



**EMA Workshop on Biosimilar Monoclonal Antibodies, 2 July 2009**

**Session 3 - Clinical Issues  
Innovator Industry Presentation**

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# Monoclonal Antibody (mAb) Biosimilars

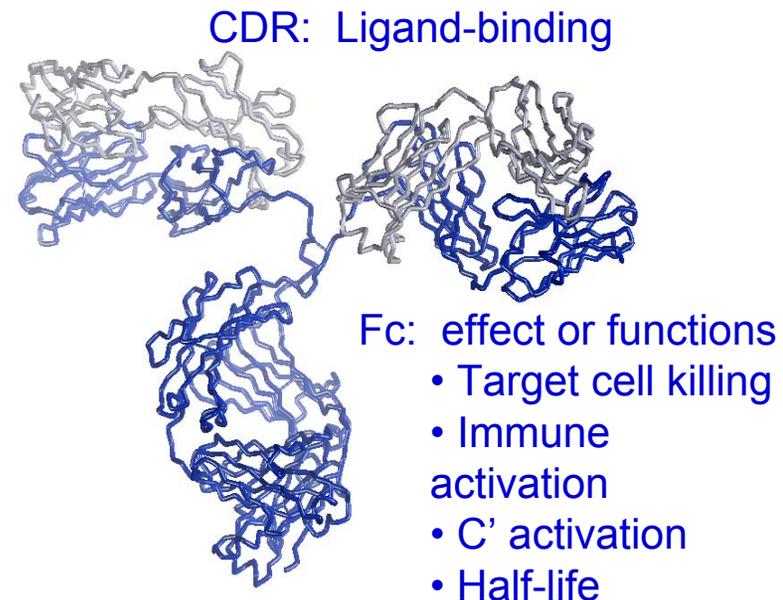
## Clinical Testing: General Principles

The approach to clinical testing of mAb biosimilars should build upon the principles used for simpler proteins:

- Identical amino acid sequence and high similarity with regard to chemical, physical, and biological characteristics should first be demonstrated in laboratory/non-clinical testing
- Clinical similarity may then be tested head-to-head
- Extrapolation across endpoints, populations, or diseases should be justified scientifically

However, application of those principles should take into account particular properties of monoclonal antibodies:

- Monoclonal antibodies are large and complex
- Multiple features determine clinical activities
- Different activities may depend on diff. features
- Critical structure-function relationships are often not well understood
- mAbs are generally used to treat serious and/or life-threatening diseases



## 3.3 Extrapolation of efficacy across indications

“Justification will depend on, e.g., . . . whether or not the same mechanisms of action or the same receptors are involved in all indications.” “Sometimes, the mechanism of action of the biologic product will be disease-specific.”\*

Smaller cytokines (e.g., erythropoietin, G-CSF, insulin, somatropin) typically have a single active site that binds the same receptor (or family of receptors) in all indications

In contrast:

- Monoclonal Antibodies have ***diverse functional activities*** derived from different features of the same molecule and interact with diverse receptors
  - Some effects may derive directly from binding, e.g., antigen neutralization, receptor blockade
  - Others may require binding plus activation of other processes, e.g., ADCC, C' fixation, clearance
  - Other activities may depend on various physicochemical characteristics, e.g., penetration or transport into specific tissues
- Monoclonal antibodies may be used in quite ***diverse indications***, e.g.,
  - Anti-TNF: psoriasis, rheumatoid arthritis, Crohn's disease, others
  - Anti-B cell: lymphoma, rheumatoid arthritis, other
  - Anti-VEGF: mCRC, mNSCLC, mBC, GBM, RCC
- Different indications can require different (combinations of) activities and receptors, in different sites, over different time courses, in different pharmacologic milieu

# 3.3 Extrapolation of efficacy across indications

Therefore, antibodies with similar effects in one disease may have different effects in a second indication if the second indication requires:

- A different mechanism(s) of action (calling on a different part of the mAb interacting with a different receptor)
- Action in a different site (tissue penetration and transport)
- Longer time frame of action (PK is largely FcR determined)
- Amount of target antigen expressed (e.g., tumor burden, antigen per cell)
- Use of different concomitant medications (which can impact PK or pharmacology)

## Regulatory considerations

- To establish efficacy in an initial indication, “Usually comparative clinical trials will be necessary . . . Margins should be pre-specified and justified, primarily on clinical grounds . . . Assay sensitivity has to be ensured.”\*
- Extrapolation of efficacy may then be considered where justified, however justification may be difficult where differences such as those listed above exist
- Such differences will often exist or be impossible to exclude due to the size, complexity, mechanisms of action, and multifunctionality of mAbs

# 3.3 Extrapolation of efficacy across indications

Examples of considerations before deciding to extrapolate:

- With regard to immunologic diseases (3.3a)
  - Of anti-TNFs that are effective in psoriasis and RA, some are not in Crohn's Disease
    - Similar efficacy in psoriasis and RA may not extrapolate to Crohn's disease
  - Methotrexate, used with anti-TNFs in RA, affects their PK, and their efficacy
    - Similar efficacy in combination with methotrexate might not predict similar efficacy as monotherapy
  - Progressive disability may be the implication of diminished efficacy (e.g., RA), even small risks of lower efficacy are a substantial concern
- With regard to anti-tumour antibodies (3.3b)
  - With anti-VEGF or anti-CD20 used in diverse tumor types, differences in target antigen expression, form, distribution, tumour burden and regimen could elicit clinical differences in one indication not apparent in another
  - Where shortened survival may be the implication, even small risks of lower efficacy should be excluded

## Anti-TNF mAb

- Rheum. Arthr.
- Juv. Idio. arthr.
- Psoriatic arthr.
- Ank. Spond.
- Plaque Psor.
- Ulc. Colitis
- Crohn's Dis.

## Anti-VEGF mAb

- mCRC
- NSCLC
- mBC
- GBM
- RCC

## 3.6 Which endpoints should be used?

### 3.6 a. Endpoints that measure benefit

- EMEA Guidance: PK/PD studies may be sufficient where, among other things
  - There is an “accepted surrogate marker for efficacy”\*
  - It can “explain changes in clinical outcome to a large extent”\*
  - The relationship between dose and this surrogate marker is well known
  - There is “Sufficient knowledge of pharmacodynamic properties of the reference.”\*
- Due to the complexity of mAbs and their multiple binding regions, activities, and mechanisms, these conditions will often not apply
  - Biomarker may not reflect all relevant activities of a mAb
  - Often relevant activity of a mAb not fully understood
  - Dose response relations of competitive inhibitors are often complex
- Thus, differences between an originator and a proposed biosimilar may impact the effect on clinical outcomes without impacting the effect on biomarkers
- Rarely do markers provide quantitative prediction of efficacy
  - Modest differences in efficacy could have significant, irreversible impact in many diseases treated by mAbs

## 3.6 Which endpoints should be used?

### 3.6 a. Endpoints that measure benefit

#### Regulatory implications

- The science-based principles presented in present EMEA guidance will, for many mAbs, dictate study of clinical benefit endpoints
- Selection of which clinical benefit endpoint(s) will raise important considerations, e.g.
  - Might short-term benefits predict long-term benefits?
  - Might PFS predict OS?
- The seriousness of diseases treated and the implications of under treatment or delay in treatment should be considered when deciding the acceptability of surrogates that may not quantitatively predict benefit
- Where clinical outcomes data are needed, biomarker data can supplement those data, potentially decreasing amount of clinical outcomes data needed and increasing confidence in clinical similarity

## 3.6 Which endpoints should be used?

### 3.6 b & c: Activity endpoints

- Biomarkers and “activity endpoints” can often be measured faster, cheaper, and with more precision than can clinical outcome measures
- A “highly similar” biosimilar should be highly similar in all effects in patients
- Similarity in effects on a biomarker will **not** always predict similarity of effects on clinical outcome

### Regulatory implications

- Head-to-head comparisons of effects on biomarkers will be powerful tools in identifying or excluding some clinical differences and may prove valuable in supporting extrapolation to other indications
- The demonstration of similar effects on easily measured biomarkers should be considered necessary, but not usually sufficient, to establish equivalence

### Examples

- In immunology, impact on circulating levels of cytokines and inflammatory markers
- For an antibody to B lymphocytes, impact on B lymphocyte counts

## 3.8: Risk-based approach to immunogenicity data

Increased or altered immunogenicity in **any** candidate biosimilar mAb has the potential for significant clinical implications

- Clinically important consequences of immunogenicity are by no means limited to the neutralization of “endogenous counterparts”
  - Impaired efficacy (e.g., due to increased clearance or neutralization) is always a risk and can be serious
  - Immunogenicity of antibodies can lead to immune complex disease
  - Injection site reactions and infusion reactions can be serious and can be related to immunogenicity
- Antibody generated in response to an immunogenic biosimilar may well cross-react with and (possibly irreversibly) impair efficacy of the innovator product

### Regulatory considerations

- All mAb should be assessed for immunogenicity as described in EMEA Guidance EMEA/CHMP/BMWP/14327/2006
- Biosimilars should be studied head-to-head with the originator (but similar incidence of immunogenicity does not necessarily mean similar immunogenicity)

# Summary – Clinical Issues

- Strong CMC and non-clinical data limiting potential differences are critical
- The EMEA guidance documents relevant to biosimilar biotechnology-derived proteins serve as a good starting point for clinical requirements for mAbs
- Some key properties of monoclonal antibodies, e.g.,
  - Monoclonal antibodies are much larger than most cytokines
  - mAbs have multiple relevant activities, determined by different sites
    - two monoclonal antibodies can be highly similar with regard to one activity but different with regard to another
  - Many monoclonal antibodies are used to treat serious and/or life-threatening disease where delayed treatment could have permanent adverse effects
- Have important implications for how EMEA guidance should be applied
  - Extrapolating data between indications should only be done where mechanisms of action in both indications are understood and highly similar
  - The implications of immunogenicity for mAbs are always potentially substantial. Immunogenicity cannot be predicted so it must be measured directly

# **Additional Questions & Back-up Slides**

# Questions 3.1 and 3.2

## Pharmacokinetics/Pharmacodynamics:

### Pharmacokinetics of Monoclonal Antibodies

- Nonlinear (dose-dependent)
- Time dependent
- Can differ across patient populations

***Clinical testing should be comparative and designed to assess the time-dependent and nonlinear characteristics of monoclonal antibody pharmacokinetics.***

### 3.1 What role could new methodologies play (e.g. simulation, modelling, biomarkers)?

- Supportive analyses
- Population PK or PK/PD modelling allows for identification of covariates (sex, age, body weight, baseline disease etc.) that may influence PK or the PK/PD relationship
- Clinical trial simulations may allow for prediction of response in patient subsets and determination of differences between the innovator product and biosimilar

### 3.2 What population(s) should PK/PD be measured?

- Should consider that PK or PK/PD relationship could be different across patient populations due to mechanism of action, concomitant medications, age, disease status etc
- Less is understood about PK of monoclonal antibodies in younger pediatric populations and thus separate studies should be considered
- Case by case basis

## 3.4 Extrapolation of safety data across indications

Extrapolation of safety across indications may be adversely impacted any of the following types of differences

- Concomitant medications
- Immune competence of patients
- Approved dose
- Susceptibility in the populations to specific potential toxicities

### Regulatory implications

- Safety and immunogenicity data in the target population and disease should be provided except where either no differences of these types exist or their possibility of their impacting safety can be shown to be negligible
- Where an innovator drug has safety concerns in a second indication that are different from or greater in magnitude than those in the first, the biosimilar generally should be assessed for those concerns as well

## Question 3.7.

# What role could new methodologies play: Modelling/simulation of endpoints

Exposure response modelling/simulation of efficacy endpoints could play a supportive role.

- Utilizes all clinical data
  - A sensitive method for identification of differences between drug and biosimilar
  - A smaller sample size may be possible to demonstrate a difference in exposure-response relationship between innovator and biosimilar
- Useful for identification of covariates (sex, age, body weight, baseline disease etc.) that may influence exposure-response relationship
  - Clinical trial simulations may allow for prediction of response in patient subsets and determination of similarities or differences between innovator product and biosimilar

Exposure response modelling of safety endpoints

- More complex other factors aside PK could contribute (ie immunogenicity)
- Some safety outcomes occur in very small percent of a patient population and difficult to assess

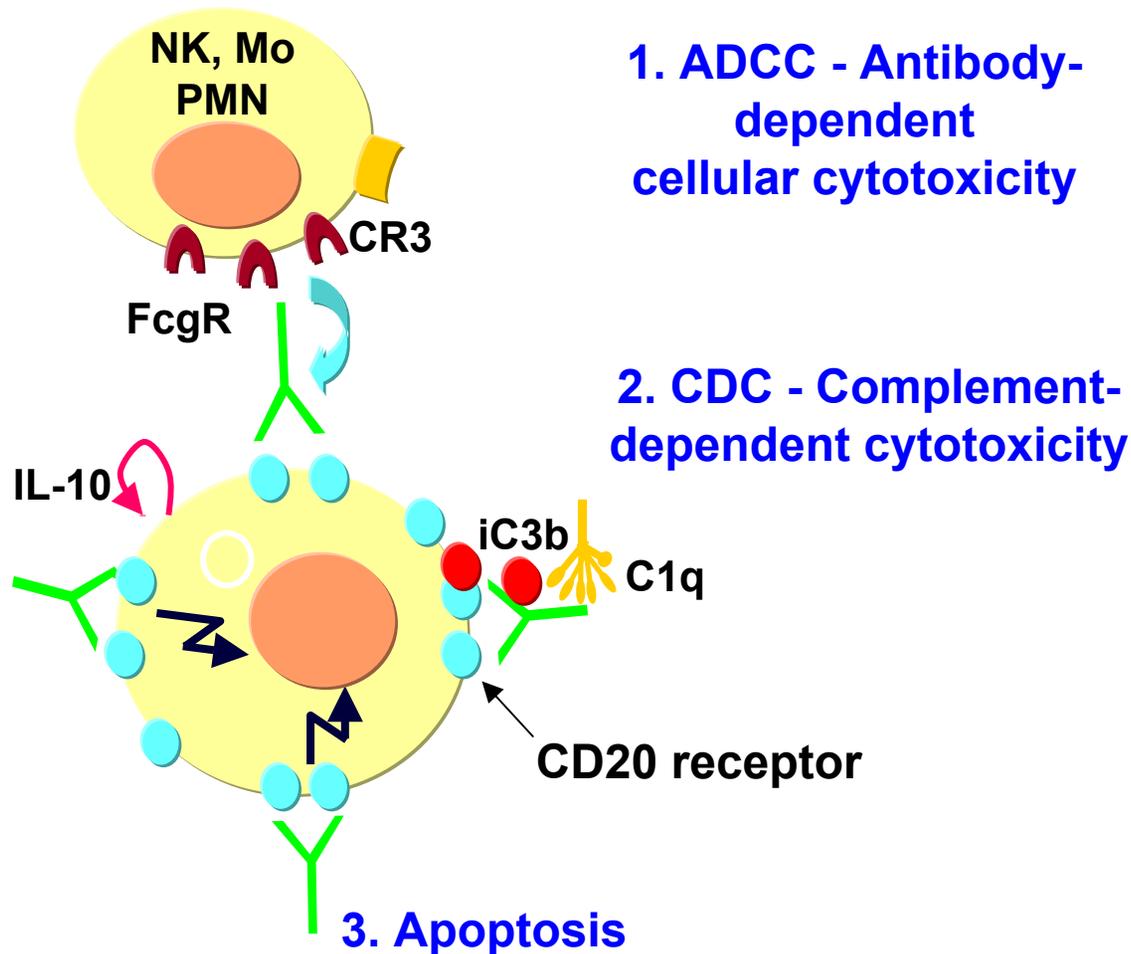
***Ideally clinical testing should be a comparative study of appropriate duration for the indication. The study should be of sufficient size to allow for identification of covariates that may influence the exposure-response relationship.***

# **Case Study**

## **Anti-tumoural MAb**

# 3.3 Extrapolation of efficacy across indications

Mode of Action of Rituximab – 3 main pathways



### 3.3 Extrapolation of efficacy across indications

Approved dose and schedule of rituximab varies across diseases

- 4 weekly infusions 375mg/m<sup>2</sup> (relapsed NHL)
- 8 infusions q 3wks 375mg/m<sup>2</sup> with chemotherapy (first-line NHL)
- 6 infusions q 4wks 500mg/m<sup>2</sup> with chemotherapy (CLL)
- 2 infusions 1000mg q 15d (RA)

## 3.3 Extrapolation of efficacy across indications

- Extrapolation of efficacy across diseases is difficult and risky
- Net contribution of each mode of action (ADCC, CDC, apoptosis) in vivo is unknown
- Preclinical and non-clinical testing suggests different contribution of mode of action, depending on host and disease factors, i.e.
  - concomitant medication (steroids, chemotherapy)
  - intact effector mechanisms (complement, NK cells)
  - CD20 receptor number and density (CLL)

# 3.3 Extrapolation of efficacy across indications

Dose and schedule of rituximab varies across diseases

- CLL – clear rituximab dose – response relationship<sup>1</sup>
- NHL – no dose – response relationship<sup>2</sup>
- RA – weak dose-response relationship with saturation<sup>3</sup>

1 O'Brien S et al. J Clin Oncol. 2001 Apr 15;19(8):2165-70

2 Coiffier B et al. Blood 92 (1998), pp. 1927–1932

3 Edwards JC et al. Rheumatology 2001 Feb;40(2):205-11

## 3.5 For antitumoural mAbs, what would be acceptable patient sub-population in different indications?

- For Rituximab, the mode of action in vivo is difficult to assess and poorly understood
- Clinical research has led to relevant differences in dosing and administration of the antibody
- As per definition, biosimilars cannot be identical to rituximab, any change in non-clinical or pre-clinical properties might induce changes in the way the molecule acts in vivo
- Consequently, any simple extrapolation from one disease to another, where the MoA might be different, puts patients at risk and needs to be avoided

# 3.5 For antitumoural mAbs, what would be acceptable patient sub-population in different indications?

- Example – Rituximab in Diffuse-large B-Cell Lymphoma (DLBCL)
- Goal of treatment is cure  
Approx 10-15 percentage points more patients are cured due to the addition of rituximab to standard chemotherapy (CHOP)<sup>1,2</sup>
- A biosimilar labeled in this indication needs to prove the same outcome in the same indication and population (i.e. first-line DLBCL) in order not to put patients at risk for inferior outcomes. A similar or higher survival benefit needs to be shown against rituximab. This can only be done in a randomised trial. Any compromises are not acceptable when the goal of therapy is cure

1 Feugier P J Clin Oncol. 2005 Jun 20;23(18):4117-26

2 Coiffier B N Engl J Med. 2002 Jan 24;346(4):235-42.  
London, 2 July 2009

## 3.5 For antitumoural mAbs, what would be acceptable patient sub-population in different indications?

- Example – Rituximab in Chronic Lymphocytic Leukaemia (CLL)
- Goal of treatment is prolonged PFS  
Approx 8-10 months median PFS gain due to the addition of rituximab to standard chemotherapy (FC)<sup>1,2</sup>
- Extrapolation from one concomitant chemotherapy to another may be possible, i.e. results of R-F seem to be in line with R-FC chemotherapy<sup>3</sup>. However, a biosimilar labeled for this indication needs to prove the same outcome in the same indication and population (i.e. first-line CLL) at least for one combination (e.g. R-FC) in order not to put patients at risk for inferior outcomes. A similar or higher PFS benefit needs to be shown against rituximab. This can only be done in a randomised trial

## 3.5 For antitumoural mAbs, what would be acceptable patient sub-population in different indications?

- Example - Rituximab
- Extrapolation from one disease to another one might put patients at risk and should be avoided (see 3.3.)
- Extrapolation from line of treatment (ie first-line vs relapsed vs refractory) might put patients at risk, due to the immune system more affected in later lines of disease treatment, and should be avoided
- Extrapolation from single-agent treatment to combination treatments is not warranted due to high probably of different net contribution of the mode of actions
- Extrapolation from one concomitant treatment to others may be possible, allowing for clinical testing of a biosimilar only with one chemotherapy or concomitant treatment