A Chinese NMPA draft technical guideline on immunogenicity of therapeutic agents: similarities and differences to existing EMA and FDA Guidelines or a new global challenge for harmonisation?

Tobias Haslberger, on behalf of the EBF
Current Regional Guidelines/Guidances on Immunogenicity Assessment

- Immunogenicity Assessment of Therapeutic Proteins – EMA 2017
A Draft Technical Guideline on Immunogenicity of Therapeutic Agents

Issued by the National Medical Products Administration (NMPA) on 24 August 2020
Goal of This Presentation

- Raise awareness in the BA community of a new immunogenicity guideline on our horizon
- Impact/Challenge for us as an Industry

- Share EBF perspective on this draft guideline
- Elaborating on ambiguities, concerns and similarities/differences to existing guidelines
How to Manage the Challenges as a Global BA Community – Timing & Translation

- **Timing**: published end Aug; EBF became aware mid Sep
- **Translation**: no official english translation available, rely on individual translations

**Ideally**

- FDA
- EMA
  - by NMPA
  - **Chinese version**
  - by NMPA
  - **English version**

**Reality**

- FDA
- EMA
  - by NMPA
  - **Chinese version**
  - Multiple **English versions** (01, 02, 03)
Similarities Between FDA/EMA Guidelines and NMPA Draft Guideline Draft

- NMPA draft is certainly not a completely new guideline!
- NMPA draft has sections that are taken 1:1 from FDA and/or EMA
- Key elements are in: IRA, limited predictive value of non-clinical results on clinical immunogenicity, multi-tiered approach, detailed information on key assay elements (e.g. PC and NC) and individual validation parameters

But ...
... there is ambiguity and concerns
EBF Survey on NMPA Draft Guideline

- Translated document was divided into 65 paragraphs
- Asked EBF community to highlight areas of
  - Ambiguity
  - Concerns
  - Differences/Contradictions to existing (EMA/FDA/ICH/S6) guidelines

- Could only allow for short time period (10 days) for providing feedback
Some Survey Statistics

- Being mindful of (i) short review timeline and (ii) not each company running business in China
- 11 responses (10 Pharma, 1 CRO), total of 175 comments
NMPA Draft Guideline: Ambiguities
NMPA Draft Guideline: Ambiguities at a Glance

- Whole sentences/chapters are **difficult to read/understand**
  - Translation issue: English → chinese → english
  - Lack of consistent use of one word for “drug” throughout the doc (drug vs antigen vs therapeutic agent vs product)
  - Some sections were taken only partially 1:1 from EMA/FDA, thereby generating risk of putting things out of context, e.g.
    - (i) single-assay concept for Biosimilars is not mentioned at all or (ii) ambiguity on how to deal with manufacturing changes

- Document could benefit from **better structuring/differentiating** dedicated sections:
  - section on risk-factors (product-/study-/patient-specific)
  - sections on consequences of unwanted immunogenicity (PK/PD/efficacy/safety)
  - ISI/IRA only briefly mentioned and might need more guidance/details
  - Text jumps from topic to topic, e.g. describe potential add. validation for Biosimilar assays in one sentence, describing SPR and the need to check surface stability after chip regeneration in the next sentence

- Consider elaborating more/better on **assay limitations**:
  - Positive control (PC) is a surrogate and not fully reflective of the study population → suggest removing the statement "Ideally, the PC antibody reflects the anticipated immune response that will occur in humans".
  - ADA assays are non-quantitative: consider to avoid using words like “STD curve” or “assessment of Ab content”
FDA/EMA Guidelines and NMPA Draft Guideline: Concerns/Differences
Scope: Emphasis on Clinical AND Non-Clinical Immunogenicity Assessment

“Therapeutic proteins show species differences in most cases, and there are limitations in predicting human immunogenicity based on animal immunogenicity studies.”

“...immunogenicity studies are always an important part of the chain evidence for non-clinical safety studies of therapeutic protein drugs.”

→ Seems to be not well aligned with principles of ICH S6(R1):

Immunogenicity assessments are conducted to assist in the interpretation of the study results and design of subsequent studies. Measurement of anti-drug antibodies (ADA) in non-clinical 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.).
Non-Clinical Immunogenicity Assessment

**Concern:** clear differentiation is obviously missing on WHAT is required WHEN for non-clinical vs clinical immunogenicity assessment. Also, leaner approaches for non-clinical assays are not discussed, like e.g. running only a screening assay, using a 1% FPR.

**Differences:**

- NMPA draft is the first guideline that is specific/prescriptive on how to assess some (but not all) validation parameters for non-clinical assays, e.g.:
  - CP: at least 15 individual samples, at least 2 variables, run 3 batches, at least 3 days
  - Precision: at least 2 variables
  - LPC determination: 1.5-2x NQC or CP
  - Sensitivity: 250-500 ng/mL (Mire-Sluis: 500-1000 ng/mL)

- NMPA draft is the first immunogenicity guideline expecting/explicitly mentioning *in vitro* cytokine release tests in addition to *in vivo* animal cytokine measurements for immune-related adverse reactions as part of a full non-clinical data package.
  - Better placed in a tox guideline?
Consolidated EBF Feedback on Concerns & Differences: Multi-Tier Assays

<table>
<thead>
<tr>
<th>Screening Assay</th>
<th>Confirmatory Assay</th>
<th>Titer Assay</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detect rapidly dissociating ADAs</td>
<td>“Confirmatory assays are expected for confirming the positive results and eliminating any false positive results…”</td>
<td>Different definition of titer:</td>
</tr>
<tr>
<td>→ challenging/impossible based on availability of key reagents like e.g. low affinity IgM</td>
<td>→ A confirmatory will not eliminate FP as the CCP is typically set to provide a 1% FPR</td>
<td>NMPA: maximal dilution where a sample gives a value above the CP</td>
</tr>
<tr>
<td>Carry out screening and confirmatory cut point determination on the same plate</td>
<td></td>
<td>FDA/EMA: reciprocal of the highest dilution that gives a value at/above the CP</td>
</tr>
<tr>
<td>Analysis strategy in duplicates, w/o providing any rationale</td>
<td></td>
<td>Titer Cut Point concept is missing: Consider 99.9% TCP to facilitate titer determination in case SCP falls on the lower plateau of the positive control dilution curve.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Good description of concepts to differentiate titers is missing (e.g. minimum significant ratio)</td>
</tr>
</tbody>
</table>
Need for Additional Characterization of Positive Anti-Drug Antibody Responses

- Consider mentioning that potential characterization (e.g. isotyping, domain specificity, neutralization activity) of ADA responses should occur based on:
  - Overall risk assessment
  - Stage of drug development

- Neutralization Assay:
  - Provide a clear statement, as early as possible in the document, that NAb assays are not required for non-clinical and early clinical phases when (i) risk is low and (ii) appropriate PK/PD assays are in place and indicative for the presence of NAbs
  - Mention that NAb assays may not achieve the sensitivity of an ADA assay
  - Provide more details on when CLBA is sufficient
Consolidated EBF Feedback on Similarities & Differences for Selected Validation Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>EMA/FDA</th>
<th>NMPA</th>
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<tbody>
<tr>
<td>Negative Control</td>
<td>NC should match characteristics of study samples (collected from treatment-naïve subjects, consider disease condition, gender, age, co-medication)</td>
<td></td>
</tr>
<tr>
<td>Positive Control</td>
<td>Human ADAs are preferred, but mentioning „where available (NMPA) or „often not available“ (FDA) (\rightarrow) pAb via animal immunization, mAb Low, mid, high PC for Dev/Val to monitor assay performance; no mid QC for routine sample analysis</td>
<td></td>
</tr>
<tr>
<td>Precision</td>
<td>Not prescriptive on how many/which variables except for days and analysts</td>
<td>non-clinical ≥ 2 variables clinical ≥ 4 variables: day, plate, analyst, instrument</td>
</tr>
<tr>
<td>Selectivity</td>
<td>FDA: spike different amounts of PC antibodies in buffer and matrix and compare ADA recovery</td>
<td>Spike ≥ 10 blank individual matrices with PC samples at 2 concentration levels all blank matrix controls should be &lt; SCP ≥ 80% of the PC samples should be &gt; SCP and meet precision criterion</td>
</tr>
<tr>
<td>Drug Tolerance</td>
<td>FDA: DT in presence of expected drug levels EMA: if DT doesn't exceed drug level, justify</td>
<td>DT has to exceed the drug levels in the sample</td>
</tr>
</tbody>
</table>
Conclusions

- While sharing basic concepts of immunogenicity assessment with EMA/FDA, the NMPA draft has its own flavour and shows differences to EMA/FDA, e.g. emphasis on non-clinical immunogenicity analysis

- Guideline differences …
  - … cause challenges when filing in different regions
  - … result in increased demands on resources/cost/time

- How can we as EBF still share our comments with NMPA in light of having missed the due date for public consultation?
  → via EFPIA?

- **Risk** (of e.g. increasing the non-clinical package for submissions in China) vs **Opportunity** (for harmonization via ICH)?
Acknowledgements

- Joanna Grudzinska-Goebel and Rob Nelson … for bringing this topic into EBF

- EBF community … for giving input on the draft guideline on very short notice
Contact Information

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