Overview of current global regulations and challenges for industry

Jo Goodman
on behalf of the EBF

EBF Autumn Focus Workshop

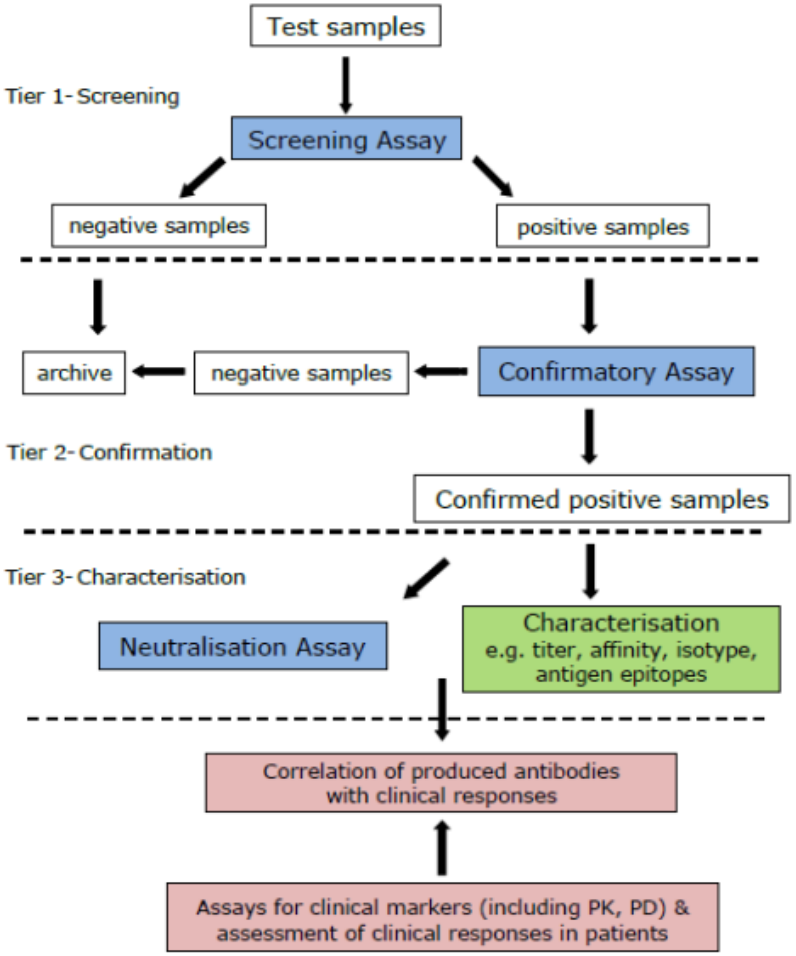
Today's challenges and solutions in assessing immunogenicity in patients

Altis Grand Hotel, Lisbon - 19th September 2018

Immunogenicity assays have their own method validation guidance documents

Description	ADA Assay
Measurement Type	Qualitative Tiered approach – multiple assay types
Calibrator	No standard curve in sample testing like PK and biomarker assays Use of a “surrogate” control, usually generated in animals Negative control
Sensitivity	Reported in mass units BUT mass unit quantification in sample testing discouraged Defined in relation to the cut point of the assay Cut points usually statistically set using drug-naïve samples
Reagents	Depends on the assay format and tier of testing (LBA/CBA/SPR etc.)

Immunogenicity assessment follows a step-wise approach



Not all tiers may be adopted for preclinical, depending on the molecule risk assessment

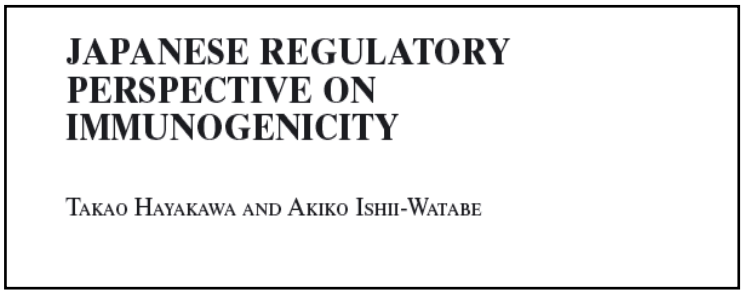
EMA and FDA are the only authorities that have issued specific guidance

- **EMA**
  - 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)
  - "Immunogenicity Assessment of Biotechnology-Derived Therapeutic Proteins"
    (**2008** - EMEA/CHMP/BMWP/14327/2006)
  - Guideline on Immunogenicity assessment of biotechnology-derived therapeutic proteins
    (**2017** - EMEA/CHMP/BMWP/14327/2006 Rev 1)

- **FDA**
  - "Immunogenicity Assessment for Therapeutic Protein Products" (**2014**)
  - "Scientific Considerations in Demonstrating Biosimilarity to a Reference product" (**2015**)
  - "Assay Development for Immunogenicity Testing" (**2009 – draft**)
  - "Assay Development and Validation for Immunogenicity Testing of Therapeutic Protein Products" (**2016 - draft**)

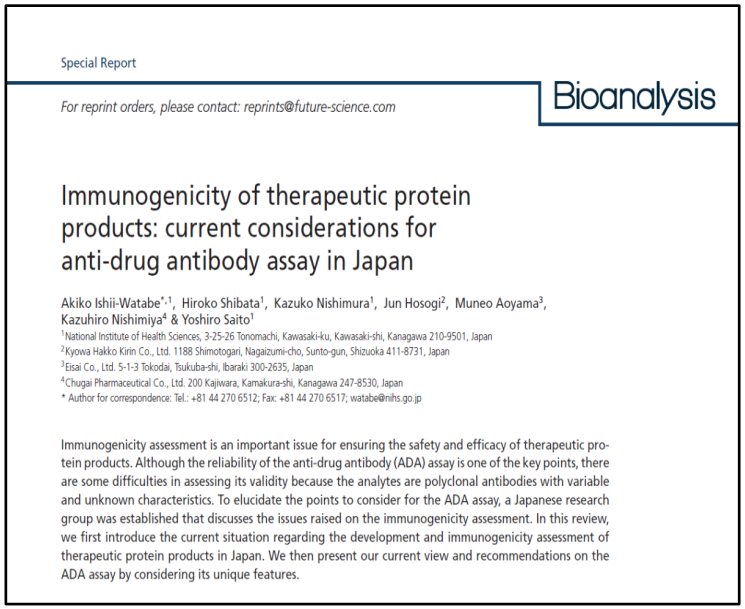
Other regions

- **Japan**
  - Two publications
  - No formal guidance
- **Brazil**
  - Applies FDA/EMA
- **China**
  - CFDA plans to form consensus among industry and research by publishing a series of “white papers”
  - After industry consensus is formed, guidance will be planned



JAPANESE REGULATORY PERSPECTIVE ON IMMUNOGENICITY

TAKAO HAYAKAWA AND AKIKO ISHII-WATABE



Special Report

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Bioanalysis

Immunogenicity of therapeutic protein products: current considerations for anti-drug antibody assay in Japan

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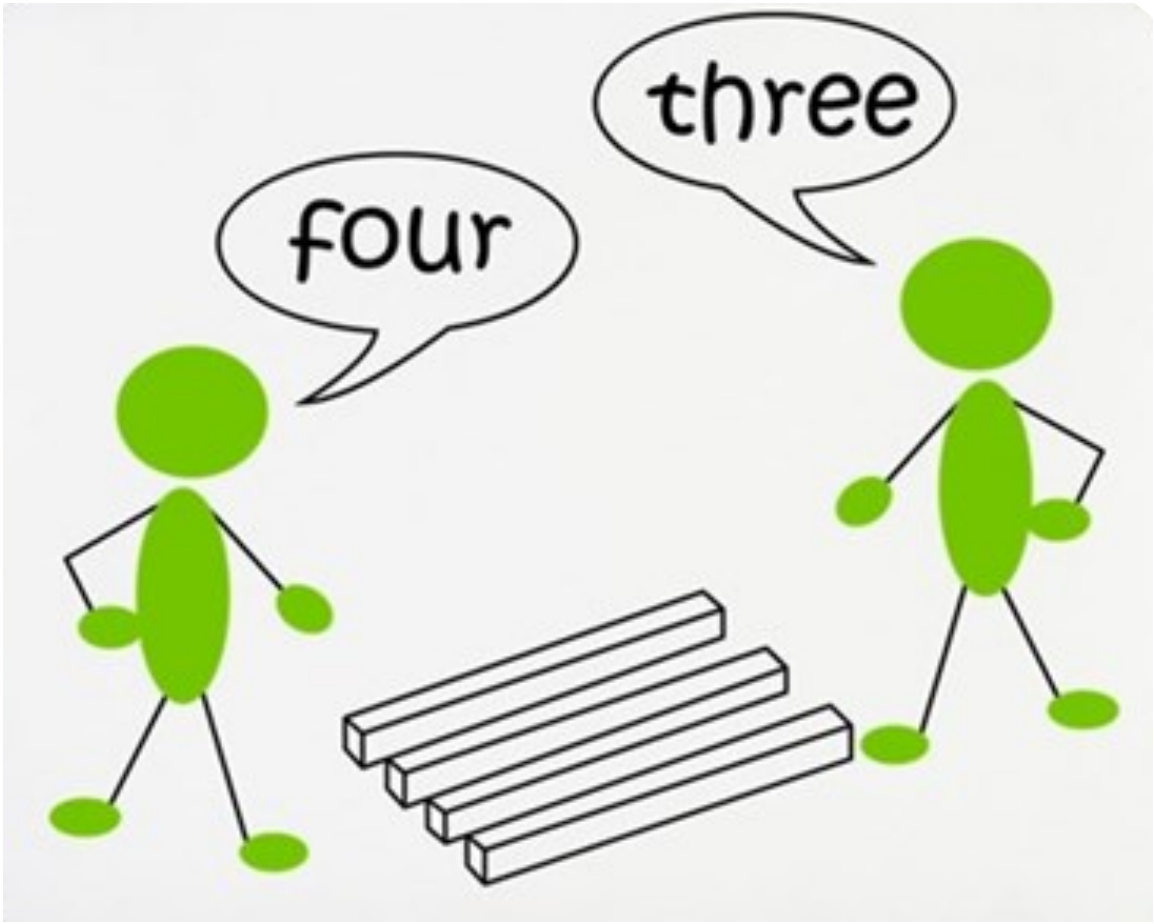
Immunogenicity assessment is an important issue for ensuring the safety and efficacy of therapeutic protein products. Although the reliability of the anti-drug antibody (ADA) assay is one of the key points, there are some difficulties in assessing its validity because the analytes are polyclonal antibodies with variable and unknown characteristics. To elucidate the points to consider for the ADA assay, a Japanese research group was established that discusses the issues raised on the immunogenicity assessment. In this review, we first introduce the current situation regarding the development and immunogenicity assessment of therapeutic protein products in Japan. We then present our current view and recommendations on the ADA assay by considering its unique features.

Differences cause challenges when filing in different regions

- Ideally guidance documents would be similar
- Differences between regions provide challenges for industry
- Often means addressing questions or re-work to enable filing in multiple regions
- ICH harmonisation is not yet possible
  - ICH rules require 3 regions to have published regulations
  - Any harmonisation will take several years

Having to resolve different perspectives



So what are some of the challenges?

Parameter	EMA (2017)	FDA (2016 – DRAFT)
Positive Control (PC)	Ideally a human preparation or animal serum against the therapeutic Panel of reference materials – variation in content and avidity Reagents used in assays need to be qualified and acceptance criteria set, at least for those which are most important For all controls the characterization data showing their properties and functionality for the intended use should be provided as part of the MAA submission	May be polyclonal or monoclonal or a human preparation Panel of mAbs may used PCs are used as system suitability controls Discuss with the agency in the rare event that the sponsor is unable to generate a positive control High, medium and low PCs used for validation (high and low for sample testing) LPC must fail in 1% of cases (statistically derived)
Negative Control (NC)	Validated with the same matrix as the samples Screening for pre-existing antibodies	Where possible same disease condition Age, sex, gender Same anti-coagulant, sample volume, co-medications, preparation and storage Close to the assay cut point

Parameter	EMA (2017)	FDA (2016 – DRAFT)
Sensitivity	No values cited and no requirement to factor in MRD	Although traditionally 250-500 ng/mL, recent data suggest that concentrations as low as 100 ng/mL may be associated with clinical events Should be reported after factoring in MRD Dilution 2- or 3-fold with a minimum of 5 dilutions Alternatively interpolating the linear portion of the dilution curve
Minimal Required Dilution (MRD)	Inclusion of data supporting MRD is important	Sample dilution that yields a signal to noise (S:N) close to that of assay diluent and allows for highest S:N. 1:5 to 1:100 Calculated using at least 10 individual serum samples
Cut Point (CP) and False Positive Rate (FPR)	Cut-off Statistical approach where justified although real data is acceptable (e.g. double background) Screening: preferably 5% FPR Confirmatory: not specified	Always statistically derived Screening CP: at least a 5% FPR with 90% CI (Shen, Dong *et al.)* Confirmatory CP: 1% FPR (0.1% not acceptable)

Parameter	EMA (2017)	FDA (2016 – DRAFT)
Precision	Not cited	In cases where intra-assay or inter-assay precision is > 20%, assay parameters need to be refined or a justification given to allow a higher CV
Selectivity	Complement components or complement receptors, mannose binding protein, Fc receptors, soluble target molecules, and rheumatoid factors Host cell proteins	Rheumatoid Factor Host cell proteins PC signal (in matrix) compared to Ab spiked in buffer alone
Haemolysed and Lipemic Matrices	Not stated	Hemolysis, lipemia, presence of bilirubin and presence or concomitant medications that a patient population may be using
Titre/Titer Reporting	For antibody positive samples, a titre needs to be determined using a standard approach and reporting the reciprocal of the highest dilution at which the sample gives a positive result. Another option is to report in mass units using a positive antibody control but this has caveats as explained above.	The reciprocal of the highest dilution that gives a readout at or just above the cut point. The MRD should be factored in the calculations of titers and provided when reporting titers.

Parameter	EMA (2017)	FDA (2016 – DRAFT)
Drug Tolerance (DT)	The Applicant has to demonstrate that the tolerance of the assay to the therapeutic exceeds the levels of the therapeutic protein in the samples for ADA testing. Otherwise the approach must be justified. Drug trough levels in relation to drug tolerance of the ADA assay (ISI) May be overcome by appropriate spacing of product administration and sampling No mention of how to report	Interference from the therapeutic drug can be minimized if the sponsor collects patient samples at a time when the therapeutic drug has decayed to a level that dose not interfere with the assay results (5 half-lives) No mention of how to report
Host Cell Proteins (HCP)	Antibody assays against impurities are also developed and validated for testing patient samples	May interfere with demonstrating assay specificity and selectivity
Neutralising (NAb) Assay	Two types of assays – Cell-based assay (CBA) and ligand-binding assay (LBA) Calculation of neutralising capacity 'titre'	CBA recommended LBA when no cell-based action (enzyme therapeutics) Sponsors should discuss the use of LBAs with FDA
Integrated Summary of Immunogenicity (ISI)	Detailed list of items to include	Not yet required

How should the industry interpret the differences?

- As with other types of method validation, the stage of development is important
  - Early stages may not need the application of guidance in its entirety
  - Generally, regulatory expectation is for fully validated assays to be used for pivotal studies
    - Usually Phase 3
    - Consideration of the risk of the therapeutic
    - Oncology indications may require different approaches
- However, industry has a tendency to be risk adverse
- Ambiguity/non-alignment between agencies will lead to extra resources and cost for industry and even post-marketing commitments
- Retrospective application of guidance by agencies is challenging
- Solid scientific justification for alternative approaches

Some examples of review/inspection agency comments

- Provision of statistical methods for cut point setting was not submitted
- Low positive control (LPC) not being set at a statistically derived 1% failure rate
- Re-calculation of confirmatory cut point using 1% rather than 0.1%
- Provide data per patient in tabular form for each tier
- Precision data was >20% CV but no justification was provided
- Justification and rationale not provided for excluding negative controls (NCs) with greater than 20% precision from cut point setting
- Provision of robustness data for passage limits for cell based assays
- Drug tolerance of assays
- Selectivity and specificity not demonstrated in haemolysed and lipemic matrices
- Level of drug used in the confirmatory assay
- Stability

Summary

- Immunogenicity assays are different in nature to PK or biomarker assays and as a result separate validation guidance have been issued
- To date, only EMA and FDA have produced such documents
  - FDA is still in draft
- Challenges exist for the industry when filing in both regions as the expectations differ
- Ideally harmonisation across the agencies will occur but ICH harmonisation is a long way off
- Trying to adhere to both documents creates increased demand on resources, time and cost
- Retrospective application of draft guidance has been one of the biggest hurdles
- Solid scientific justification for alternative approaches can be considered by the agencies
- Continued discussion between regulatory agencies and industry

EBF

19/sep/2018

08.45 – 09.00	**Welcome and aim of the meeting – Philip Timmerman (EBF)**
09:00 – 12.30	**Harmonized approaches for immunogenicity method validation**
09:00 – 09:25	Introduction to the session – Overview of current global regulations *Jo Goodman, on behalf of the EBF*
09:25 – 09:50	Harmonisation of immunogenicity testing : The EU perspective *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 *Anna Laurén, Wieslab/Eurodiagnostics*
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 *Alexandra Hawes, LGC*
11:10 – 11:30	Practical solutions to outlier decisions, pre-existing and treatment-boosted ADA and low biological variability *Viswanath Devanarayan, Charles River*
11:30 – 11:50	Experiences in clinical immunogenicity testing: switching from validation to routine analysis *Szilard Kamondi, Roche*
11:50 – 12:30	Panel discussion *Moderator: Robert Nelson. Panelists: Viswanath Devanarayan, Jo Goodman, Meenu Wadhwa, Michaela Golob*
12:30 – 13:40	**Lunch**

12:30 – 13:40	**Lunch**
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 *David Egging, Synthon Biopharmaceuticals BV*
14:00 – 14:20	Feedback on EBF immunogenicity harmonisation activities *Jo Goodman, on behalf of EBF*
14:20 – 14:40	AAPS-sponsored ADA Validation Testing and Reporting Harmonization *Meina Liang, on behalf of the AAPS community*
14:40 – 15:00	Panel discussion *Moderator: Michaela Golob. Panel: Meina Liang, Shobha Purushothama, Jo Goodman, Robert Nelson*


Questions