

# **EBF Feedback on EMA and FDA Draft Immunogenicity Guideline/Guidance**

***Presenter: Jo Goodman  
on behalf of EBF***

Immunogenicity Focus Workshop  
27<sup>th</sup> September 2016  
Lisbon

# Overview

- Documents
- EBF process for consultation
- Key themes
  - Focussed sessions throughout the Workshop
- Acknowledgements

# Two new **draft** regulatory documents for Immunogenicity



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

1 24 September 2015  
2 EMEA/CHMP/BMWP/14327/2006 Rev. 1  
3 Committee for Medicinal Products for Human Use (CHMP)  
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6 **Guideline on Immunogenicity assessment of**  
7 **biotechnology-derived therapeutic proteins**  
8 **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

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10 This guideline replaces 'Guideline on Immunogenicity assessment of biotechnology-derived therapeutic  
11 proteins' (EMEA/CHMP/BMWP/14327/2006).  
12 Comments should be provided using this [template](#). The completed comments form should be sent to  
13 [BMWP.secretariat@ema.europa.eu](mailto:BMWP.secretariat@ema.europa.eu)  
14

<b>Keywords</b>	<b><i>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</i></b>
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## 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### *DRAFT GUIDANCE*

This guidance document is being distributed for comment purposes only.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be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance.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

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4/20/16

# EBF process

EBF members informed of draft documents and invited to comment



Expert Group (EG) formed; comments collated and reviewed



EG output reviewed and approved by EBF Steering Committee



Submission to the respective regulatory authority

# EBF Comments received for EMA draft guideline

**EG involved in summarizing EBF comments:**  
Marianne Scheel Fjording (Lead), Birgitte Buur  
Ramussen, James Munday, Jo Goodman

# EBF comments received for FDA draft guidance

**EG involved in summarizing EBF comments :**  
Jo Goodman (Lead), Jonas Blanes, David Egging,  
James Munday, Robert Nelson, Elizabeth Wilson

# Key themes: general comments

## EMA

- Assay requirements/details have been removed in new draft
- Recommend addition of a section on reporting for clinical immunogenicity

## FDA

- Inserting a section on target interference
- Add an integrated assessment of PK, PD and ADA to evaluate neutralising capacity of the immunogenic response. The guidance should provide clear direction on how the risk assessment should translate into ADA/nAb sampling and testing strategy.
- Clarify the use of (purified) ADA compared with positive control antibodies in relation to sensitivity, selectivity and matrix interference
- A medium positive control is not considered informative, and we suggest to omit in the guidance

# Molecule formats

## EMA

- Recommendation that the scope is further defined
- Include what the expectation is for other molecule formats such as ADCs (and DAR species), DNA/RNA, oligonucleotides, gene therapy, chemically synthesised peptides

## FDA

- Include expectation for other molecule formats
- Multiple functional domain molecules; request for further clarity whether specific assays are needed for all components
- Would whole molecule be sufficient in early clinical phases?
- Examples of risk categories for different therapeutics



# Biosimilars

EMA

- ***“Analytical assays should be performed with both the reference and biosimilar molecule in parallel (in a blinded fashion) to measure the immune response against the product that was received by each patient”***
- EBF recommends the use of a single assay

FDA

- ***“When a true comparison of immunogenicity across different therapeutic protein products that have homology is needed, it should be obtained by conducting a head-to-head clinical study using a standardized assay under the same conditions that has equivalent sensitivity and specificity for both therapeutic protein products”***

# Sensitivity

## FDA

- ***“FDA recommends that screening and confirmatory ADA assays achieve a sensitivity of at least 100 nanograms per milliliter (ng/mL)”***
- Positive control is normally a surrogate and defines the sensitivity
- May not reflect the clinical situation
- Too stringent for such assay platforms (e.g. SPR)
- How many cases where patient safety was impacted by a less sensitive assay, i.e. 250-500 ng/mL sensitivity?
- PK assays often more sensitive and will pick up potentially impactful ADA responses

# Positive control (PC)/negative control (NC)

## EMA

- ***“Ideally, an antibody positive control should be a human preparation with a significant antibody content which is available in sufficient quantity for continued use”***
- Virtually impossible in sufficient quantity at the timing required
- Informed consent for further use

## FDA

- Allows use of human derived PC but also makes reference to the lack of availability in early trials
- EBF Recommend no benefit from including a mid PC in validation
- Long-term stability should not be a requirement (Pihl *et al.* (2014))
- % CV criteria too stringent; recommend 25% CV for PCs and 30% CV for NCs

# Drug tolerance (DT)

## EMA

- ***“Applicant has to demonstrate that the drug-tolerance of the assay exceeds the levels of the therapeutic protein in the samples for ADA testing.”***
- Not always possible
- Sampling includes times when drug is cleared
- Recommend that the sponsor should evaluate and define DT relative to their PC

## FDA

- Recommend defining what is acceptable for nAb assays
- What approaches would the Agency find acceptable for overcoming DT?

# Cut points (CPs)

EMA

- ***“A statistical approach should be used to establish the assay cut-off value. Alternatively, real data (e.g. double background value) can be used to determine what will be considered the lowest positive result”***
- Contradicts the expectation of no false negatives

FDA

- Substantial text on in-study CPs, statistics and outliers
- Recommend that sponsors can justify their cut point approach and that the Agency include clarification on whether they would accept non-statistically derived approaches
- In-study cut points EBF recommends not using unless the patient populations differ

# Characterisation/specificity

EMA

- ***“Antibodies present in confirmed positive samples need to be examined for specificity for the active protein and, in relevant cases, distinguished from antibodies which bind to product-related and process-related components (e.g., host cell proteins)”***
- Recommend further clarification for HCP assays and how isolated forms are produced

FDA

- ***“Isotyping and cross-reactivity assay designs should be discussed with FDA”***
- Is this only for endogenous counterparts or is isotyping routinely expected?
- Is a confirmatory assay using endogenous counterpart acceptable for cross-reactivity?

# Neutralising antibodies (nAb)

## EMA

- Recommend to see an integrated PK/PD/ADA approach
- Use of relevant biomarkers in the place of nAb assays

## FDA

- Recommend to see an integrated PK/PD/ADA approach
- More detail around expectations of sensitivity and drug tolerance
- Clear guidance on when LBA is acceptable; if the LBA is more sensitive and drug tolerant, EBF would recommend LBA over CBA

# EMA workshop 9<sup>th</sup> March 2016, London

- Attendees on behalf of EBF:
  - Michaela Golob
  - Jo Goodman
  - James Munday
  - Andy Roberts
  
- 500+ pages of comments received
- Presentations
- Panel Sessions
- Discussions
- Possibility of another workshop once comments fully reviewed
- Full meeting and slides available on EMA website



# Acknowledgements

- EBF members that contributed to the consultation
- EG members for their time, knowledge and fruitful discussions
- EBF Steering Committee