

Aligning immunogenicity evaluation with the Regulator's needs for an integrated data analysis

Paul Chamberlain
NDA Advisory Board

EIP Congress, Copenhagen, 8 February 2012



CHMP benefit-risk assessment

Structured and mainly qualitative approach:

1. Identify main evidence and uncertainties

Primary requirement = convincing efficacy

Negative effects considered in terms of probability and severity

2. Compare the benefits vs. risks for the particular therapeutic setting

Immunogenicity-related risks (identified or uncertain) may be more influential if efficacy is equivocal

Evolution of risk-benefit balance with time ?



Benefit-risk assessment methodology



European Medicines Agency

London, 19 March 2008
Doc. Ref. EMEA/CHMP/15404/2007

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
(CHMP)

REFLECTION PAPER ON BENEFIT-RISK ASSESSMENT METHODS IN THE CONTEXT
OF THE EVALUATION OF MARKETING AUTHORISATION APPLICATIONS OF
MEDICINAL PRODUCTS FOR HUMAN USE

Benefit-risk methodology project

Work package 2 report: Applicability of current
tools and processes for regulatory benefit-risk
assessment



EMA 4-fold model

| | |
|----------------------|-------------------------------------|
| Favourable effects | Uncertainty of favourable effects |
| Unfavourable effects | Uncertainty of unfavourable effects |

"Framing of the problem"
by initial **qualitative** step,
involving structuring of
problem, reduces bias of
intuitive aggregation –
especially for uncertainty

| Approach/method | Relevance to regulators | Usefulness |
|---------------------------|---|------------|
| Qualitative approach | Essential to follow a structured set of steps for any regulatory decision and to develop a quantitative model. | High |
| Discrete event simulation | Complex models such as Archimedes could be relevant post-approval to understand actual drug usage. Lack of transparency restricts understanding of its results. | Low |
| Probabilistic simulation | Can illuminate the risk/benefit trade-off when uncertainty is a major feature of a regulatory decision. | Medium |



Risk equivalents

Risk-benefit Analysis by Richard Wilson & Edmund AC Crouch
Harvard Univ Press 2001

➤ The following 4 activities carry the same risk of premature death:

- Driving a car for 4000 miles
- Smoking 100 cigarettes
- Rock-climbing for 2 hours
- Working in the chemical industry for 1 year

However...

If you enjoy smoking a cigarette while you drive to your job in the chemical industry and engage in rock climbing on the weekends
It is unclear if these risks are **additive** or **multiplicative**



How to systematically evaluate immunogenicity of therapeutic proteins – regulatory considerations

Eva-Maria Jahn¹ and Christian K. Schneider^{1,2,*}

New Biotechnology – Volume 25, Number 5 – June 2009

¹Paul Ehrlich Institut, Division B3 Cooperation/Immunobiology, Langen, Germany
²Twincase Centre for Experimental and Clinical Infection Research, Marburg, Germany

"In summary, quality, non-clinical and clinical questions should be addressed **in conjunction** regarding the immunogenicity risk assessment. **The three aspects are interlinked and influence each other**, and therefore they cannot be evaluated individually as each part is influenced by the other two."



Priorities for Immunogenicity Review

| | Question |
|---|---|
| 1 | Has Applicant identified all pertinent risks? |
| 2 | Have studies been designed correctly to enable a reliable estimate of clinical outcomes? |
| 3 | Do the monitoring methods have appropriate specificity and sensitivity? |
| 4 | Has the Applicant correlated the bioanalytical signals with the relevant clinical endpoints? |
| 5 | Is the proposed Risk Management Plan adequate? |
| 6 | Are there sufficient data to enable a reliable judgement on overall clinical benefit and risk for use in the intended population? |



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Immunogenicity: Common Gaps

| | Issues |
|---|--|
| 1 | Impact of Product Quality dimension not discussed |
| 2 | Sampling schedule insufficient to describe dynamics of immune response |
| 3 | Uncertainty about specificity & sensitivity of ADA assays to detect pre-existing vs. treatment-emergent ADA's to full range of product variants and process-related impurities |
| 4 | Incomplete correlation of ADA vs. PK vs. PD |
| 5 | No linkage of results of immunogenicity evaluation to RMP |
| 6 | Uncertain impact of undesirable immunogenicity on long-term benefit-risk for intended therapeutic setting |



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Procedural challenges

- Immunogenicity-related data typically distributed in *different* sections of dossier
- Step-wise procedure
 - Initial review by 2 Member States
 - CMC + Non-clinical + Clinical reviewers responsible for respective parts of dossier
 - Difficult to integrate comments from different reviewers
- Time-scale is fixed
 - Limited time for responding to questions
- Biologicals Working Party Members consulted secondarily



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Helping the Regulator

Büttel IC, Völler K & Schneider CK
Current Drug Safety 2010, 5, 287-292

"Biologicals have to be seen as individuals, and fortunately (or unfortunately) there is no "fit-for-purpose recipe" for immunogenicity evaluation"

"Knowing risks can mean controlling risks, and thus a comprehensive database based on the recommendations given in the EMA guideline might be an important determinant for a successful marketing authorization application."

"The Risk Management Plan post-approval should be borne in mind where immunogenicity testing can on a case-by-case basis be performed after approval"



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Provide context for "framing of the problem"

- Intrinsic immunogenic motifs
 - B / T-cell epitopes
- Systems biology
 - Structural and functional relationship to native proteins
 - Extent of immune tolerance
 - Abundance of natural inhibitors
 - Redundancy of function of endogenous counterparts
 - Functional impact of gene knock-out



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Provide context for "framing of the problem"

- Control of product quality
 - Choice of host cell substrate
 - Control of product variants and process-related impurities
 - Formulation development
 - QC specifications
 - Comparability at different stages of development



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Example

- Recombinant (re-engineered) human cytokine
 - 12 aa modified
 - *Saccharomyces* host cell
 - Glycosylation heterogeneity
 - Liquid formulation for chronic sub-cutaneous administration by immune-competent subjects
 - Limited solubility in physiological matrix
 - Incomplete immune tolerance to native counterpart
 - Considerable redundancy of function
 - Abundant natural inhibitors

Can we predict how these risk factors might interact?

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Implications for bioanalytical strategy ?

REGULATORY CONCERNS

Allergenicity
Compromised physiological homeostasis
Product QC
Impact on related therapies
Maintenance of efficacy

DATA ELEMENTS

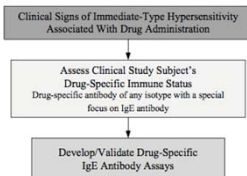
- Sufficient data points to define ADA response dynamics relative to observed AE's
- Specificity of pre-existing antibodies
- Follow-up investigation of affected subjects for cross-reactive IgE
- Cross-reactivity vs. endogenous counterpart
- Cross-reactivity vs. process-related impurities
- Neutralising capacity of ADA's relative to endogenous inhibitor pool
- Absence of long-term impact of ADA's on 1° and 2° PD markers in non-clinical studies
- Persistence of immune memory

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Design and Validation of Immunoassays for Assessment of Human Allergenicity of New Biotherapeutic Drugs; Approved Guideline



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Data elements to integrate

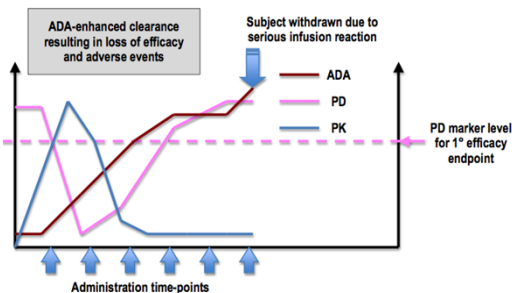
- **Specificity** of signals measured in bioanalytical assays
 - Extent of cross-reactivity vs. endogenous counterparts
 - Variants of therapeutic protein / related products
 - Process-derived impurities
 - Different moieties of fusion protein / conjugate
- **Sensitivity** to detect **clinically significant ADA**
 - ADA (LBA & bioassay) vs. PK vs. PD
- **Dynamics** of ADA response
 - vs. incidence / severity of hypersensitivity reactions
 - vs. long-term efficacy
 - Intermittent administration / switch to related product

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Efficacy & safety are not mutually exclusive



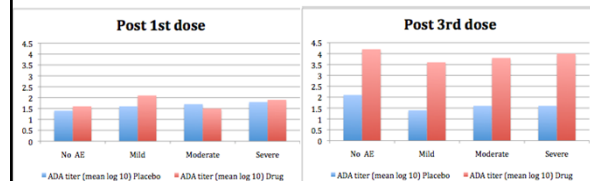
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Data correlation

- Incidence & severity of systemic hypersensitivity reactions relative to:
- disease epidemiology
 - drug administration
 - pre-existing / treatment-emergent antibodies



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Data Presentation

Summarise key assay performance characteristics

If different methods were used at different stages of development, explain the impact on assay performance

Explain Quality Control of Critical Reagents

Table X: Assay for human anti-XXX antibodies

| | |
|---|--|
| Assay format | |
| Coating | |
| Detection antibody | |
| Test matrix | |
| MRD of test sample | |
| Positive control | |
| LOD in undiluted matrix | |
| Threshold for drug interference at Low QC | |
| Screening cut-point | |
| % False positive at cut-point | |
| Confirmatory assay cut-point | |
| Concentration competing antigens for confirmatory assay | |
| Development Report No. | |
| Validation Report No. | |

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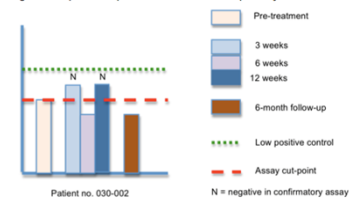
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Data Presentation

Clear presentation of individual subject profiles is extremely helpful

Figure: Example of data presentation for clinical sample analysis



Include as Annex to Integrated Summary of Immunogenicity?

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ICH S6 Addendum effective Dec 2011

Addendum takes precedence over Parent Guideline

Apparent moderation of role of ADA testing in pre-clinical safety evaluation:

- Evidence of altered PD activity
- Unexpected changes in exposure in the absence of a PD marker
- Evidence of immune-mediated reactions

Characterisation of neutralising potential is warranted

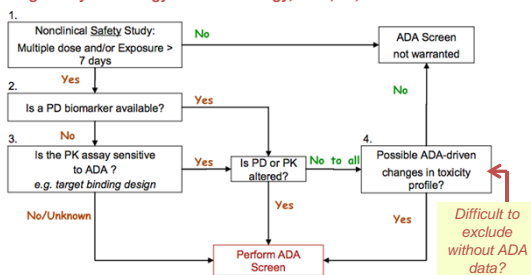
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Non-clinical evaluation: Industry Position

Rafael Ponce et al
Regulatory Toxicology & Pharmacology, 2009, 54, 164-182



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Linkage: RMP & Immunogenicity

EU Risk Management Plan

Describe safety profile

- Identified risks
- Important potential risks
- Important missing information

structured basis for Pharmacovigilance Plan & ongoing risk minimisation activities

Data from controlled clinical studies, collected at a sufficient number of time-points to enable effective correlation of ADA vs. PK/PD/etc

- Association with hypersensitivity reactions
- Loss of efficacy
- Non-clinical observations not yet explained
- Persistent "cross-reactive" antibodies ...

- Impact of product quality dimension?
- Immune complexes ?
- Epidemiology...

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Impact on Risk Minimisation

Büttel IC, Völler K & Schneider CK
Current Drug Safety 2010, 5, 287-292

Tysabri® (natalizumab)

Thorough evaluation of the dynamics of the ADA response relative to efficacy and safety signals in Phase 3 studies enabled minimisation of risks in the post-marketing setting

Detection of "persistent" antibodies was associated with decreased efficacy and increased hypersensitivity reactions

SmPC Section 4.4: Test for ADA if there is ongoing disease activity and/or infusion-related reactions;

If positive, re-test 6 weeks later to confirm "persistent" ADA status; If persistent ADA's are confirmed, treatment should be discontinued

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Integrated Summary of Immunogenicity ("ISI")

1. Product-related risk factors

Intrinsic immunogenic motifs
Control of Product Quality

CTD Format
§ 5.3.5.3

2. Potential clinical risks

3. Bioanalytical strategy

4. Immunogenicity-related signals

Non-clinical
Clinical

Overview of database
Integrated data presentation

= Consolidated Module
for CMC & (NON-)
CLINICAL Reviewers

5. Impact on overall clinical benefit-risk

6. Recommendations for Risk Management Plan

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Acknowledgements

Frits Lekkerkerker, NDA Advisory Board
Christian Schneider, Danish Medicines Agency
Isabel Büttel, Paul Ehrlich Institute

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THANK YOU !



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