Revised EMA immunogenicity guideline, other guidelines and reflections on unwanted immunogenicity.

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Unwanted Immunogenicity

Current Position

Testing for unwanted immunogenicity is integral to product development (clinical & post-marketing phase) for ensuring:

- The clinical safety of a biotherapeutic
- Product Comparability
- When a Biosimilar product is developed

European Medicines Agency

London, 13 December 2007
Doc. Ref. EMEA/CHMP/BMWP/14327/2006

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

GUIDELINE ON IMMUNOGENICITY ASSESSMENT OF BIOTECHNOLOGY-DERIVED THERAPEUTIC PROTEINS

DRAFT AGREED BY BMWP	July 2006
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	January 2007
END OF CONSULTATION (DEADLINE FOR COMMENTS)	July 2007
AGREED BY BMWP	October 2007
ADOPTION BY CHMP	December 2007
DATE FOR COMING INTO EFFECT	April 2008

KEYWORDS	*Immunogenicity, unwanted immune response, biotechnology derived proteins, immunogenicity risk factors, assays, clinical efficacy and safety, risk management*

Guideline On Immunogenicity Assessment Of Biotechnology-Derived Therapeutic Proteins

- Executive Summary
- Introduction
- Scope
- Legal Basis
- Main Guideline Text
- Factors that may influence the development of an immune response against a therapeutic protein
  - Patient and disease related factors,
  - Product related risk factors of immunogenicity
- Non-clinical assessment of immunogenicity and its consequences
- Development of assays for detecting and measuring immune responses in humans.
  - Assay strategy
  - Antibody assays
  - Assay validation
  - Characterization of antibodies to a therapeutic protein
- Potential clinical consequences of immunogenicity
  - Consequences on Efficacy
  - Consequences on Safety
- Immunogenicity and Clinical Development
  - Rationale for sampling schedule and kinetics of the antibody response
  - Consequences on pharmacokinetics of the product
  - Methodology aspects to assess comparability of immunogenicity potential as part of a comparability exercise
  - Immunogenicity in paediatric indications
- Risk Management Plan
- References
- ANNEX 1 - Further details on methods for assessment and characterisation of immunogenicity
- ANNEX 2 - An example of a strategy for antibody detection and characterisation.

Immunogenicity Guideline

- General Guideline has been generally well received.
- Guideline has been used by manufacturers and regulators.
- One criticism has been that it is ‘too general’, does not deal with specific products.
- It is clearly not possible (or desirable) to write specific guidelines for all products.
- However some product classes may merit more specific guidelines.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 May 2012
EMA/CHMP/BMWP/86289/2010
Committee for Medicinal Products for Human Use (CHMP)

Guideline on immunogenicity assessment of monoclonal antibodies intended for in vivo clinical use.

Draft agreed by Similar Biological Medicinal Products Working Party	October 2010
Adoption by CHMP for release for consultation	November 2010
End of consultation (deadline for comments)	May 2011
Final agreed by BMWP	March 2012
Adoption by CHMP	24 May 2012
Date for coming into effect	1 December 2012

Disclaimer: This guideline is intended as an addendum to Guideline on Immunogenicity assessment of biotechnology-derived therapeutic proteins EMEA/CHMP/BMWP/14327/2006 and should be read in conjunction.

Keywords	**Immunogenicity, monoclonal antibodies, similar biological medicinal products, clinical use, assay strategy.**

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mAb Immunogenicity Guideline

- Aimed at development and systematic evaluation of an unwanted immune response against a therapeutic or in vivo diagnostic mAb in recipients.
- Applies to mAbs, their derivatives, products where antibodies are components, e.g., conjugates, Fc linked fusion proteins.
- Aimed at products at final development stage (e.g. marketing authorization application) although principles are relevant to earlier phases of development.
- Considers the major quality and clinical aspects that are important for addressing the problems with detection of and risk related to the development of an unwanted immune response to a particular mAb in a particular clinical indication.

Other EU Guidelines-with immunogenicity content

- **Guideline on similar biological medicinal products containing monoclonal antibodies -** non-clinical & clinical issues

  Came into effect December 2012.

  Mainly concentrates on non-clinical & clinical issues.

  Provides some (additional) guidance on assessment of comparative immunogenicity.

- **Guideline on Similar Biological Medicinal Products Containing Interferon Beta.**

  'External consultation' currently underway. Contains quite a lot on unwanted immunogenicity. For NAb, recommends MxA assay or NAb assay validated against the MxA assay.

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SCIENCE MEDICINES HEALTH

30 May 2012
EMA/CHMP/BMWP/403543/2010
Committee for Medicinal Products for Human Use (CHMP)

Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues

Draft Agreed by Similar Biological Medicinal Products Working Party	**October 2010**
Adoption by CHMP for release for consultation	18 November 2010
End of consultation (deadline for comments)	31 May 2011
Final agreed by BMWP	March 2012
Adoption by CHMP	30 May 2012
Date for coming into effect	1 December 2012

Keywords	***Biosimilars, monoclonal antibodies, similar biological medicinal products, relevant animal model, non-clinical studies, in vitro studies, clinical use, clinical endpoints, extrapolation***

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Immunogenicity Guideline

More recently, some criticism has been made of some parts of the general immunogenicity guideline.

This has been from various users.

Some parts are considered (by some) to be ‘out of date’.

This guideline came into effect in June 2008. Since then CHMP has assessed many marketing authorization applications for biotherapeutics, including biosimilars.

There have been considerable changes in some areas since the guideline was drafted.

Some regulators consider that the guideline is often not followed.

Immunogenicity Guideline-Revision

A revision of the general immunogenicity guideline is planned.

This is proposed in a concept paper which is at (hopefully) the late drafting stage.

It is at present being considered by the working parties of the CHMP (internal consultation phase).

If this is positive the next phase will be external consultation.

Immunogenicity Guideline-Revision

- More specific guidance for the presentation of immunogenicity data.
- Requirements for data needed for antibody assays.
- Roles of *in vitro* and *in vivo* non-clinical studies.
- Use of risk-based approaches to immunogenicity.
- Clinical data needed for assessing correlation of the induced antibodies to allergic and anaphylactoid reactions pharmacokinetics, lack of efficacy.
- Comparative immunogenicity studies for production changes and biosimilars.
- Post-licensing immunological studies.

Important points-Potency

- Assessment of neutralizing activity crucial– Clarification of what is meant by ‘neutralizing antibody’ - abs directed against antigen binding site alone or also those interfering with immunobiological mode of action.
- Requirement for Neutralization assays needs to be considered- Pros & Cons of Bioassays vs Competitive ligand binding (CLB) assays. In some cases CLB assays may be the method of choice.
- Relevance of neutralizing antibody for safety and efficacy needs to be considered. Integration of Ab data with PK/PD assessments required.

Immunogenicity Guideline-Strategy

Having an appropriate STRATEGY in place for immunogenicity assessment as early as possible is clearly important.

This is stressed in the current guideline.

However, strategy is often unclear or absent in dossiers etc.

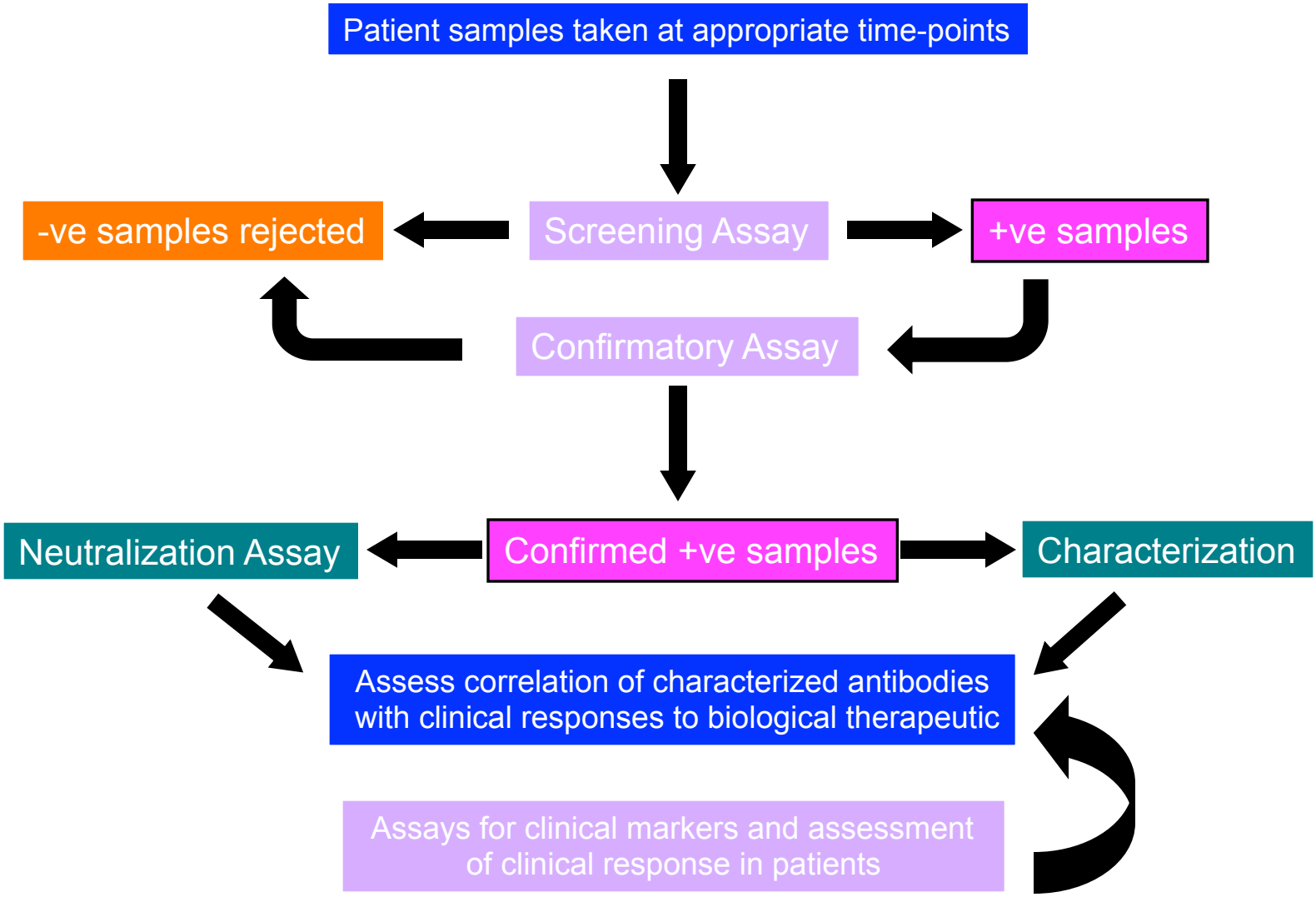
It is sometimes claimed that a strategy e.g. like that shown in the guideline is followed when it isn’t.

Strategy is now more complex than when the guideline was drafted. The importance of biosimilars has significantly affected this.

Immunogenicity Assessment Strategy Design and Interpretation

- **Studies need to be carefully and prospectively designed to ensure all procedures are in place prior to initiation**
  - **Selection, assessment, characterization and validation of assays**
  - **Identification of appropriate sampling points, duration of testing**
  - **Sample volumes and sample processing/storage**
  - **Selection of statistical methods for analysis of data**
- **This applies to all assays as shown in strategy slide**
- **Strategy needs to be established on a case-by-case basis – product, patients, expected clinical parameters**
  - **In chronic use – sequential sampling for a year**
  - **In view of variability of antibody responses, adequate numbers of patients needed**
- **However, unwanted immunogenicity may occur at a level, which is not detected in studies pre-approval so assessment post-approval, as part of pharmacovigilance surveillance is needed**

Strategy for Antibody Detection and Characterization



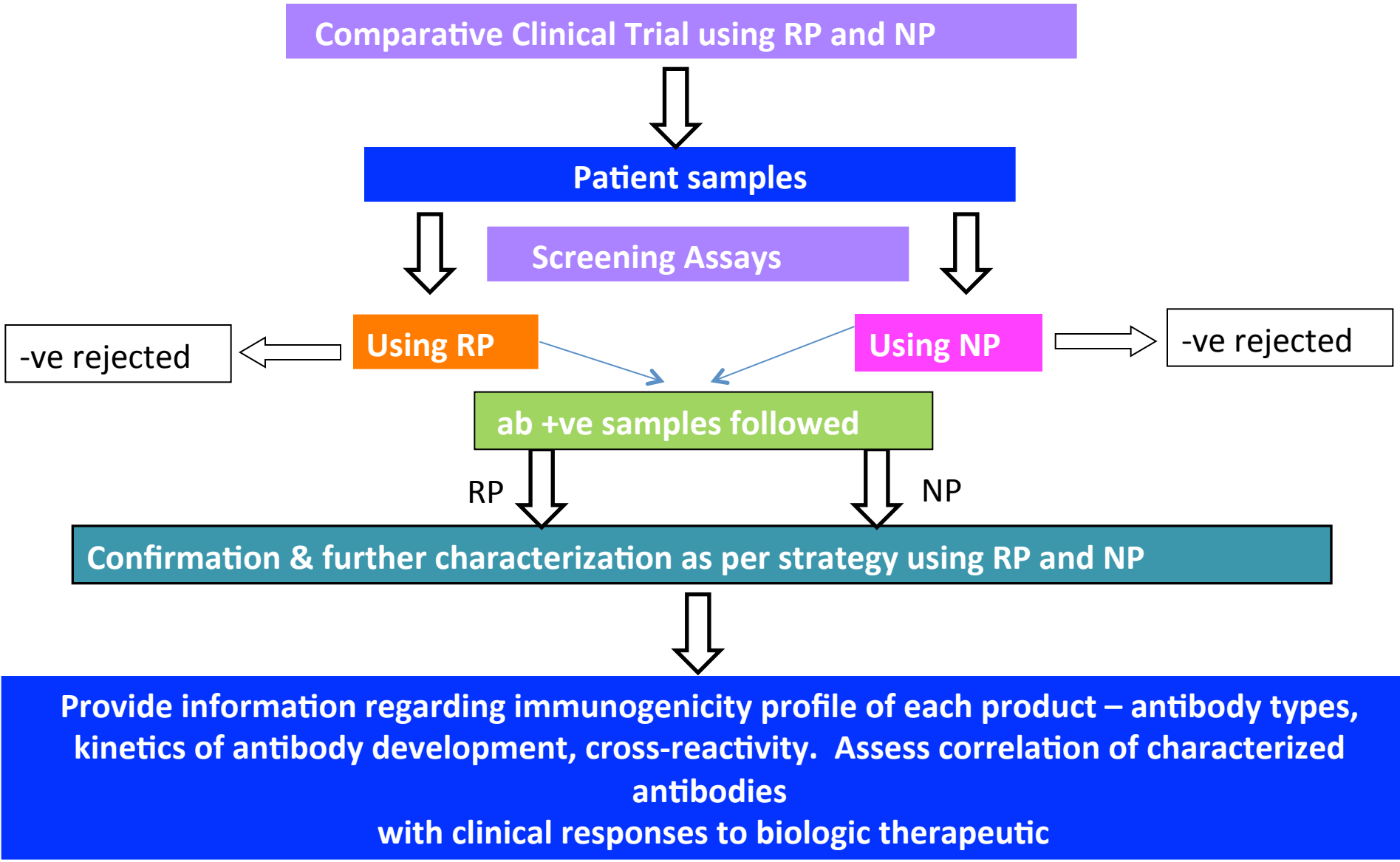
Immunogenicity Guideline

Two biosimilar TNF-alfa monoclonal antibody (mAb) products were approved for clinical use in the European Union on 10 September 2013, following a positive opinion by the Committee for Medicinal Products for Human Use (CHMP) in July 2013. This approval shows the feasibility of using the biosimilar pathway for mAbs and paves the way for further biosimilar mAb products.

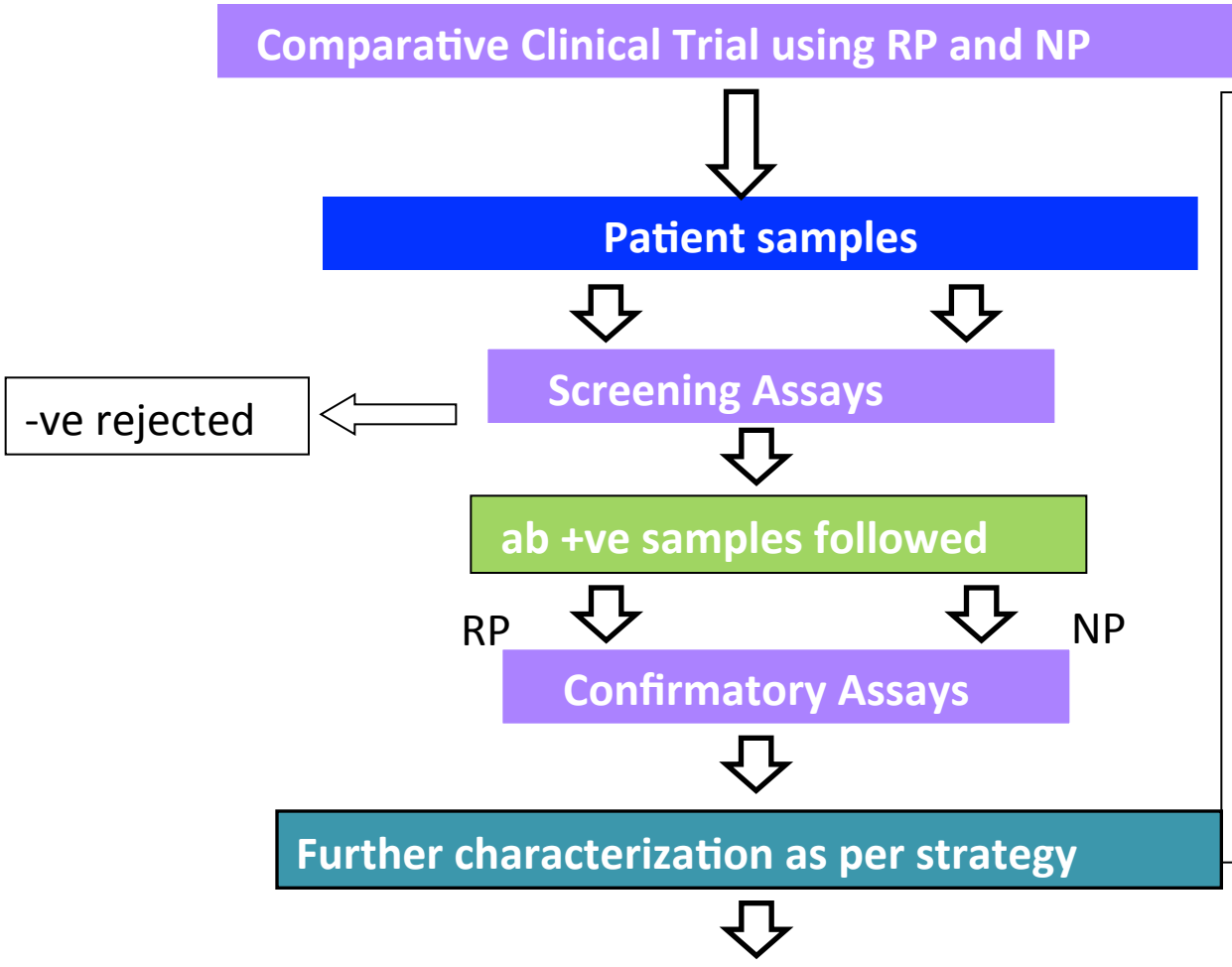
Comparative Immunogenicity

- Compares immunogenicity of different products ;
  Studies need to be designed to demonstrate whether the immunogenicity of the products is the same or significantly different.
- This is likely to affect the design of the studies & their interpretation.
- For this, a homogeneous and clinically relevant patient population should be selected. Head-to-Head studies needed. Same assays & sampling strategy should be used.
- The consequences of immunogenicity also must be compared.
- Post-approval assessment may be necessary, usually as part of pharmacovigilance surveillance.

Relative Immunogenicity



Relative Immunogenicity



If +ve ab controls for both RP and NP comparable in assay using NP as antigen & satisfy certain criteria, an assay using only NP (pos antibody against NP & NP as antigen) possible for both arms. However, if expression systems different, this may not be the right approach

Provide information regarding immunogenicity of each product – titres etc, kinetics, cross-reactivity. Assess correlation of characterized antibodies with clinical responses to biologic therapeutic

Unwanted Immunogenicity-Reflection

- Unwanted immunogenicity is clearly regarded as a problem with biologicals.
- But it is still misunderstood by many!
- Unfortunately, this situation has not significantly changed since the ‘early days’.
- Understanding of the concept of unwanted immunogenicity is generally better than it was.
- But which biologicals or types of biologicals are immunogenic is less well understood.
- Consequences of immunogenicity are also often not judged correctly.

Unwanted Immunogenicity-Reflection

Much immunogenicity data is published or available in other ways.

This is often not difficult to understand or interpret.

Immunogenicity studies are often conducted well and this contrasts with the situation in the ‘early days’, although there are still exceptions to this.

But the data often seems to be ignored when making general statements relating to immunogenicity.

It seems to be often forgotten that ALL biologicals have the potential to be immunogenic.

Unwanted Immunogenicity-Reflection

So: data is around in profusion, some of it good and clear.

It unambiguously shows that many (most!) biotherapeutic products can be immunogenic.

Consequences are also usually clear.

But all of this is often ignored.

Unwanted Immunogenicity-Reflection

Common misconceptions:

‘All mAbs are immunogenic’

‘All mAbs are immunogenic and it doesn’t matter’

‘MAbs are not immunogenic, because they are low risk’

‘Biosimilars are a real problem because they are dangerously immunogenic whereas innovator versions are safer because they are not immunogenic’

‘Biosimilar mAb X is OK from the immunogenicity perspective because the reference product showed very low immunogenicity’

Unwanted Immunogenicity-Reflection

Common misconceptions:

‘Biosimilars are unsafe because they are immunogenic. A clear example of this is erythropoietin where biosimilars are dangerously immunogenic whereas innovator erythropoietins are not’

Clearly all of these are incorrect.

Perhaps they reflect ignorance or a deliberate attempt to mislead.

Conclusions

- Unwanted Immunogenicity remains an important concern for all biotherapeutics.
- Much data is now available on unwanted immunogenicity.
- There are still misconceptions over unwanted immunogenicity.
- The CHMP (EMA) general immunogenicity guideline is to be revised, taking account of developments since its drafting and other factors.

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