Challenges in assessing relative immunogenicity (biosimilar and manufacturing change)

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Declaration of Interest statement:

Paul Chamberlain has received Consulting fees from different companies in respect of strategic and operational advice relating to biopharmaceutical development; he is self-employed, and serves as a Member of the NDA Advisory Board, a company that provides market access consultancy services to pharmaceutical companies.

The content of this presentation reflects the personal opinions of the author.

Q: What is meant by relative immunogenicity?

Do we mean:

- Difference in ***clinically meaningful*** immune responses?

Lines 77-79:

*"In the clinical setting, the investigation of immunogenicity should be based on **integrated analysis** of immunological, pharmacokinetic and clinical efficacy and safety data in order to understand the clinical consequences"*

ADA assays:

- Provide a more or less biased index of a difference in antigenicity between pre- *vs*. post-treatment samples

Clinical endpoints:

- May be less sensitive than ADA assays
  - Although steady-state drug concentration and AUC 0-inf can represent suitably sensitive indices

= Relative index that interprets *in vitro* signals of immune response *vs*. clinical impact

Q: Biosimilarity *vs*. manufacturing changes

Clinical evidence is always required for biosimilars, but rarely for manufacturing changes

Why should there be a different approach to the assessment of relative immunogenicity in the biosimilarity scenario compared to manufacturing changes for innovator products?

Reflects possibility that clinically-impactful differences might not be detected by analytical techniques alone

… But, does this represent a real difference in the level of risk, or an overly conservative regulatory approach?

Reality check

Highest-scale negative clinical impact was associated with a change in formulation-primary container combination for an innovator product, i.e. increased incidence of amPRCA for Eprex®

With accumulating experience of biosimilars, it is becoming evident that the quality standards applied for registration in EU are effective at excluding an increased in immunogenicity, even in the case of "high-risk" products

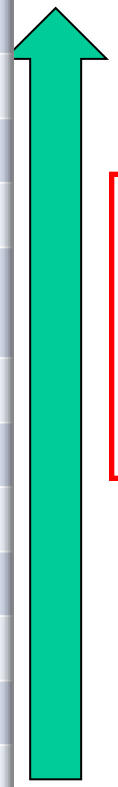
Clinical weight of evidence should be driven, to the same extent for biosimilarity & manufacturing changes, by combination of:

- Nature of risks for given molecule; *and*
- Differences detected at analytical level; *and*
- Scale of uncertainty about impact of defined differences

Q: Influence of nature / scale of clinical risk(s)?

To what extent does the nature of identified and potential risks influence the type and weight of evidence?

Product	Clinical impact of immunogenicity / ADA
epoetin-alfa	Cross-reactive neutralizing ADAs causing amPRCA
cetuximab	Severe allergic reactions in pre-sensitised subjects
infliximab	Immune complex-related hypersensitivity & loss of efficacy
adalimumab	Loss of efficacy & increased incidence of injection site reactions
rituximab	Loss of efficacy in patients with severe pemphigus & rare cases of hypersensitivity reactions
somatropin	Possible reduction in PK / PD / efficacy in rare cases
insulin	Possible reduction in PK / PD / efficacy in rare cases
follitropin-alfa	Negative impact not identified
bevacizumab	Negative impact not identified
trastuzumab	Negative impact not identified
etanercept	Negative impact not identified
(peg)filgrastim	Negative impact not identified



Increasing weight of evidence[#] required

analytical + clinical

Q: What are the risk factors?

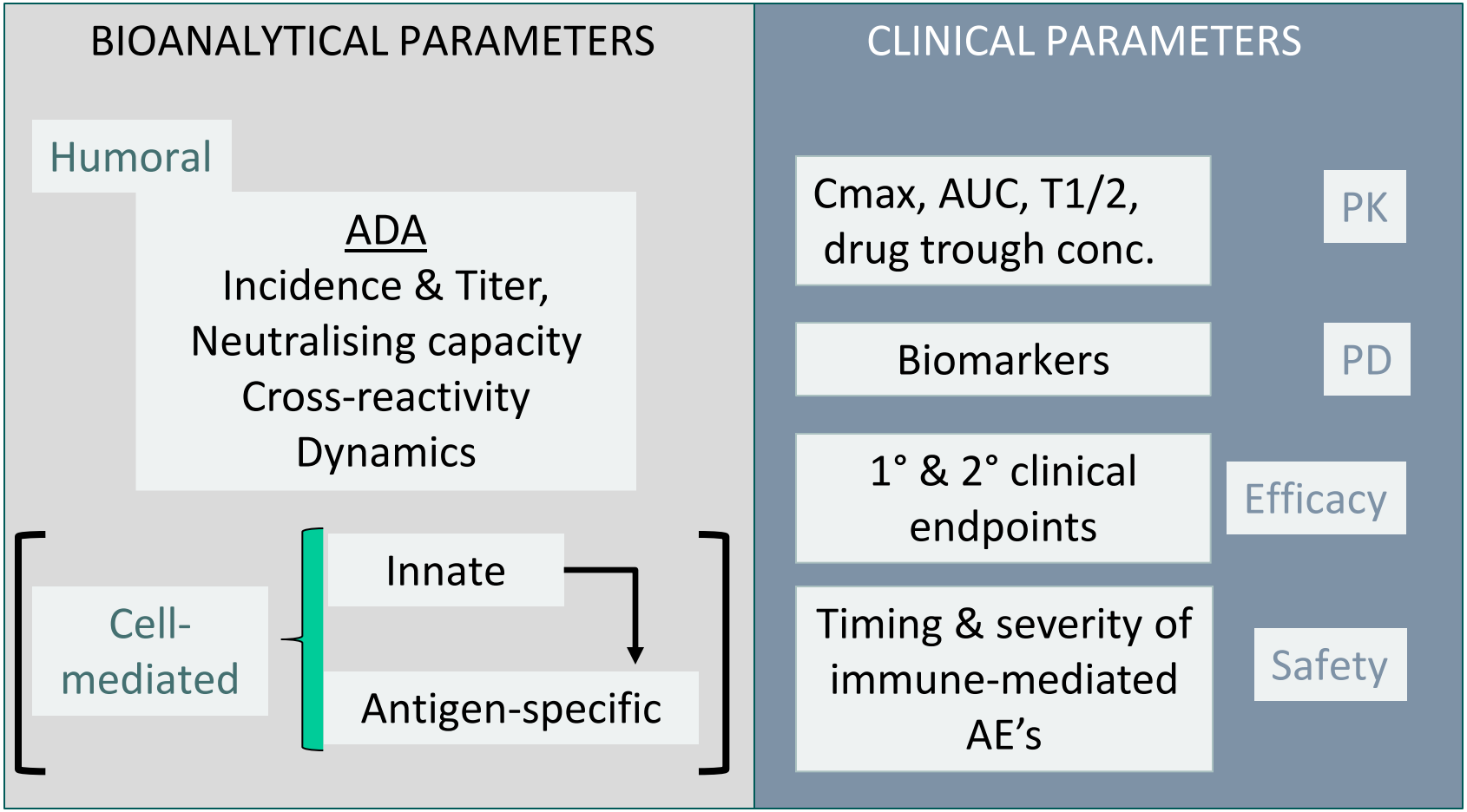
What product quality attributes could influence the relative immunogenicity of the different product versions?

- Instability of the active substance in formulation-container
- Structural / conformational differences in the active substance
- Differences in post-translational modification
- Altered pattern of positional isomerization of polyethylene glycol-conjugated protein
- Different qualitative or quantitative composition of host cell-derived, or other process-derived, impurities

All of these could apply to biosimilars and manufacturing changes

Risk evaluation & mitigation requires combination of methods

Q: Which parameters should be monitored / correlated?



Q: How to manage bioanalytical bias?

How can we minimize methodological bias to ensure objective and sensitive comparison?

ADA assays are susceptible to multiple sources of bias:

- Residual drug
- Target ligand
- Non-specific binding factors
- Choice of assay format
- Positive control antibody reagent
- Chemical conjugation of antigens
- Inter-assay and inter-operator variability
- Random variation due to low absolute signal level

All of these factors require careful control for accurate assessment of related ADA response

Q: Acceptable margin of difference?

Is it feasible to pre-define an acceptable margin of difference based on ADA incidence or magnitude?

No, because:

- ADA assay sensitivity / drug tolerance is not standardised
- Do not have an adequate understanding about the relationship of bioanalytical indices of ADA formation *versus* clinically-meaningful parameters for a given molecule across different clinical indications
- Probability of risk may be too low to detect in controlled pre-authorisation clinical studies

Q: Which clinical indication?

Is it necessary to assess relative immunogenicity in the highest risk population?

Yes: Experience with rhEPO demonstrated that it was instructive to assess risk in the renal anemia population using subcutaneous administration

…*But*, choice needs to balance sensitivity to detect negative **clinical impact** with **feasibility**

e.g. rh insulin / insulin glargine:

- majority of population will have been previously-treated
- not necessary to include paediatric population for comparison

Decision to be driven by severity of clinical consequences, not by "reported ADA incidence"?

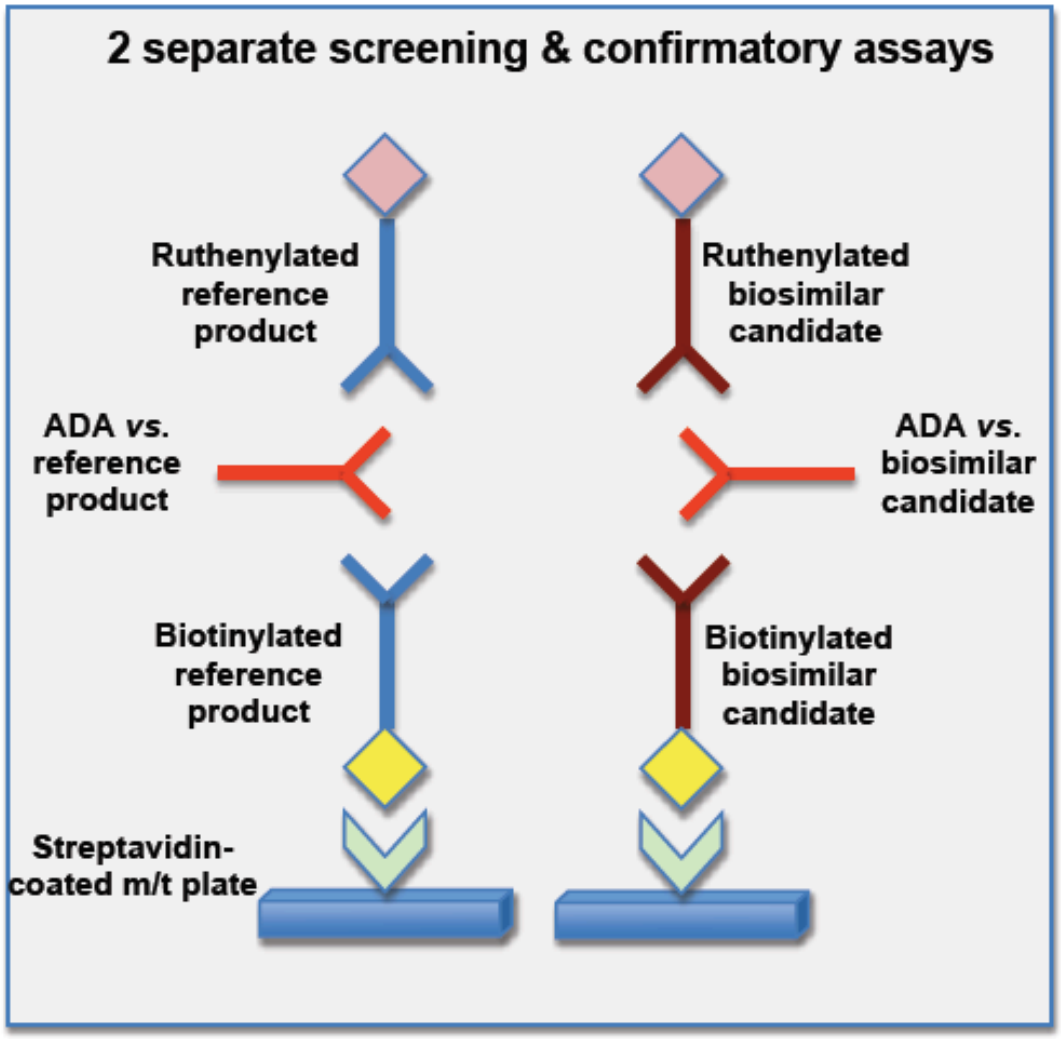
Q: Clarity of guidance for bioanalytical evaluation?

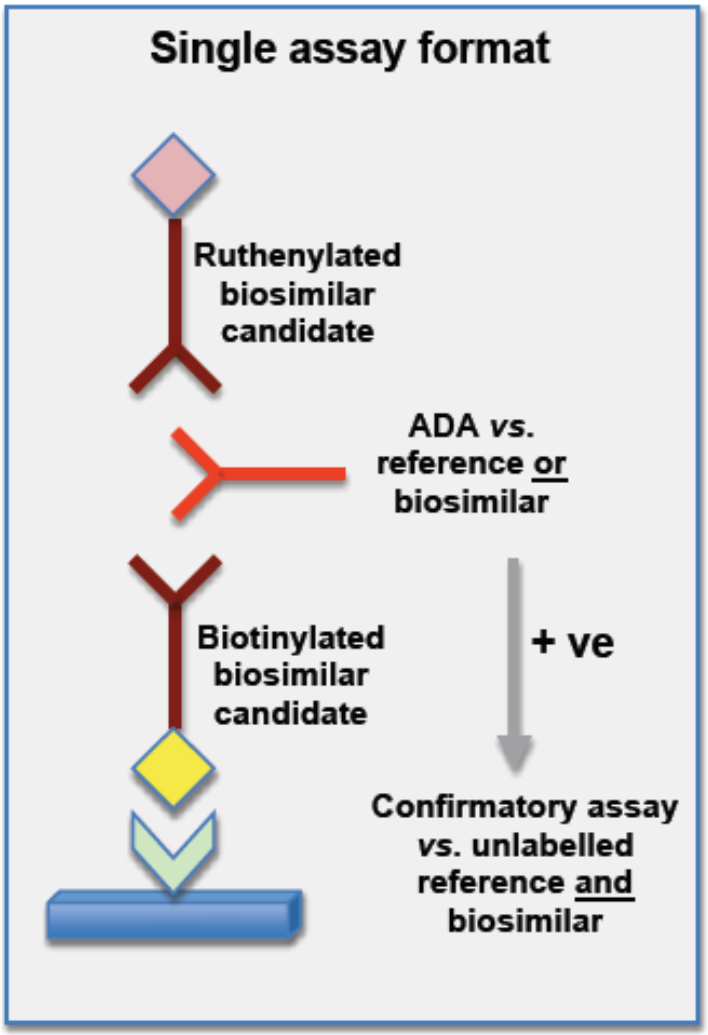
One *vs*. Two assays

Lines 584 to 589

"Immunogenicity testing of the biosimilar and the reference product should be conducted within the biosimilar comparability exercise by using the same assay format and sampling schedule which must meet all current standards. Analytical assays should be performed with both the reference and biosimilar molecule in parallel (in a blinded fashion) to measure the immune response against the product that was received by each patient. The analytical assays should preferably be capable of detecting antibodies against both the biosimilar and the reference molecule but should at least be able to detect all antibodies developed against the biosimilar molecule. "

Minimizing bias: single assay format





Experience of 2-assay approach

Two bridging assays require:

•Labelled (chemically-conjugated) versions of the antigen

➔ 4 chemical conjugates, with non-site-specific derivation

- Increases bias due to labelling procedure
- Introduces additional vector of assay variability
- Creates unnecessary redundancy: all samples assayed twice, using different labelled antigens, in assays that can yield different results
- Often have different assay cut-points:
  - 2 screening assay cut-points, and 6 confirmatory cut-points if comparing EU and US versions of reference product *vs*. biosimilar
- Sometimes have different apparent drug tolerance level
- Increased sample volume

Experience for Remsima®

- Initial MAA submission presented data from 1-assay approach
- Agency requested re-assay using two assays (BS + reference)
- Outcome was same in 1- *vs*. 2-assay approach

EPAR for Remsima ®

"The same assay using Remicade as the immunocompetition anti-TNF was initially used to detect antibodies to both Remicade and CT-P13. As this was not endorsed by the CHMP, the Applicant re-tested samples from both treatment arms with the same assay using tagged CT-P13. A very high concordance between the results of the two assays was demonstrated, and thus, the two assays can be considered as interchangeable."

Regulator's concern was *not* substantiated by the outcome

Q: Pro's *vs*. Con's of 1-assay approach?

PRO's:

- Can validate "antigenic equivalence" of comparator products by comparing reactivity *vs*. positive control antibody
- Minimizes scale of assay-related variability
- Avoids redundant testing (and potentially conflicting results)
- Signal specificity of screened positive samples is confirmed by inhibition using unlabeled biosimilar and reference product
- **Maximizes sensitivity to detect antibodies reactive with biosimilar version = conservative approach**

CON:

- *Might* not detect antibodies reactive only with the reference product?

Would this represent a real regulatory risk?

Q: What about manufacturing changes?

Lines 594 to 596

"*When comparative immunogenicity studies are required in the context of a manufacturing change of a given product, assays to compare the pre- and post-change products need to be developed.* ***Ideally, there should be two assays****, one using the pre-change protein and the other with the post-change protein as the target antigen*."

- Is there any scientific to support improved sensitivity of 2-assays to detect an increased risk for the post-change protein?
- What particular manufacturing changes were concerned?

1-assay approach using post-change protein as labelled antigen represents a conservative regulatory approach that minimizes assay-related variability / reliability of comparison (= same as biosimilar case)

Q: Value of a universal positive control antibody?

Although the ADA assay is not quantitative, validation of assay performance using a universal antibody positive control may help regulators understand the relative sensitivity of the method applied

Use single reference antibody specific for molecule to:

- Validate antigenic equivalence of the comparator products
- Benchmark sensitivity
- Confirm level of drug tolerance
- Create universal quality control samples for monitoring routine assay performance & impact of changes in critical reagents

Possible role for WHO standards?

Q: How much post-authorization data?

Additional ***post***-authorisation immunogenicity evaluation required only where there are identified risks / missing information

Ref: EPAR's

epoetin
somatropin
infliximab

→ Immunogenicity-related risks monitored within PASS's

→ Extent of interventional ADA monitoring not clear from EPAR's

filgrastim
follitropin
insulin

→ No additional monitoring required (SmPC warnings only)

Can we make more effective use of prospectively-designed, observational cohort (comparative) studies for higher-risk products?

Summary

1-assay approach is optimal for relative ADA measurement
➔ Validate for antigenic equivalence using universal positive control

ADA assay results should be interpreted relative to clinical indices, including PK, PD, efficacy and safety

There can be no pre-defined “biosimilarity / comparability” margin based on relative immune response (ADA) dynamics *alone*

Same weight of evidence should apply to biosimilarity & manufacturing changes, guided by scale of risk for given molecule + uncertainty associated with detected analytical differences

Post-authorisation monitoring might be useful to identify risks associated with low probability / high severity consequences