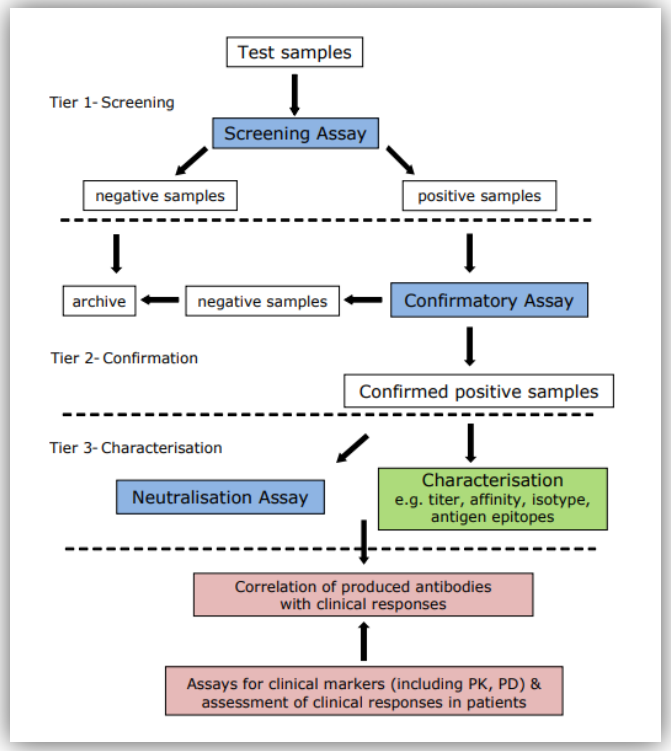
- Previous EBF discussions:
  - "Current analysis of immunogenicity – Best Practices and Regulatory Hurdles", September 27-28, 2016: https://e-b-f.eu/fw201609-slides/
  - FW Paper: https://pubmed.ncbi.nlm.nih.gov/29345496/
  - "Today's challenges and solutions in assessing immunogenicity in patients", 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

How the landscape has ‘evolved’



- After 20+ years much of what we are doing still follows the EPO case
- Is this still fit for purpose or is there a better way?

Regulatory expectations led us to the 3-tiered paradigm



- Intended purpose was clinical immunogenicity assessment
- Approach will depend on risk and stage of development

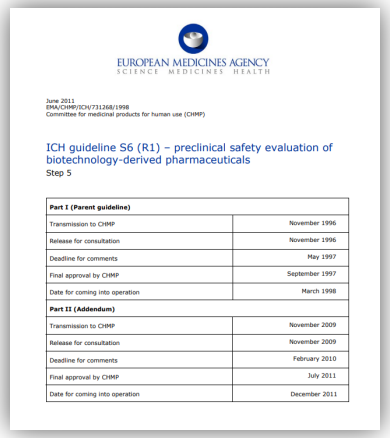
- Screen, confirmatory, titer are non-orthogonal assays
- Yet, 3-tiers often favoured for operational reasons
- Heavy burden on sample volumes and multiple aliquots that need storage
- Is this approach still adding value and is it always needed?

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

Clinical expectations morphed into nonclinical assessments

- Human protein administered in animals = likely immune response
- Know responses do not translate to the clinic!

- Yet many still perform nonclinical assessments
- Often applying clinical expectations
  - 3 tiers
  - Sensitivity
  - Drug tolerance
- Externalisation to CROs and timelines for scheduling may drive this
- Sponsor expectations
- **PK assay is usually the first and most sensitive indicator of ADA**



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

June 2011
EMA/CHMP/ICH/731268/1998
Committee for medicinal products for human use (CHMP)

ICH guideline S6 (R1) – preclinical safety evaluation of biotechnology-derived pharmaceuticals
Step 5

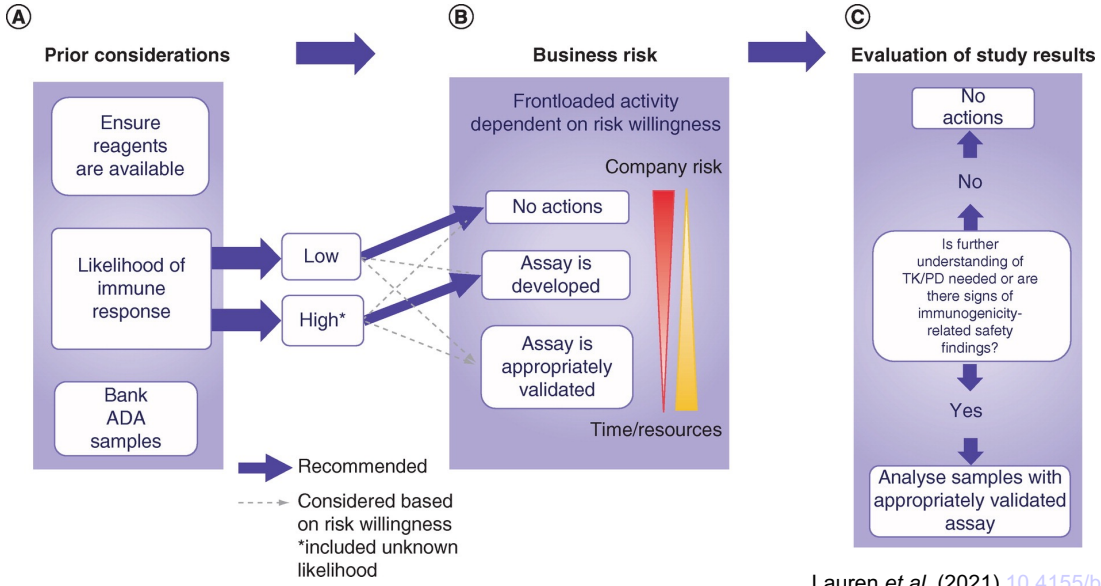
Part I (Parent guideline)	
Transmission to CHMP	November 1996
Release for consultation	November 1996
Deadline for comments	May 1997
Final approval by CHMP	September 1997
Date for coming into operation	March 1998
Part II (Addendum)	
Transmission to CHMP	November 2009
Release for consultation	November 2009
Deadline for comments	February 2010
Final approval by CHMP	July 2011
Date for coming into operation	December 2011

"Such analyses in nonclinical animal studies are not relevant in terms of predicting potential immunogenicity of human or humanized proteins in humans."

Measurement of anti-drug antibodies (ADA) in nonclinical studies should be evaluated when there is

1) evidence of altered PD activity;
2) unexpected changes in exposure in the absence of a PD marker; or
3) evidence of immune-mediated reactions (immune complex disease, vasculitis, anaphylaxis, etc.).

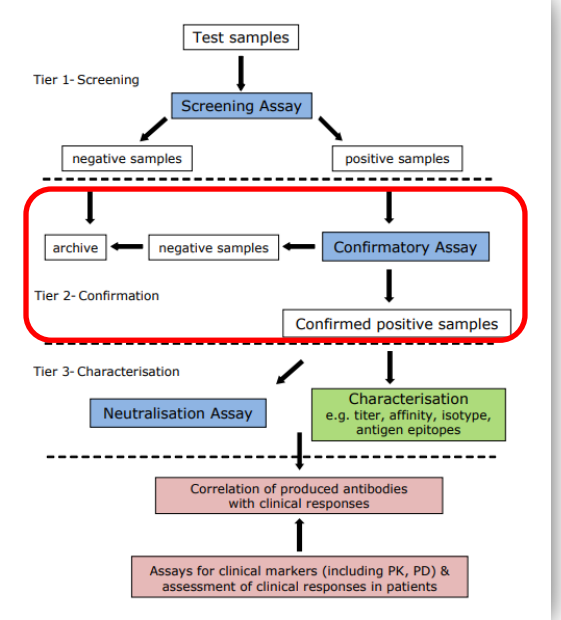
EBF strategic recommendation for nonclinical assessment



Lauren *et al.* (2021) 10.4155/bio-2021-0028

- If nonclinical assessment is performed, then only the screening tier with a false positive rate (FPR) of 1% or 0.1% is enough

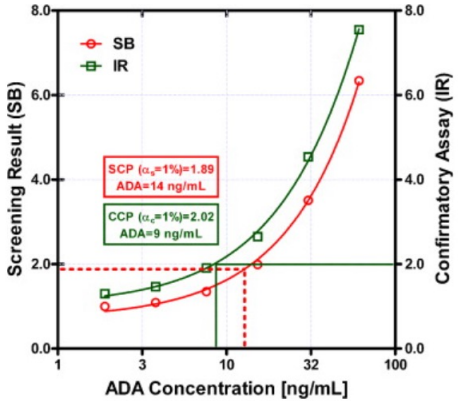
Even in the clinic we may not need 3 tiers



- Confirmatory tier intended to reduce number of false positive results and confirm positive/negative result
- Usually the same assay format, but with the inclusion of drug added in the confirmatory tier
- Often moderate to strong positive correlation between the tiers
- Likely to generate similar results

- Kubiak *et al.* (2013)
  - Screening assay only using 1% FPR

Case studies from Kubiak *et al.* (2013) show statistically positive correlation between 1% and 5% FPR



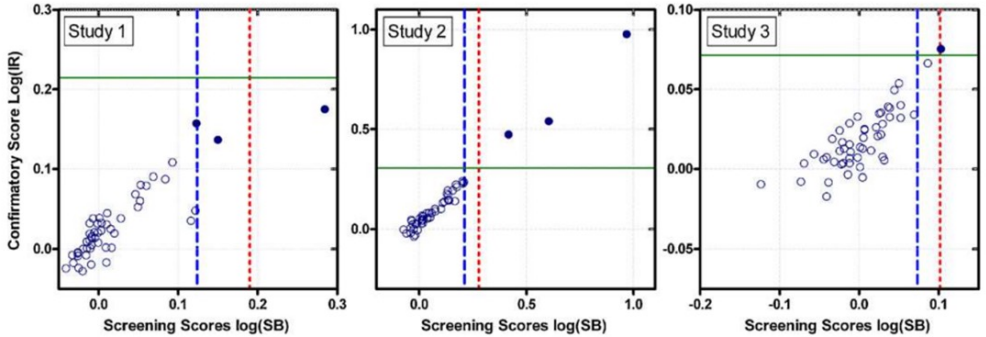


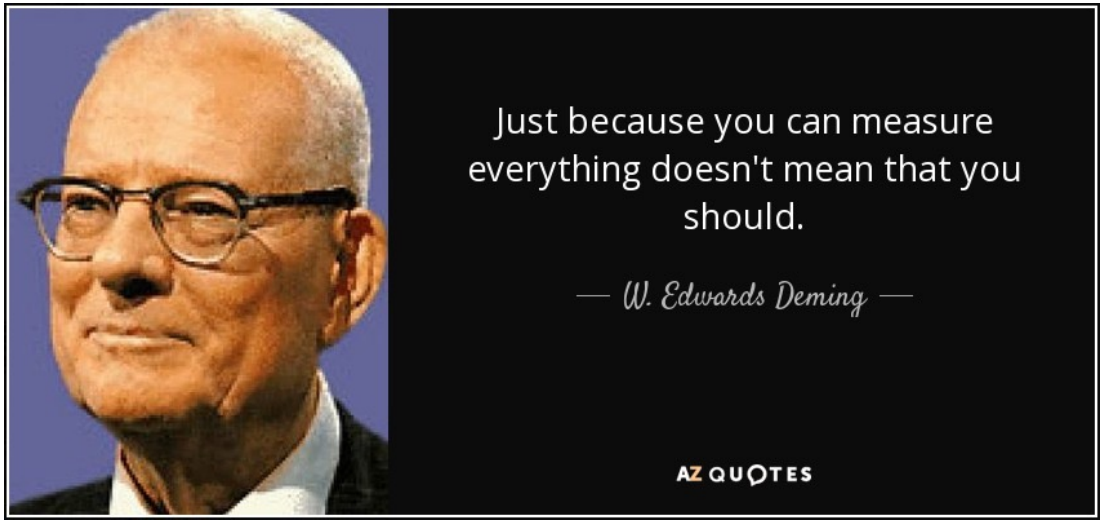
Fig. 1. Correlation between the screening and confirmatory scores. Graphs show average screening and confirmatory scores for 50 drug-naive serum samples measured in validation Studies 1–3. The vertical lines correspond to the screening cut points calculated using false positive rates of 5% (----) and 1% (·····), while the horizontal line marks the confirmatory cut point with the false positive rate of 1% (——). Solid circles (●) represent samples identified as biological outliers in both screening and confirmatory data sets. All cut point values were calculated after exclusion of biological outliers as shown in Table 2.

Balance between sensitivity and drug tolerance

- Technology has improved
  - Improved sensitivity
  - Measuring more low responses which are potentially non-impactful
  - Bringing in more low-level responses may confound or mask the interpretation

- Known that free drug can interfere in an assay
  - Are we overdoing the assessment in validation?
  - Approaches to overcome drug tolerance
    - Often further diluting samples
    - Using harsh treatments which could impact the ability the detect responses

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

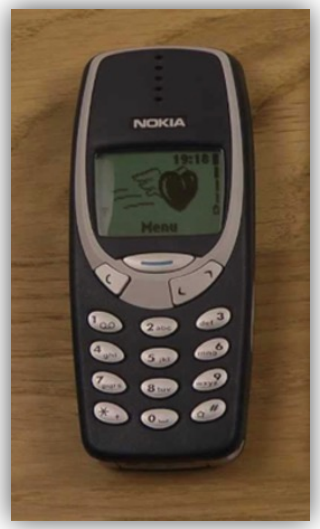
All assays need a context of use, not only biomarker assays!

- **Purpose of the assay and the decisions being made with the data**
  - Understanding the ability and limitation of the assay(s)
  - Use of the data and decisions being made
  - Scientific value
  - Stakeholder management
  - Stage of development (nonclinical, clinical, Ph1 *Vs*. Ph3)
  - Tier of immunogenicity assessment (which assay(s) are appropriate)

- Just because assays are compliant with current regulatory guidance, it may not be good science or guarantee a successful submission
  - New(er) modalities

- Stop to ask
  - What is the question being asked?
  - How data will be used?
  - Will anything change based on data?
  - One size does not fit all

Thinking about the purpose and the outcome

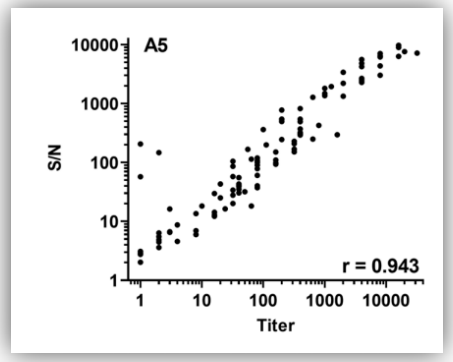


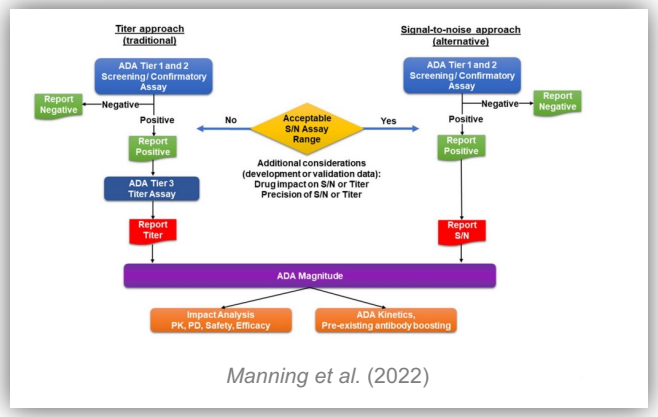
- Sometimes you just need to make a phone call ……

However, innovation can lead to new things and offer ways to think differently

- How can we bring innovation and scientific thinking to add value?
- Our ultimate purpose is bringing safe and efficacious medicines to patients in need
  - By doing things that don't always add value are we really serving them well?
- Companies are expecting faster approvals and smarter ways of working

Re-thinking the titer tier with signal/noise (S/N)





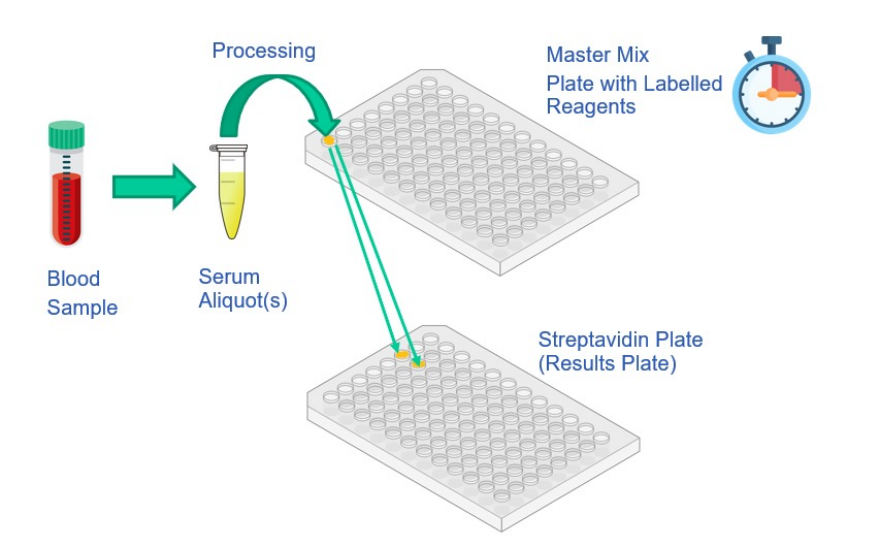
Manning et al. (2022)

- Intended purpose is characterise magnitude of response
- Serial dilution of samples is resource and matrix intensive and shifts equilibrium
- S/N can be a valid alternative

- However, fear of change
  - Physicians used to titer
  - Regulators won't accept S/N
- <u>But remember</u>
  - Assays cannot be compared
  - Incidence between drugs cannot be compared
  - Regulators open to scientific, and data driven approaches
  - Focus on clinical impact

Singlicate analysis for ADA

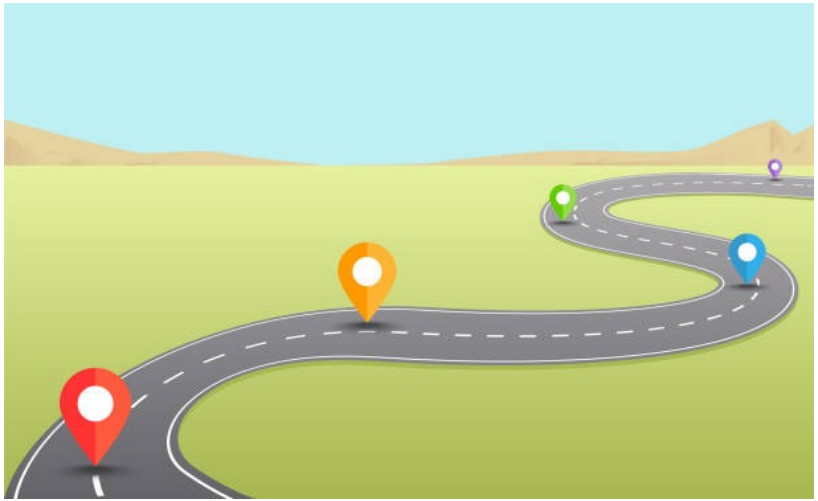
What we do currently ….



- No mention of duplicates as a requirement yet we bring previous PK ways of working into these assays
- We have a constant fear around pipetting skills!
- In a bridging format we usually only have **one well in the master mix plate, yet we split the sample halfway through**

- Benefits:
  - Time
  - Reagents, Plates etc.
  - Patient blood volume

Where do we want to go and what should be the EBF recommendations?

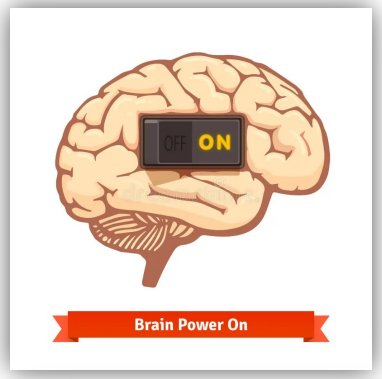


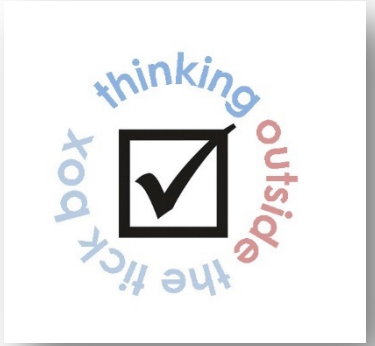
Setting the scene for the workshop and roundtables

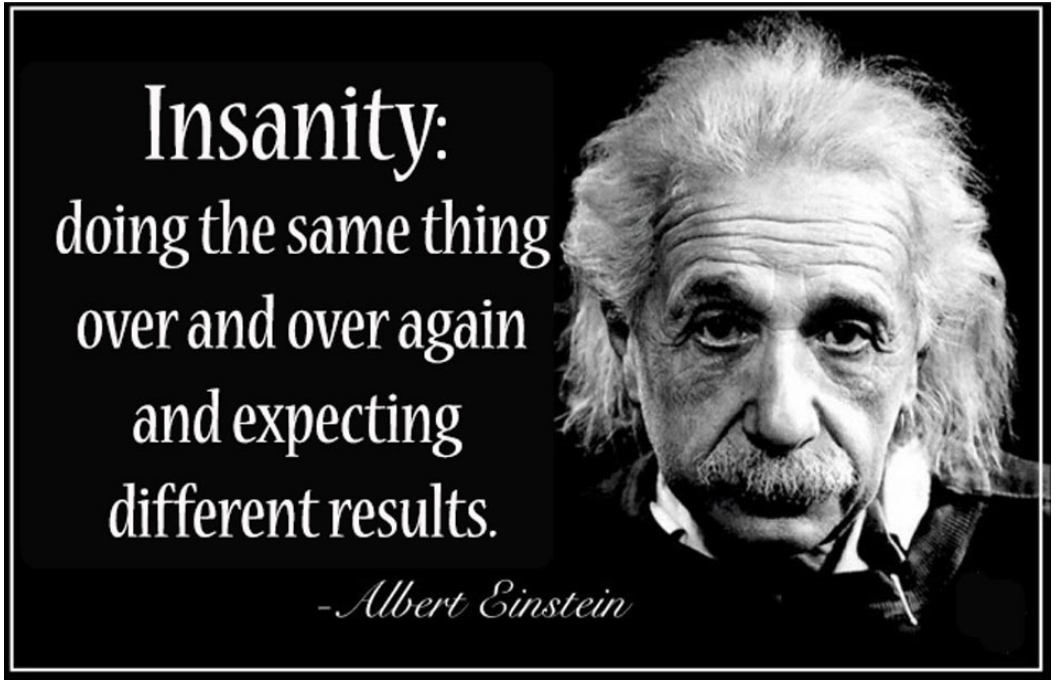
- Immunogenicity assessment **should not** be a tick box
  - Regulatory guidance lags behind what industry is seeing
  - Guidance takes time and data to change
  - The landscape is ever changing and so are the biotherapeutics being assessed
  - Guidance may not appropriate in all situations

- 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>**






Insanity:
doing the same thing
over and over again
and expecting
different results.
-Albert Einstein

Acknowledgements

- EBF community
- EBF ADA team members
- EBF steering committee

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