Practical Advice for the Integrated Summary of Immunogenicity

EIP Training Course

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Daniel Kramer

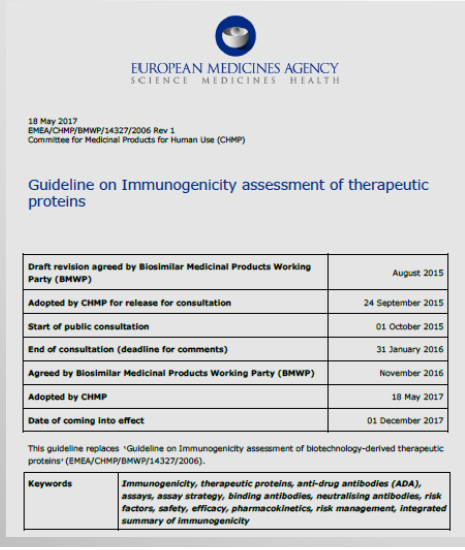
Integrated Summary of Immunogenicity

Previous Situation

- **Previously immunogenicity information is scattered throughout the eCTD in a BLA/MAA file**
- 2.7.3 Summary of Clinical Efficacy
- 2.7.4 Summary of Clinical Safety

} Impact of immunogenicitiy on efficacy &safety

- 5.3.1.4 Reports on Biopharmaceutical Studies
  - Immunogenicity testing strategy
  - Assay Validation Reports
- 5.3.5 Reports of Efficacy and Safety Studies
  - Clinical Study Reports with raw ADA data from ADA testing
- **Both EMA and FDA recommend an "Integrated Summary of Immunogenicity" to submit in a licensing dossier**



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

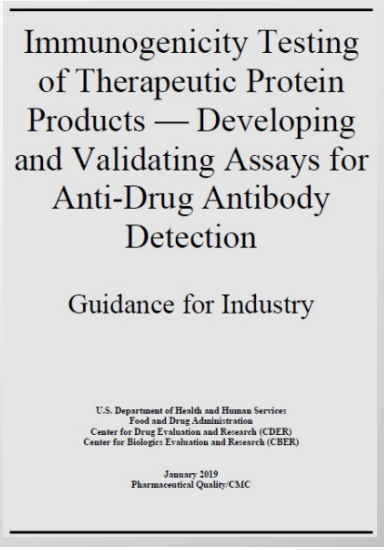
18 May 2017
EMEA/CHMP/BMWP/14327/2006 Rev 1
Committee for Medicinal Products for Human Use (CHMP)

Guideline on Immunogenicity assessment of therapeutic proteins

Draft revision 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
Agreed by Biosimilar Medicinal Products Working Party (BMWP)	November 2016
Adopted by CHMP	18 May 2017
Date of coming into effect	01 December 2017

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

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*



Immunogenicity Testing of Therapeutic Protein Products — Developing and Validating Assays for Anti-Drug Antibody Detection

Guidance for Industry

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)

January 2019
Pharmaceutical Quality/CMC

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Integrated Summary of Immunogenicity
Content

- **The "Integrated Summary of Immunogenicity" should be included in eCTD section "5.3.5.3 Reports of Analysis of Data from More than One Study"**
- **It should include:**
  - **Immunogenicity risk assessment**
    - Discussion of risk factors (product-, process-, posology, and patient-related factors) and how these may impact the immunogenic potential (likelihood & clinical sequelae of ADAs/NAbs)
  - **Tiered strategy and bioanalytical assays with stage- appropriate information**
    - Description of the immunogenicity testing strategy (3-tiered approach)
    - Characterization of the various methods that were developed & used throughout the program
  - **Clinical study design and sampling strategy**
    - Discuss how selected immunogenicity sampling time points help to
      - Reveal the incidence, persistence, and clinical significance of ADAs and NAbs
      - Minimize drug interference (report drug concentration at ADA sampling time points)
  - **Clinical immunogenicity data analysis**
    - Summary results of ADAs and NAbs for all clinical studies (incidence, titers, kinetics)
    - Impact of ADAs on PK/PD, efficacy and safety
  - **Conclusions and risk mitigation**
    - Discuss impact of immunogenicity on the benefit/risk of drug to the patient
    - Discuss how immunogenicity will be monitored post-marketing (if warranted)

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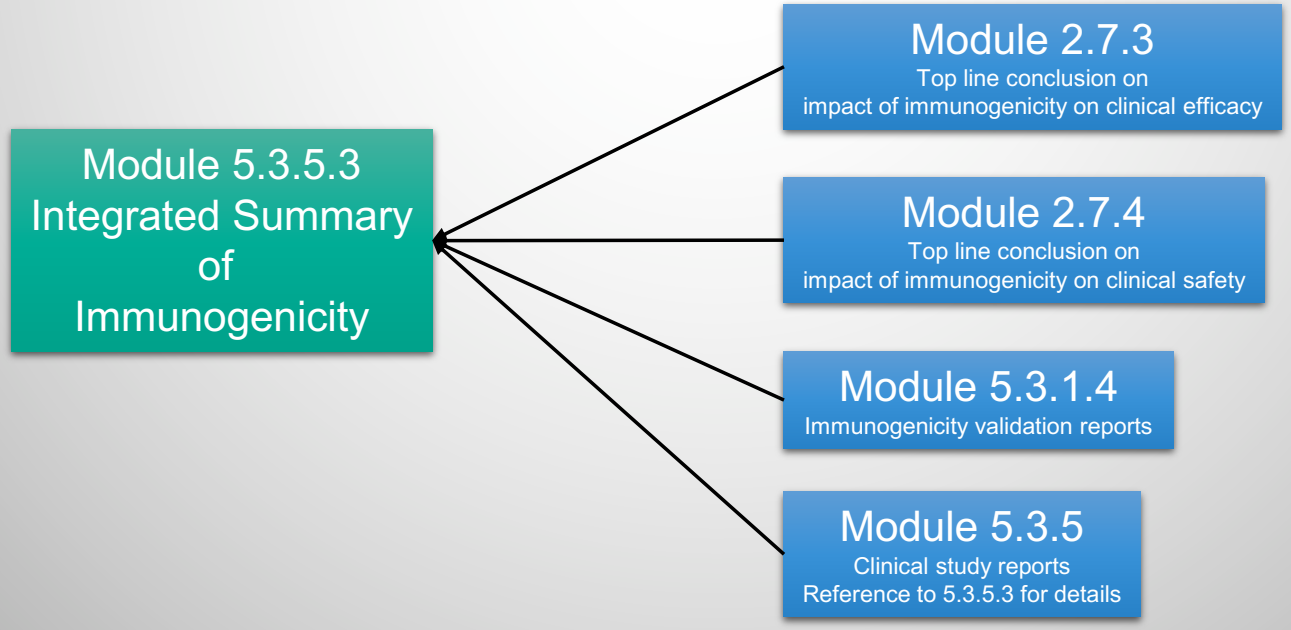
Integrated Summary of Immunogenicity
New vs. Old Structure of the eCTD

- **All immunogenicity data should be presented in the „Integrated Summary of Immunogenicity“ as a “self-standing” package**
- Other modules should “just“ contain top level conclusions and/or reference to 5.3.5.3



Immunogenicity Information for an IND/IMPD

- **Immunogenicity Risk Assessment**
  - Product / CMC related factors
    - What is the intrinsic immunogenic potential of the product?
    - What are the CQAs related to immunogenicity and their control/testing strategy?
  - Patient related factors
    - How likely is the patient population and clinical indication to produce an immune response to the product?
  - Trial design-related factors
    - How likely are the study conditions to facilitate an immunogenic response?
- **Description of tiered testing approach**
- **Description of bioanalytical methods**
- **Immunogenicity sampling plan**

Chapter 2.7.2.4
or 5.3.5.3
in an IND/IMPD

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ADA Summary Results per Clinical Trial

Example

	Dose group 1	Dose group 2
Number of evaluable subjects [a]	40	
Number of subjects ADA positive at baseline [b]	3/40 (7.5 %)	
Median titer	64	
IQR	8-128	
Number of subjects with treatment boosted ADAs [c]	2/3 (67 %)	
Median Peak titer	512	
IQR	64-1024	
Number of subjects ADA negative at baseline [d]	37/40 (93 %)	
Number of subjects with treatment induced ADAs [e]	5/37 (14%)	
Median Peak titer	2048	
IQR	256-4096	
Number of subjects with transient ADA response	0/5 (0 %)	
Number of subjects with persistent ADA response	5/5 (100 %)	
Number of subjects with indeterminate ADA response	0/5 (0 %)	
Number of ADA positive subjects [(c+e)]	7/40	
ADA prevalence [((b+e)/a)]	20 %	
ADA incidence [((c+e)/a)]	17.5 %	

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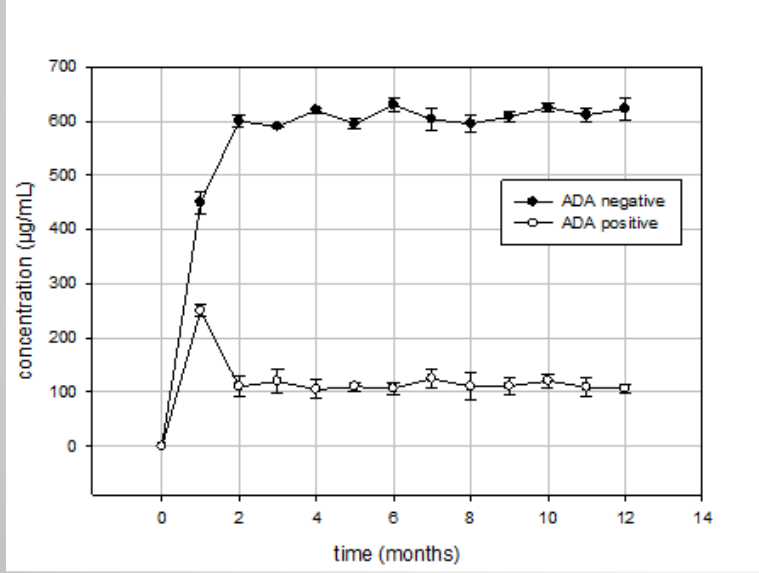
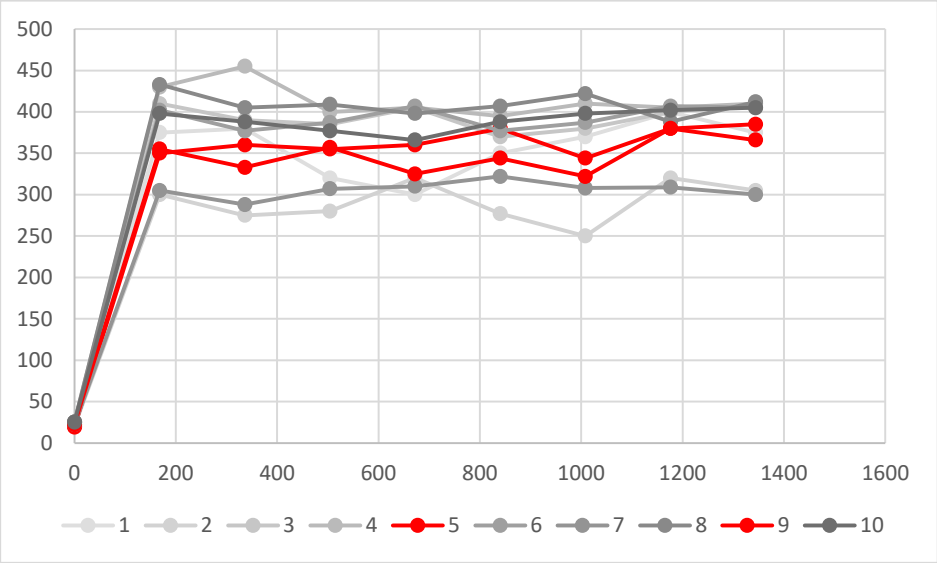
Impact of Immunogenicity on PK/PD/Efficacy

- **Determine the impact of ADA on PK/PD**
  - Plot median trough serum drug concentrations over time in ADA-positive versus ADA negative groups of drug-treated subjects or Spaghetti Plot





- **Determine the impact of ADA on clinical efficacy**
  - Assess the levels of efficacy in ADA positive versus ADA negative subjects
    - Could use same plots as for PK/PD

Impact of Immunogenicity on Safety

- **Determine the impact of ADA on clinical safety**
  - Examine the relationship between ADA and acute adverse events
    - Infusion reactions
    - Type I hypersensitivity (IgE mediated anaphylactic reactions due to prior sensitization)
  - Examine the relationship between ADA and non-acute adverse events
    - Type III hypersensitivity (IgG mediated reactions due to prior sensitization, deposition of immune complexes)
    - Worsening of disease (cross neutralization of endogenous counterpart)
    - Increased drug toxicity (due to overexposure caused by a drug sustaining ADA response)

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