

Lääkealan turvallisuus- ja kehittämiskeskus | Säkerhets- och utvecklingscentret för läkemedelsområdet | Finnish Medicines Agency

#### 8th OPEN SCIENTIFIC EIP SYMPOSIUM ON IMMUNOGENICITY OF BIOPHARMACEUTICALS

### **Draft EMA immunogenicity guideline**

Vilamoura 22-24.5.2016 Pekka Kurki Finnish Medicines Agency



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### **Purpose of the Guideline**

- Harmonization of assessment
  - Common standards
  - (Education of assessors)
- Regulatory requirements for marketing authorization
  - General principles
  - What regulators need to know
  - Presentation of the data
- Promotion of a multidisciplinary approach
- Not a technical cookbook

# European guidance for immunogenicity of therapeutic proteins<sup>1</sup>

- Immunogenicity assessment of biotechnology-derived therapeutic proteins, EMEA/CHMP/BMWP/14327/2006 (2008) → revision ongoing
- Immunogenicity assessment of monoclonal antibodies intended for in vivo clinical use. EMA/CHMP/BMWP/ 86289/2010 (2012)
- Biosimilar guidelines
- Guidelines for coagulation factors
- (Scientific advice)

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/ general\_content\_000043.jsp&mid=WC0b01ac05800240cb

Immunogenicity assessment of biotechnologyderived therapeutic proteins, EMEA/CHMP/BMWP/14327/2006 Rev. 1

#### Concept paper:

- Requirements of data on antibody assays
- Role of non-clinical studies
- Clinical data to study the correlations of the induced antibodies to allergic and anaphylactic/anaphylactoid reactions, delayed immunological reactions, pharmacokinetics, lack of efficacy
- Comparative immunogenicity studies
- Post-licensing immunological studies
- Specific guidance for the presentation of immunogenicity data
- Risk-based approach to immunogenicity

Immunogenicity assessment of biotechnologyderived therapeutic proteins, EMEA/CHMP/BMWP/14327/20@ducation rev1



Immunogenicity assessment of biotechnologyderived therapeutic proteins, EMEA/CHMP/BMWP/14327/2006/ rev1

- Immunogenicity and Clinical Development
- Rationale for sampling schedule and kinetics of the antibody response
- Consequences on pharmacokinetics of the product
- Impact of immunogenicity on safety and efficacy
- Methodological aspects to assess comparability of immunogenicity
- Management of immunogenicity
- Pharmacovigilance

#### Summary of the immunogenicity program

information

squeezing

of

### Scope

- Evaluation of an unwanted immune response against a therapeutic protein
- Proteins and polypeptides, their derivatives, and products of which they are components, e.g. conjugates.
- Focus on biotechnology-derived proteins, "therapeutic proteins"
- Coagulation factors excluded

#### **Requirements of data on immunogenicity** Issues to be considered – ADA assays

- Assay strategy
  - Screening → confirmation → neutralisation (→ further characterisation?) → → correlation to PK and PD
- Basic immunogenicity package: ADA
  - incidence,
  - persistence,
  - titer,
  - neutralisation,
  - · clinical impact, and
  - risk management



### **Requirements of data on antibody assays** Issues to be considered – ADA assays

- No ADAs  $\rightarrow$  no immunogenicity: true or not?
  - tolerance, pharmacological effect of the product or immunosuppression (concomitant medication)
  - dose/dosing, drug interference, insufficient sample size
- Neutralising antibodies (when not necessary, alternative ways, PK/PD)
- When to do additional testing?
  - Ig isotypes
  - Epitopes, antigenic domains
  - T-cell responses?

### **ADA assays** Drug tolerance, positive controls and cut points



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### **Drug tolerance** How about regulatory tolerance?

#### Draft guideline:

• "In any case, the Applicant has to demonstrate that the drug-tolerance of the assay exceeds the levels of the therapeutic protein in the samples for ADA testing."

### WRIB 2015:

 Elimination of drug interference and inter-patient variability through standard LBA mechanisms is <u>encouraged</u>. If this is not possible, it is imperative to have a good understanding of the ADA assay including <u>the immunogenicity risk</u> <u>assessment and mitigation plan</u> so as to interpret the data accurately across functions (bioanalytical scientists to clinical pharmacologists and clinicians).

### **Comments from written consultation**

- XXX suggests editing the text to read: "In any case, the Applicant has to demonstrate justify that the drug-tolerance of the assay is adequate for the intended purpose exceeds the levels of the therapeutic protein in the samples for ADA sampling."
- XXY: since this may not be possible for all samples due to dosing and half-life, it should be sufficient that **some samples** can be measured in the respective ADA assay
- XYY: The Applicant should know the drug tolerance of their assay, bearing in mind that this is with a surrogate positive control in most cases, and aim to exceed expected drug levels wherever possible.
- YYY: "It is recommended that applicants optimize the assay to demonstrate that the drug-tolerance exceeds the levels of the therapeutic protein in the samples for ADA testing, <u>if feasible</u>."

### How to deal with drug tolerance?

EMA will probably have a more critical view on ADA assays, including drug tolerance, since it will not be possible to define the level and clinical impact of immunogenicity if the ADA assay is looking only at the tip of the iceberg.

- How to determine drug tolerance?
  - The relevance of positive control sera from hyperimmunised animals
  - Drug holiday or post-treatment samples
- When the drug tolerance is unacceptable for regulatory purposes?
- How to present data when significant drug interference is obvious?

### **Relative immunogenicity**

- Relative immunogenicity scenarios
  - Manufacturing process change (EMEA/CHMP/BMWP/ 101695/2006; ) EMA/CHMP/BPWP/144533/2009 )
  - Biosimilar development (EMEA/CHMP/BMWP/42832/2005 Rev. 1)
  - Line extensions (e.g. IV to SC)
- Assay strategy
  - Single assay strategy
  - Two assays-strategy

### **Relative immunogenicity**

= two assays

#### Draft guideine

 The analytical assays should preferably detect (all) antibodies against both the biosimilar and the reference molecule but should at least be able to detect all antibodies developed against the biosimilar molecule.

=one assay

• Usually, the incidence, titer and nature (e.g. crossreactivity, target epitopes and neutralising activity) of antibodies and interpreted in relation to their potential effect on clinical efficacy and safety parameters.

### Single assay strategy

- Single assay = single antigen/active substance
- Theory: measures antibodies to all epitopes of the new version/product
- Is it always conservative?
- Does it overemphasize the immune response against the protein used as the antigen?
- Recommended for process changes and biosimilars?

### **Applicant's conclusion on immunogenicity**

The **overall incidence of ADAs to etanercept ...was significantly lower in the SB4 treatment group** compared to the EU Enbrel® treatment group at Week 24.

Although indicating a lower ADA formation and immunogenicity of the proposed biosimilar SB4 as compared to Enbrel®, **there was no observed impact on the PK and safety profile** with regard to the type, frequency and severity in each part of the study.

Emery P et al **s 10.1136/annrheumdis-2015-207588** "The incidence of antidrug antibody development up to week 24 was lower in SB4 compared with ETN (0.7% vs 13.1%)."

### **Pitfalls of comparative immunogenicity** Case biosimilar etanercept



### **Regulatory interpretation**

- Based on the current knowledge of the low drug tolerance of the ADA assay and the possibility of more false negative results in the SB4 arm, it is premature to conclude that SB4 is less immunogenic than Enbrel.
- The results of the ADA assays demonstrate that SB4 is not more immunogenic than Enbrel.
- http://www.ema.europa.eu/docs/en\_GB/document\_library/EPAR\_-\_Public\_assessment\_report/human/004007/WC50



#### Two assay strategy

- Two assays have to be developed and validated
- Two antigens/targets = active substances of the comparators
- Two positive controls?
- How to set the cut points?
- Standardization, cross-testing?

# **Two assay strategy** biosimilar infliximab

- Initial testing by using a single antigen test (with active substance of the <u>reference</u> product)
  - → no difference between the treatment arms but additional data were requested
- Development of the second test by using the biosimilar AS
  → no difference between treatment arms, including ADA titers
- Cross testing of sera with both assays
  → good concordance
- Further additional testing by using the BS-based assay



### Is the product immunogenic or not?

- The median trough concentration of abatacept on treatment was consistent at approximately 30 µg/mL, ranging from 27.12 µg/mL to 31.86 µg/mL
- Isolated positive samples on treatment, 0-3% per visit
- Good adherence to therapy, efficacy and stabile safety profile

### A non-immunogenic protein?

### Is the product immunogenic: definitely yes

Subjects have decreasing abatacept levels post-treatment; with a median concentration of 0.19  $\mu$ g/mL 85 days post treatment.

Post-treatment ADA incidence	
28 Days	2.7%
56 Days	5.5%
85 Days	7.7%
168 Days	16.8%

Persistent immune response to a regulatory protein of the immune system? No clinical safety signal.

### Summary of the immunogenicity program

- Analysis of risk factors
- The risk-based immunogenicity program
- Immunogenicity results
- Conclusions on the risk(s) of immunogenicity
  - Impact of the immunogenicity on the benefit/risk
  - Tools to manage the risk
  - How to link adverse events to immunogenicity post-marketing

### The risk-based immunogenicity program

#### Assay strategy

- a. Rational for the choice of assays
  - i. screening and confirmation
  - ii. neutralizing
  - iii. other, e.g. immunoglobulin class, sub-class
- b. Specificity and sensitivity of the selected assays in the context of the particular product
  - i. selection of the positive control(s)
  - ii. determination of the threshold for ADA-positivity
- c. Drug tolerance of the assay at therapeutic concentrations

### The risk-based immunogenicity program

#### Approach to immunogenicity in clinical trials

- a. Sampling for immunogenicity testing
- b. Justification for the length of the follow up
- c. Pharmacokinetics
- d. Pharmacodynamics, efficacy and safety trials

#### Impact on the risk assessment on the immunogenicity program

# Summary of the immunogenicity program Why???

• Currently, it is difficult to understand the rationale of the immunogenicity studies and to find the relevant data



Unnecessary questions by the assessors

- Promotion of multidisciplinary collaboration <u>before</u> the conduct of clinical studies
- Comments from the public consultation
  - Interpretation of the results require some understanding of the assay methodology
  - Pitfalls of various assay formats: more guidance for the clinical assessor?

## Conclusions

- Planning and assessment of immunogenicity studies requires multidisciplinary team work.
- It is impossible to study immunogenicity without valid assays for ADAs
- Immunogenicity assessment needs to be integrated into PK/ PD, safety and efficacy
- An integrated summary of the immunogenicity program benefits applicants and assessors

