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

Paul Chamberlain
NDA Advisory Board

EIP Congress, Copenhagen, 8 February 2012

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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

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New Biotechnology • Volume 25, Number 5 • June 2009

*"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 outpoints?
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?

Implications for bioanalytical strategy ?

REGULATORY CONCERNS	DATA ELEMENTS
Allergenicity Compromised physiological homeostasis Product QC Impact on related therapies Maintenance of efficacy	■ 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

I/LA34-A
Vol. 31 No. 12
Replaces I/LA34-P
Vol. 30 No. 19

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

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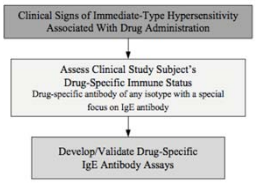
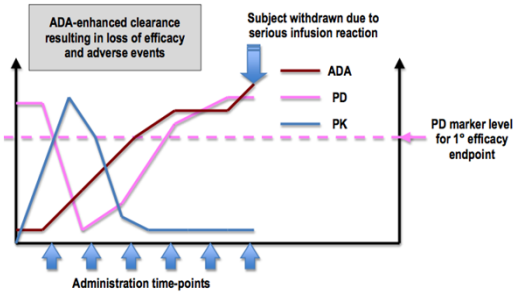


Data elements to integrate

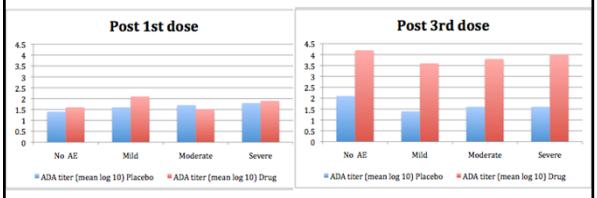
- ***Specificity*** of signals measured in bioanalytical assays
  - Extent of cross-reactivity *vs*. endogenous counterparts
  - Variants of therapeutic protein / related products
  - Process-derived impurities
  - Different moieties of fusion protein / conjugate
- ***Sensitivity*** to detect ***clinically 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

Efficacy & safety are ***not*** mutually exclusive



Data correlation

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



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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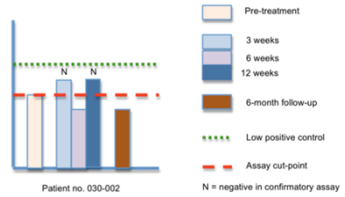
Data Presentation

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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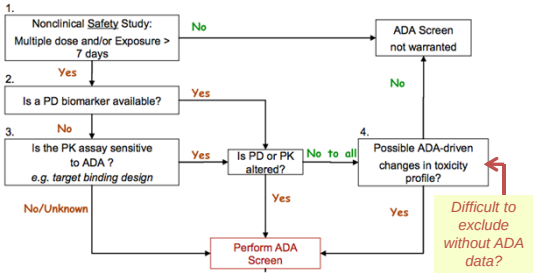
Non-clinical evaluation: Industry Position

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
2. Potential clinical risks
3. Bioanalytical strategy
4. Immunogenicity-related signals
   - Non-clinical
   - Clinical

   } Overview of database; Integrated data presentation
5. Impact on overall clinical benefit-risk
6. Recommendations for Risk Management Plan

CTD Format § 5.3.5.3

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

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THANK YOU !

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