European Bioanalysis Forum

Alternative Approaches for Assessment of Drug Neutralizing Activity of ADA Responses

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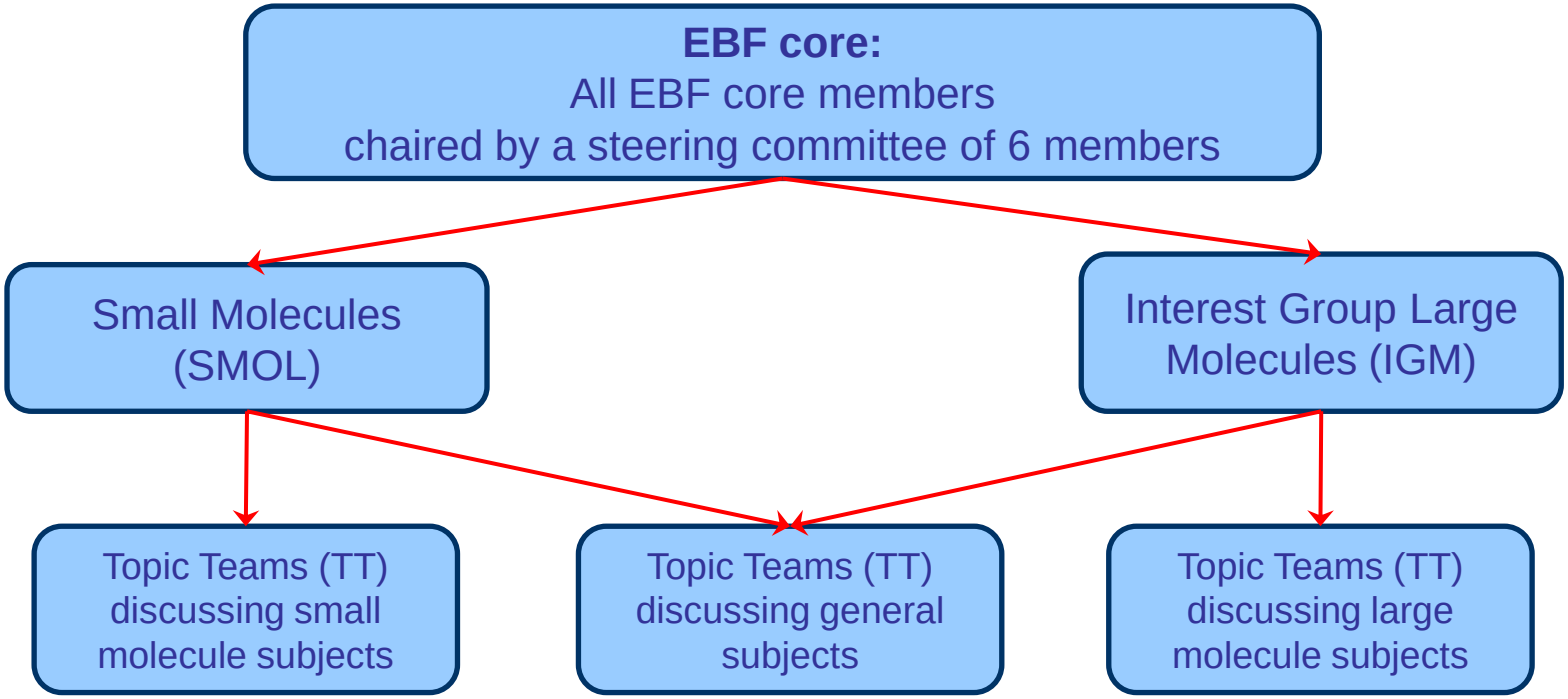
EIP meeting Lisbon
25 February 2014

EBF: who we are, what we do

- EBF: **E**uropean **B**ioanalysis **F**orum
- Founded: 2006 as an initiative of 12 pharmaceutical companies with bioanalytical lab activities in Europe
- The goal of forming our Forum was to create a platform for discussions of science, day-to-day procedures, business tools, technologies and last but not least regulatory issues
- Today, EBF counts >50 company members, or the vast majority of Pharma companies and CRO (global and EU based) with regulated bioanalysis activities in EU

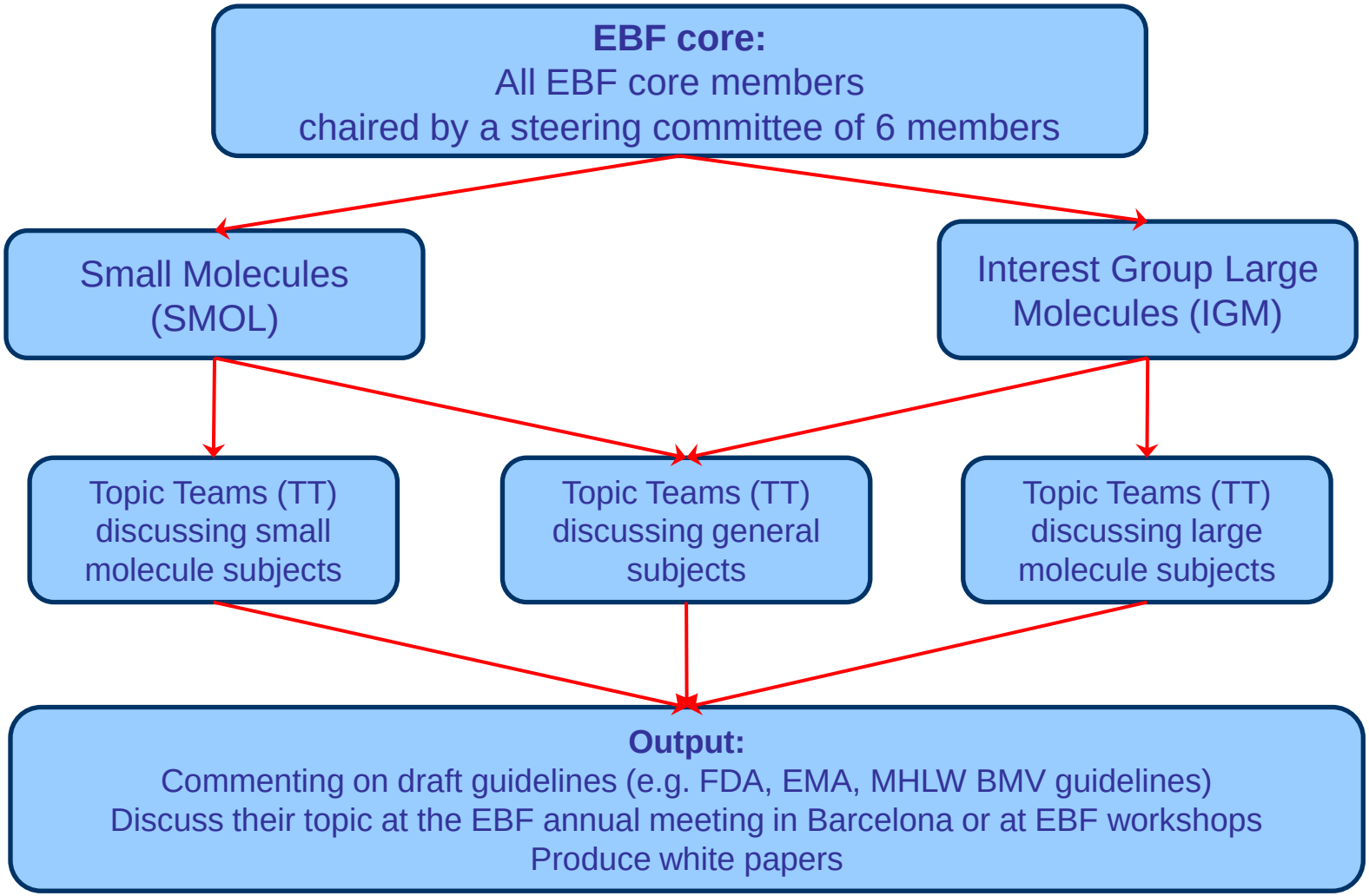
EBF: organization and structure



EBF Mission

- In Topic Teams we share, discuss, optimize and seek alignment on a broad array of bioanalytical topics including science, procedures, business tools and technology, and regulatory issues

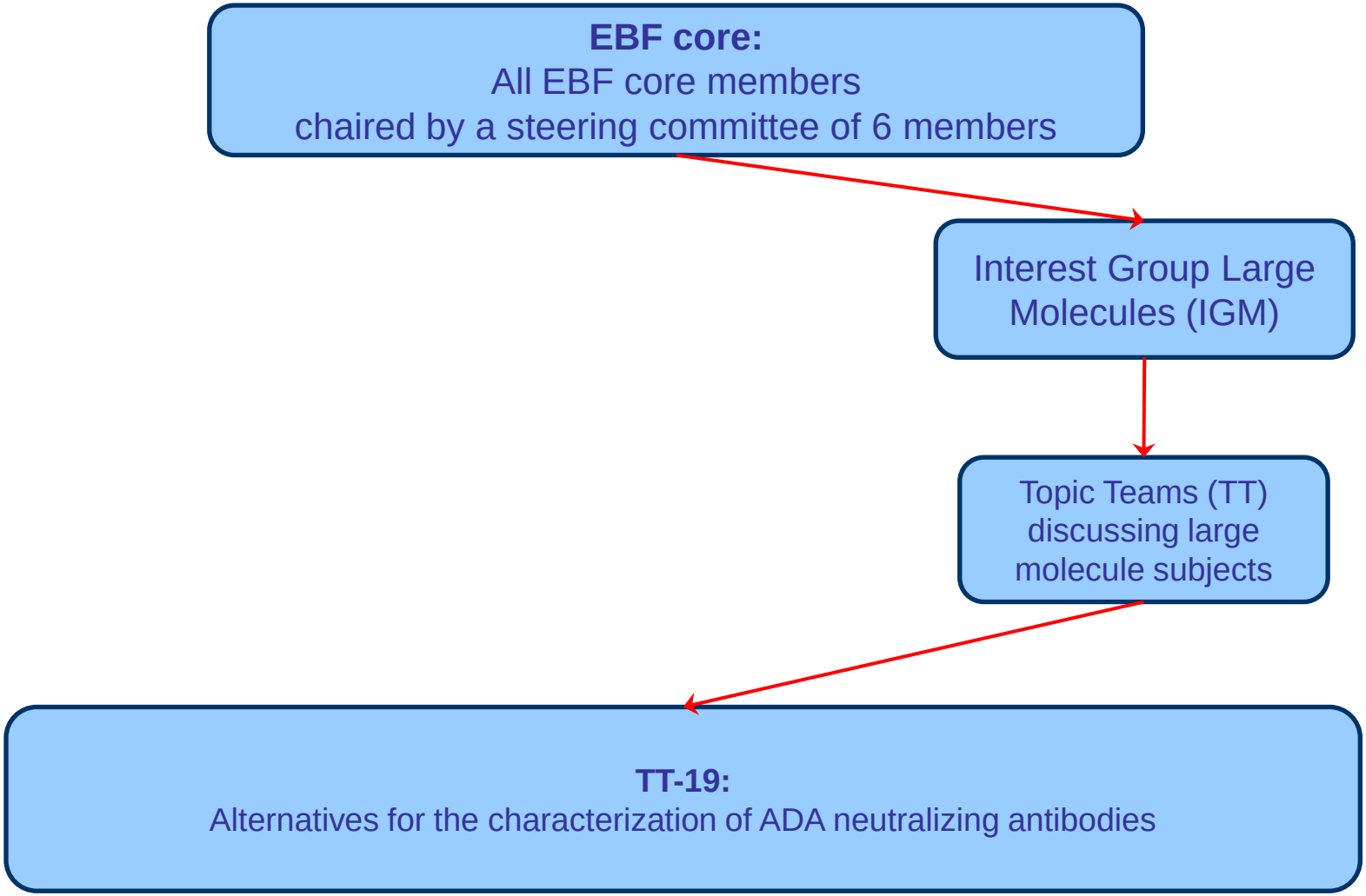
EBF: organization and structure



EBF Mission

- In Topic Teams we share, discuss, optimize and seek alignment on a broad array of bioanalytical topics including science, procedures, business tools and technology, and regulatory issues
- We aim to recommend or influence opinions/procedures towards our members, business partners, regulatory bodies and any other stakeholders
- Going forward, EBF is providing consolidated assistance and recommendations to the European and Global bioanalytical community
- Finally, support development opportunities for EU based scientists by joining cross company collaborations and contributions to peer reviewed journals, international meetings and symposia

EBF Topic Team-19



Assessment of ADA responses:

What do we have to do and what is in the guidelines

- Identification and characterization of ADA responses requires a detailed program during development of therapeutic proteins
- For identification of ADA in clinical studies a screening and confirmatory assay should be in place
- The procedure for characterization of ADA is described in guidelines of FDA and EMA
- The development of a neutralizing Ab assay (NAb-assay) is recommended:

Assessment of ADA responses:

What do we have to do and what is in the guidelines

- EMA guideline on immunogenicity assessment of biotechnology-derived therapeutic proteins:
  - *Neutralization assays*

Assessing the neutralizing capacity of antibodies usually requires the use of bioassays. An assay must be selected or developed which responds well to the biological product. Bioassays used for measuring the potency of biological products e.g. for lot release purposes can often be adapted to assess neutralising antibodies. However, they frequently require refining if they are to perform optimally for measuring the neutralizing capacity of antibodies. If neutralising cell-based assays are not feasible/available, competitive ligand binding assays or other alternatives may be suitable. However, when these are used it must be demonstrated that they reflect neutralizing capacity/potential in an appropriate manner.

- FDA draft guideline for assay development for immunogenicity testing of therapeutic proteins:

Two types of assays have been used to measure neutralizing antibody activity: cell-based biologic assays and non cell-based competitive ligand-binding assays. While competitive ligand-binding assays may be the only alternative in some situations, generally FDA considers that bioassays are more reflective of the in vivo situation and are recommended. Because the cell-based (bioactivity) assays are often based on the potency assay, historically, the format of these assays has been extremely variable. These bioassays are generally based on a cell's ability to respond to the product in question. For NAB assays, the bioassay should be related to product mechanism of action, otherwise the assay will not be informative as to the effect of NAB on clinical results.

Assessment of ADA responses:

What do we have to do and what is in the guidelines

- EMA guideline on immunogenicity assessment of monoclonal antibodies intended for in vivo clinical use:

Antibodies which neutralize the biological activity of biological products may diminish clinical efficacy of the product. It is normally expected that the neutralizing capacity of any antibodies induced will be measured. Any deviations from this need to be justified. For most biological products, the most appropriate neutralizing antibody assay is a bioassay which measures the neutralization of the bioactivity of the product by antibodies. However, the nature of the clinical mode of action of mAbs implies that induced antibodies which block mAb binding to target are those which are mostly associated with reduced clinical efficacy. Therefore, competitive ligand binding assays may be the neutralizing assays of choice for mAbs rather than classic bioassays. This distinguishes mAbs from other classes of biologicals with regard to immunogenicity assessment.

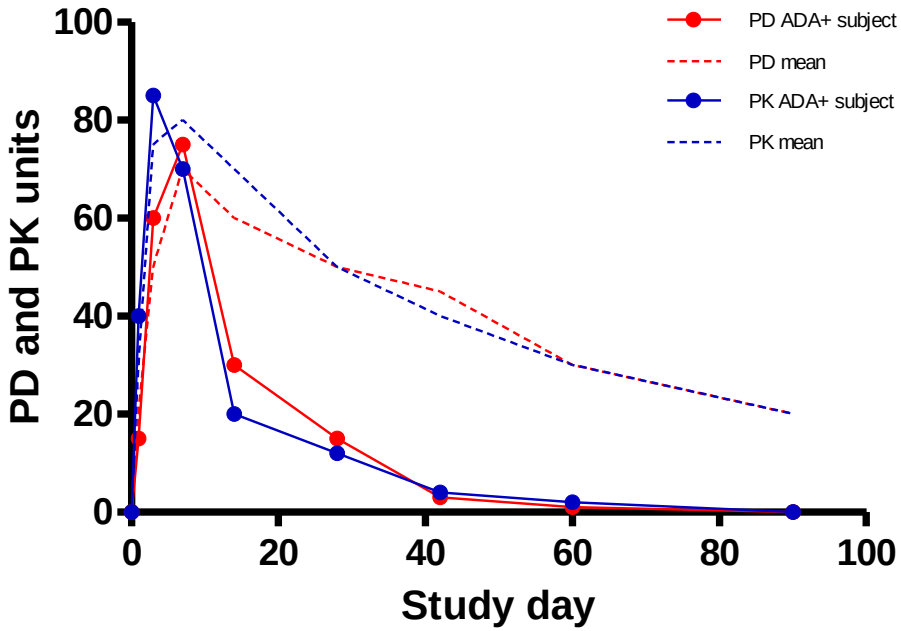
Assessment of ADA responses:

What do we have to do and what is in the guidelines

- *Identification and characterization of ADA responses requires a detailed program during development of therapeutic proteins*
- *For identification of ADA in clinical studies a screening and confirmatory assay should be in place*
- *The procedure for characterization of ADA is described in guidelines of FDA and EMA*
- *The development of a neutralizing Ab assay (NAb-assay) is recommended*
- During this session we would like to discuss alternative approaches for the assessment of NAb activity of ADA

Are there alternative ways to assess ADA NAb responses?

- PK/PD profiles may be used to identify the neutralizing effect of an ADA response



Please note: simulated example

- Can we use PK/PD profile analysis as an alternative to the assessment of NAb activity by means of a NAb-assay?

Are there alternative ways to assess ADA NAb responses?

- To investigate the use of the PK/PD approach at EBF member companies we performed two surveys

- First survey:
  Insight into approach of ADA NAb assessment by different EBF pharma companies developing biotherapeutics

- Second survey:
  More specific on PK/PD analysis in HAHA positive subjects and comparison with NAb assessment (MAb products)

Approach of ADA NAb assessment by different EBF pharma companies

- First survey: out of the then ~37 EBF-IGM companies, 10 (i.e. 27%) answered the survey questions
- All companies start ADA assessments already during pre-clinical phase
- “Low-risk” protein: some companies perform NAb-assays in Phase-II while others start to develop those by Phase-III
- “High-risk” protein: all companies perform NAb-assays during all phases and during pre-clinical on case-by-case basis
- Some companies have a strategy in place and some do a case-by-case decision which depends on the drug, extent of the immune response and adverse events
- All companies investigate PK/PD profiles of ADA^+ subjects and compare these with ADA^- subjects. Implementation of cellular or competitive ligand binding assay is a case-by-case decision

The case of the “high” and “low” risk molecules

- With “high” and “low” risk we do not mean overall risk but only in respect of effect of anti-drug NAb-responses

- Risk analysis determines the molecule to be of „high risk“:
  - Consequence of a neutralizing ADA response:
    - Impaired efficacy
    - Impact on safety (neutralization of the endogenous counterpart(s))
  - Required actions:
    - PK/PD read-out
    - NAb-assays to detect neutralizing antibodies against:
      -- the drug,
      -- the endogenous counterpart
      -- and if nessessary against endogenous protein very similar to drug

The case of the “high” and “low” risk molecules

- With “high” and “low” risk we do not mean overall risk but only in respect of effect of anti-drug NAb-responses

- Risk analysis determines the molecule to be of „low risk“:
  - Main consequence of neutralizing ADA response:
    - Impaired efficacy
    - No direct impact on safety
  - Loss of efficacy might be self evident through low patient response and a PD read-out may be considered the most biologically relevant neutralizing assay
  - If this is not feasible, the use of target binding inhibition assays (competitive ligand binding assays) for antagonistic MAb drugs and the use of cellular assays for agonistic MAb drugs are recommended

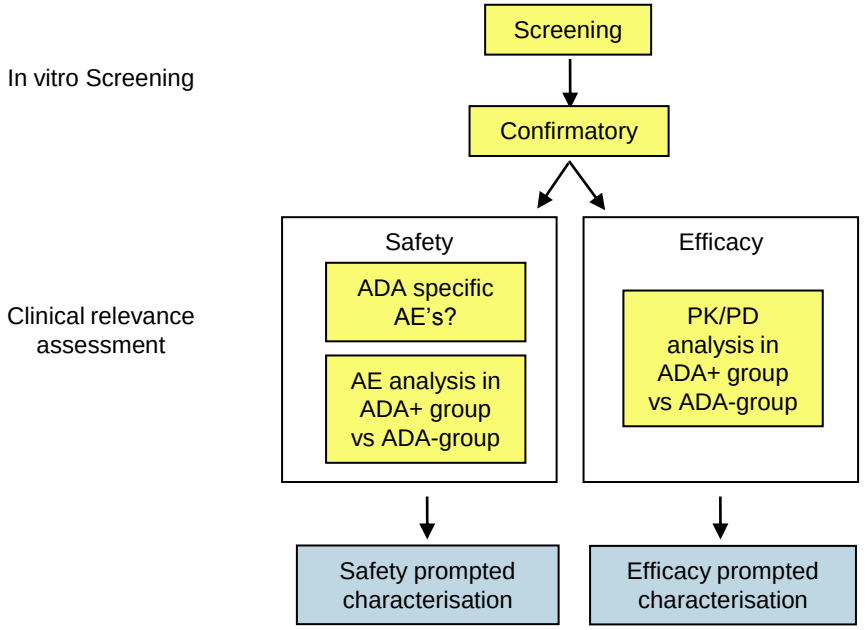
- Focus of second survey: MAb-drugs (i.e. HAHA responses)

Approach of HAHA NAb assessment by different EBF pharma companies

- Second survey: Focus on MAb-drugs (i.e. HAHA responses)
- 15 pharma/CRO companies of the EBF-IGM companies answered the questions (compared to the 1st survey EBF was enlarged and now included CRO as well)
- 60% perform assessment of PK/PD profiles (even when there is a NAb-assay in place)
- Comparison of PK/PD profiles of $HAHA^+$ vs. $HAHA^-$ subjects was done by 40% of the companies
- In most of the studies NAb-data correlate with the PK/PD data
- For 43% of the companies NAb-assays were not sensitive enough to detect NAb-activity of HAHA

Points for discussion

- PD assays are usually more sensitive than NAb-assays and as a consequence better for analysis of neutralizing ADA responses
- A decrease in PK/PD levels in ADA^{+} subjects imply occurrence of NAb
- Safety markers should be included when replacing NAb-assays by PK and PD markers



Points for discussion

- PD assays are usually more sensitive than NAb-assays and as a consequence better for analysis of neutralizing ADA responses
- A decrease in PK/PD levels in ADA^+ subjects imply occurrence of NAb
- Safety markers should be included when replacing NAb-assays by PK and PD markers
- NAb-assays are not sensitive enough and are prone to drug interference
- Do we agree that for low risk molecules PK/PD assessment is enough?
- How should we discriminate “low” from “high” risk molecules?
- What kind of PD assay could replace NAb-assays?
- What do the regulators expect from us and what are our experiences?

Acknowledgements

- EBF TT-19 team:
  - Inge Dreher (AbbVie)
  - Martin Nemansky (PRA)
  - Craig Stovold (Quotient Bio Analytical Sciences)
  - Denise Sickert (Novartis)
  - Yvonne Katterle (Bayer Pharma AG)
  - Edwin Janssen (Eurofins)
  - Margarete Brudny-Klöppel (Bayer Pharma AG and sponsor)

- All EBF-IGM members involved in the discussion