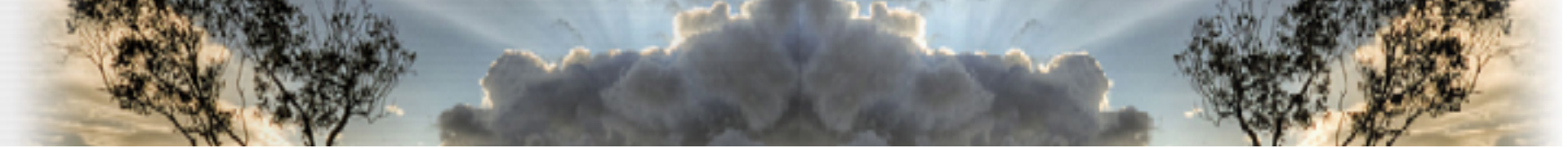
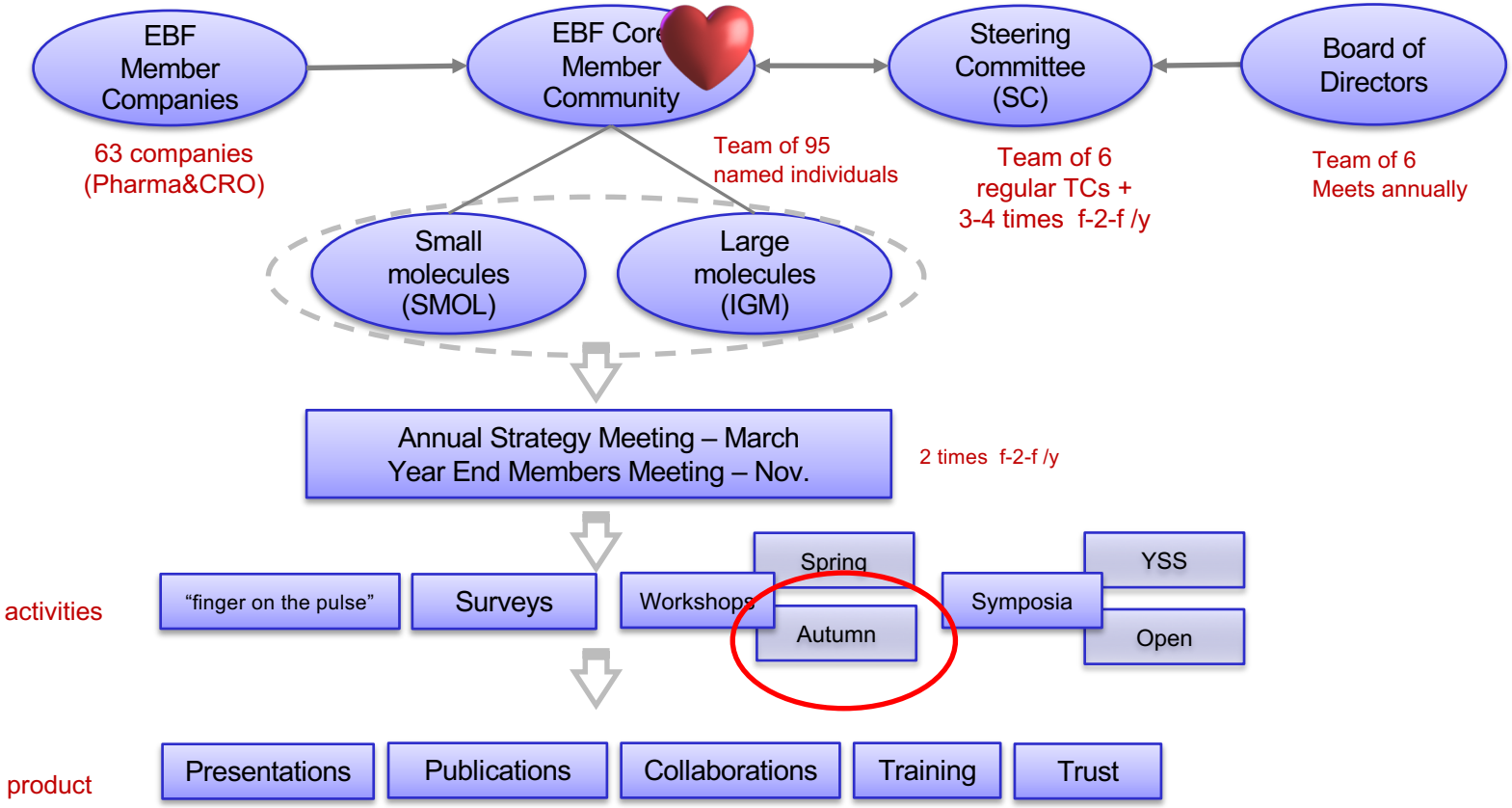


# Feedback from the Autumn Focus Workshop on Immunogenicity

*Jo Goodman, on behalf of the EBF*

**11th EBF Open Symposium**
**Raise the Anchor - Set Sail for Science**
Barcelona - 21-23 November 2018

# EBF Operating Model



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# This autumn, the focus was on immunogenicity


**EBF Autumn Focus Workshop:**

## Today's challenges and solutions in assessing immunogenicity in patients

19-20 September 2018
Altis Grand Hotel, Lisbon, Portugal

**1st ANNOUNCEMENT**

### INTRODUCTION AND AIM OF THE MEETING

We want to dedicate our Autumn Focus Workshop (FW) to the clinical aspects of immunogenicity and correlating what happens in the bioanalytical laboratory with the impact for the patient. Recent regulatory requirements have placed immunogenicity assays under greater scrutiny with more emphasis on assay performance and in-depth characterization of the immune response. Whilst patient safety is always of upmost concern, are we taking the best approach(es)? This FW will discuss current requirements/practices and utilize recent case studies.

# Building on the previous immunogenicity FW discussions

Conference Report

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

Bioanalysis

## Feedback from the European Bioanalysis Forum: focus workshop on current analysis of immunogenicity: best practices and regulatory hurdles

Joanne Goodman[1], Simon Cowen[2], Viswanath Devanarayan[3], David Egging[4], Thomas Emrich[5], Michaela Golob[6], Daniel Kramer[7], Jim McNally[8], James Munday[9], Robert Nelson[10], João A Pedras-Vasconcelos[11], Timo Piironen[12], Denise Sickert[13], Venke Skibeli[14], Marianne Scheel Fjording[15] & Philip Timmerman*,[16]

# The aim of the Focus Workshop

- Clinical aspects of immunogenicity
- Correlation of bioanalytical laboratory activities with the impact for the patient
- Immunogenicity assays are under greater scrutiny with more emphasis on assay performance and in-depth characterization of the immune response
- Whilst patient safety is always of upmost concern, are we taking the best approaches?


3 main areas:

1. Harmonised approaches for immunogenicity method validation
2. Clinical nAb assays and alternative approaches
3. Clinical reporting of immunogenicity and the value for patient and physician

# Harmonised Approaches for Method Validation – The Regulatory Perspective

Program of EBF Focus Workshop "**Today's challenges and solutions in assessing immunogenicity in patients**"

September 19-20, 2018.
Lisbon, Portugal

**19/sep/2018**

| | |
|---|---|
| **08.45 – 09.00** | **Welcome and aim of the meeting** |
| **09:00 – 12.30** | **Harmonized approaches for immunogenicity method validation** |
| 09:00 – 09:25 | Introduction to the session - Overview of current global regulations<br>*Jo Goodman, on behalf of the EBF* |
| 09:25 – 09:50 | Harmonisation of immunogenicity testing : The EU perspective<br>*Meenu Wadhwa (National Institute for Biological Standards and Control)* |
| 09:50 - 10:10 | Case Study: Request for a full tiered approach assay validation for a well-known drug used for a new indication – when clinical experience was not sufficient<br>*Anna Laurén, Wieslab/Eurodiagnostics* |

# Immunogenicity Guidance for Method Validation Session: Key Messages

- Still areas of ambiguity in issued guidance (EMA vs draft FDA)
- On the whole: EMA allows more scientific rationale, FDA is more prescriptive although awaiting final version of FDA guidance
- ICH harmonisation is a far off reality and would usually require 3 regions to have published guidance
- Approach regulators early for advice
- Caution: regional expectations can be different
- Guidance needs to be adaptive based on new data examples – once we learn more and gain new insight then the approach may need to adapt
- Close interaction of industry and regulators needs to continue


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# Harmonised Method Validation Session

| | |
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| **10:10 – 10:50** | **Coffee break & networking** |
| 10:50 – 11:10 | Analytical scientists and the statisticians collaborate to make the right decision for cut-points<br>*Alexandra Hawes, LGC* |
| 11:10 – 11:30 | Practical solutions to outlier decisions, pre-existing and treatment-boosted ADA and low biological variability<br>*Viswanath Devanarayan, Charles River* |
| 11:30 – 11:50 | Experiences with different cut-point approaches in clinical immunogenicity testing<br>*Szilard Kamondi, Roche* |
| 11:50 – 12:30 | Panel discussion<br>*Moderator: Robert Nelson. Panelists: Viswanath Devanarayan, Jo Goodman, Meenu Wadha, FDA representative (approval pending)* |
| **12:30 – 13:40** | **Lunch** |


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# Harmonised Method Validation Session

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|---|---|
| **13:40 – 15:00** | **Harmonized approaches for immunogenicity method validation - cntd** |
| 13:40 – 14:00 | Effect of different approaches on perceived assay sensitivity and drug tolerance – sense and nonsense of positive controls<br>*David Egging, Synthon Biopharmaceuticals BV* |
| 14:00 – 14:20 | Feedback on EBF immunogenicity harmonisation activities<br>*Jo Goodman, on behalf of EBF* |
| 14:20 – 14:40 | AAPS-sponsored ADA Validation Testing and Reporting Harmonization<br>*Meina Liang, on behalf of the AAPS community* |
| 14:40 – 15:00 | Panel discussion<br>*Moderator: Michaela Golob. Panel: Meina Liang, Shobha Purushothama, Jo Goodman, Robert Nelson* |


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# Harmonised Method Validation: Key Messages

- Collaborative relationship between statisticians and bioanalytical scientists
- Statistics for cut point (CP) setting is becoming more accessible
- Low CPF is considered to be <1.2
- If the CP is low, it is not necessarily due to low biological variability or low signal
- Low SCPF does not always result in high in-study false positive rate (FPR) and therefore does not always require in-study CPs
- In-study CPs verses pre-study CPs are only needed when there is demonstrable differences in populations and FPR is outside 2-11%
- Subjective manipulation of outliers is not necessary if robust (Median/MAD) method is used with 1.5 x IQR criteria
- Minimal required dilution (MRD) and titre – ambiguity in the definition (PK perspective) - make sure it is clear in documentation
- Monitoring of PCs, NC is recommended
- Limits of failure rate of LPC – require a range rather than strictly 1%
- Titration assay – SNR for early studies build data from Ph1 and early Ph2 – if adequate correlation can be shown then those data can be used for Ph3


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# Progress in Clinical Neutralising Antibody Assays Session

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| **15:40 – 17:30** | **Progress in Clinical nAb assays** |
| 15:40 – 15:50 | Introduction to the session<br>*James Munday, on behalf of the EBF* |
| 15:50 – 16:10 | Integration of PK-PD-ADA data for assessment of immunogenicity impact<br>*Robert Nelson, Novimmune* |
| 16:10 – 16:30 | Developing neutralising assays – challenging molecules and challenging requirements<br>*Carina de Lemos Rieper, Novo Nordisk* |
| 16:30 – 16:50 | Inferring Neutralising Antibodies – When data integration is appropriate?<br>*Shobha Purushothama, Biogen* |
| 16:50 – 17:30 | Q&A |


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# Progress in Clinical Neutralising Antibody Assays Session: Key Messages

- PK-PD-ADA/nAb integration is key
- For anti-TNFs (natalizumab etc.) where there are data, the need for nAb assays for biosimilars is not needed
- Competitive LBA (CLBA) is becoming more accepted if cell-based assays (CBAs) are not sensitive or drug tolerant enough
- Wish: in the drug label capture only clinically relevant ADA
- Use of Shankar (2014) – harmonised terminology and reporting
- Standalone assays for nAb – for molecules where the impact is on efficacy (not safety) then data driven approaches may be used (PK or PD)
- Molecules in the future may move away from mAbs so tailor the strategy on the risk
- Case study data of fully humanised Abs – is nAb actually needed (should be neutralising by definition)
- 100 ng/mL is based on one paper and all assays are relative to the positive control used, industry will still challenge this (data example presented where a less sensitive was the more FFP assay)
- Relative sensitivity and DT may be potentially challenged – dependent on PC and poor at predicting what a PC will bring for our assays
- Scientific rationale for alternative approaches – approach early regulatory agencies early


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# Clinical Immunogenicity and the Value for the Patient and Physician Session

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|---|---|
| **08:45 – 09:00** | **Introduction to day 2** |
| **09:00 – 12:00** | **Clinical immunogenicity and the value for the patient and physician** |
| 09:00 – 09:20 | Introduction to the session<br>*Michaela Golob, on behalf of the EBF* |
| 09:20 – 09:40 | Clinical relevance of unwanted drug-induced immune responses<br>*Arno Kromminga, BioAgylitix* |
| 09:40 – 10:00 | Considerations of immunogenicity assessment at different clinical phases<br>*Kate Peng, Genentech* |
| 10:00 – 10:20 | Evaluation of clinical impact of immunogenicity and its challenges<br>*Veerle Snoeck, UCB* |
| **10:20 – 11:00** | **Coffee Break & networking** |
| 11:00 – 11:30 | After 20 Years of immunogenicity testing, where do we stand today<br>*Daniel Kramer, Sanofi* |
| 11:30 – 12:00 | Taking the "false" out of ADA testing results: towards better interpretation of clinical relevance<br>*Lorin Roskos, MedImmune* |

# Clinical Immunogenicity and the Value for the Patient and Physician Session

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|---|---|
| **12:00 – 13:15** | **Lunch** |
| **13:15 – 14:30** | **Panel discussion – Clinical immunogenicity and the value for the patient and physician** |
| 13:15 – 13:30 | Introduction to the closing panel discussion<br>*Jo Goodman, on behalf of the EBF* |
| 13:30 – 14:30 | Panel discussion<br>*Moderator: Jo Goodman. Panel: Lorin Roskos, Venke Skibeli (Norwegian Medicines Agency, member of the Biosimilar Medicinal product Working Party (BMWP), Robert Nelson and Daniel Kramer.* |
| **14:30 – 15:00** | **Summary, conclusion and next steps** |
| **15:00 – 16:00** | **Closing Tea break and adjourn** |

# Clinical Immunogenicity and the Value for the Patient and Physician: Key Messages

- Stronger focus on clinical relevance will provide more meaningful data for HAs
- We should be brave and driven by science, rather than blindly following guidance
- Immunogenicity risk assessment driving clinical sampling and testing strategy
- Consider extrinsic factors and their impact on immunogenicity
- We have come a long way since EPO, assays improved, standardisation of terminology, understanding of predictive tools
- There is still a way to go - continue to build mutual understanding and trust with HAs
- A 5% screening false positive rate mandated by FDA Guidance followed by non-orthogonal confirmatory assays contaminates final ADA data sets with false positives, resulting in a low positive predictive value for many ADA assays
- Consider increasing specificity by modifying outlier exclusion practice and reduce FPR if the desired sensitivity and DT can be maintained
- This should lead to removing the confirmatory tier (change in mindset)


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# Summary

- Immunogenicity continues to be a topic of discussion
- Understanding and experience is continuously growing
- Guidance should not be considered as a tick box exercise
- Impact on the patient is of course paramount
- Correlation of PK-PD-ADA data should be considered and the impact assessed with clinical relevance
- Continue collaborative approaches with the HAs and industry
- EBF will continue the strategic discussion

# Acknowledgements


- David Egging
- Michaela Golob
- Anna Laurén
- Sabrina Lory
- James Munday
- Rob Nelson
- Timo Piironen
- Philip Timmerman



Questions