Feedback on the Focus Workshop on Current Analysis of Immunogenicity – Lisbon, September 2016

Presenter: Jo Goodman
on behalf of EBF

8th JBF Symposium
8th-9th February 2017
Tokyo

Overview

- Recent EBF activities related to immunogenicity
- Focus Workshop held in Lisbon
- Session summaries
- Focus Workshop output

Two new draft regulatory documents for immunogenicity assay development and validation

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 September 2015
EMEA/CHMP/BMWP/14327/2006 Rev. 1
Committee for Medicinal Products for Human Use (CHMP)

Guideline on Immunogenicity assessment of biotechnology-derived therapeutic proteins

Draft

Draft agreed by Biosimilar Medicinal Products Working Party (BMWP)	August 2015
Adopted by CHMP for release for consultation	24 September 2015
Start of public consultation	01 October 2015
End of consultation (deadline for comments)	31 January 2016

This guideline replaces 'Guideline on Immunogenicity assessment of biotechnology-derived therapeutic proteins' (EMEA/CHMP/BMWP/14327/2006).

Comments should be provided using this template. The completed comments form should be sent to BMWP.secretariat@ema.europa.eu

Keywords	***Immunogenicity, therapeutic proteins, anti-drug antibodies (ADA), assays, assay strategy, binding antibodies, neutralising antibodies, risk factors, safety, efficacy, pharmacokinetics, risk management, integrated summary of immunogenicity***

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Assay Development and Validation for Immunogenicity Testing of Therapeutic Protein Products

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Susan Kirshner at 301-827-1731; (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010; or (CDRH) Office of Communication and Education, 800-638-2041 or 301-796-7100.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

April 2016
Pharmaceutical Quality/CMC
Revision 1

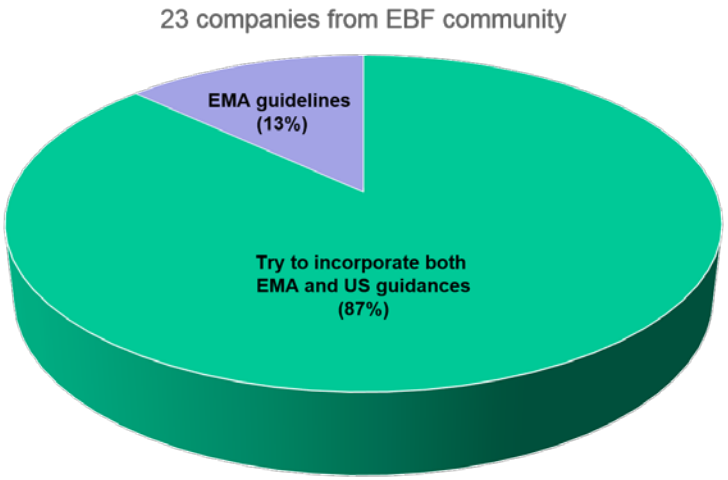
I:\16645dftR1.doc
4/20/16

Main areas of comment on both EMA and FDA draft documents

- Risk assessment
  - Better guidance for determining risk
- Positive controls (PC)
  - Assay sensitivity, source of PC, long-term stability
- Expectations for molecule types other than monoclonal antibodies, therapeutic enzymes and fusion molecules
  - Peptides, ADCs, oligonucleotides etc.
- Specificity
  - Can less be done in earlier stages, e.g. whole molecule specificity rather than individual components?
- nAb assays
  - Better definitions of requirements, can alternative assay formats be used?
- Cut points
  - Different approaches across both documents
- Biosimilars
  - One vs. two assays and harmonisation across documents

EBF – “Finger on the Pulse” survey

- What guidance for immunogenicity do you currently follow for your immunogenicity strategy and assay/validation decisions?



- Any other guideline from other regions to your knowledge?
  - No

EBF – “Finger on the Pulse” survey

- Any experiences in other countries other than EU or US for immunogenicity discussions/data submissions?
  - *“Not aware of any specific immunogenicity guidance for many other regions, but there are biosimilar guidance documents from many regions that cover immunogenicity assessment”*
  - Example of Korean agency requesting nAb assays in pre-clinical studies for a low risk molecule
  - China and Japan request immunogenicity data in their own population and in general follow the EMA guideline. Data can be included in a bioanalysis report.
  - Swiss Medic follows EMA
  - Health Canada working on their own internal document
  - Brazil ask for a separate immunogenicity report

Japan

- Currently no regulation or guideline on immunogenicity published by the Japanese Health authorities

JAPANESE REGULATORY PERSPECTIVE ON IMMUNOGENICITY

TAKAO HAYAKAWA AND AKIKO ISHII-WATABE

Detection and Quantification of Antibodies to Biopharmaceuticals, First Edition. Edited by Michael G. Tovey.

- <u>In preparation:</u>
  Research paper: “Points to Consider for ADA Assays” is in preparation by a research group founded by AMED (Japan Agency for Medical Research and Development)
  - Members are from NIHS, PMDA, pharmaceutical companies and CROs
  - Not a regulatory guideline

Current landscape on Immunogenicity outside of ICH?

- Brazil (ANVISA)
  - Now accepted as an ICH member as of November 2016
  - Currently there is are no regulations or guidelines
  - 2010 Biologics regulation mentions that immunogenicity clinical data need to be presented as part of the marketing licence application, however it does not instruct on how to do it
  - International guidelines (FDA or EMA)
- China (CFDA)
  - Plans to form consensus among industry and research by publishing **a series of "white papers**" which includes immunogenicity
  - After industry consensus is formed, guidance will be planned

EBF Immunogenicity Strategic Workstream:
Focus Workshop in Lisbon, Portugal (Sept. 2016)

Scientific organising committee

- David Egging
- Michaela Golob
- Jo Goodman
  - *EBF Strategic Workstream Leader for Immunogenicity*
- James Munday
- Robert Nelson
- Timo Piironen
- Marianne Scheel Fjording
- Philip Timmerman

http://focus201609.europeanbioanalysisforum.eu/slides-2/

Meeting format consisted of main sessions and panel discussions

- Main Sessions
  - Regulatory
    - Regulatory landscape
    - EBF feedback on the draft EMA and FDA guideline and guidance
  - Challenges of drug tolerance and interferences
  - Alternatives for neutralising antibody (nAb) assessment
  - Cut point setting

- Panel sessions
  - Regulatory and cut point setting
  - Request for questions/burning issues ahead of the meeting

Summary of the immunogenicity regulatory landscape

- Recommendation for an ICH harmonisation guideline
  - However this requires more regions
- Multi-factorial approach to define the molecule risk
  - Endogenous non-redundant counter-part means high risk
  - Peptides needs immunogenicity assessment depending on the risk level and size (FDA)
- Validated assays needed at BLA
  - The assay is not validated until the regulators agree!
  - Crucial to have appropriately stored samples
- Pivotal trial = generally Phase 3
- Mid PC is expected during validation (FDA) yet not in sample analysis
- Long-term stability – trending analysis could be a viable alternative

Summary drug tolerance and target interference

- Importance of addressing these issues as part of the integrated immunogenicity assessment
- Reviewed current assay techniques to overcome issues
- Drug Tolerance
  - Acid dissociation/method - pro/cons discussed
  - Use of dilution to shift equilibrium to free ADA
  - Recommendation for standardised reporting across industry
- Target interference
  - Target depletion/blocking strategies

Summary of alternatives for nAb assessment

- Only a minority of safety issues have been detected due to nAb assay findings
- PK/PD assays can predict the nAb status in some cases
  - Regulatory view PK/PD assays are no alternative (yet) for dedicated nAb assays
  - The validation of the PD assay can be challenging
- Retrospective and prospective analysis is needed to get more data
- In some cases, a single PK assay for the detection of active drug may be enough to detect nAb status
- Competitive Ligand Binding Assays (CLBAs) can be used to replace cell-based nAb assays
- May be beneficial to develop both CLBA and cell-based assay early on
- Risk-based approach should be used (MoA)

EBF

Summary of cut point setting

- Different approaches to setting cut points
  - **Parametric** (mean) and **Robust Parametric** (median) often most appropriate/used
- 5% (average) false positive rate recommended for screening assays
  - Acceptable range of false positives is 2-11%
- FDA discourages to use dynamic cut-point
  - Further investigation is required
  - Most common approach is a floating cut point
- For pre-existing antibodies use a titer approach to verify treatment boosted responses
- In-study cut point is not needed if the trial population is similar to the validation population

Actions from the workshop

- Presentation given at EBF 2016 Open Meeting in Barcelona
- Workshop report
- Recommendation on standardised reporting on drug tolerance and titer
  - Define goal and timelines before end of 2016
  - Collaborate with European Immunogenicity Platform (working group)
- EBF to reflect on training – tutorial if focused on topics (EBF not placed to repeat existing training provided by industry)
- Case study workshop on immunogenicity affecting PK
- Consortium to share data → learning

Acknowledgements

- EBF-IGM members
- Workshop attendees
- EBF contacts in Japan, Brazil and China
- Scientific organising committee

ありがとうございます


Questions

Back up slides

Regulations on immunogenicity in EU

- "Immunogenicity assessment of biotechnology-derived therapeutic proteins"
  (**2008** – EMEA/CHMP/BMWP/14327/2006)
  - currently in revision

- "Immunogenicity assessment of monoclonal antibodies intended for in vivo clinical use
  (**2012** - EMA/CHMP/BMWP/86289/2010)

- Guideline on similar biological medicinal products
  (**2015** - CHMP/437/04 Rev 1)

- Guideline on immunogenicity assessment of biotechnology-derived therapeutic proteins
  (**2015** - EMEA/CHMP/BMWP/14327/2006 Rev 1)

EBF

Regulations on Immunogenicity in US

- “Assay development for immunogenicity testing” (2009 – draft)
- “Immunogenicity assessment for therapeutic protein products” (2014)
- “Scientific considerations in demonstrating biosimilarity to a reference product” (2015)
- Assay development and validation for immunogenicity testing of therapeutic protein products (2016 - draft)