

Clinical Development Programmes for Biosimilars

- **Regulatory scenario**
- **Prerequisites and points to consider for clinical development**
- **What needs NOT to be done**
Extension of indication
- **Core clinical development programme**
- **Potential role of Clinical Pharmacology**

REGULATORY SCENARIO

EMA "similar biological medicinal products" are
no generic medicinal products

Set of guidelines with emphasis on biotechnology-
derived proteins

Decision on a case by case basis

SCIENTIFIC ADVICE

Health Canada "Subsequent Entry Biologics" (SEBs)

Draft guidance available, issued 2008/01/30

consultation in Ottawa in May 2008

US FDA "Follow On Proteins" (FOPs)

No guidance available yet

EMA GUIDELINES WITH IMPACT ON CLINICAL DEVELOPMENT

The overarching guideline (EMA/CHMP/437/04)
Guideline on similar biological medicinal products

Biotechnology-derived proteins
(EMA/CHMP/BMWP/42832/05)
Non clinical and clinical issues

Annex: recombinant erythropoietins
(EMA/CHMP/BMWP/94526/2005 Corr.)

Annex: recombinant granulocyte-colony stimulating factor
(EMA/CHMP/BMWP/31329/2005)

Annex: somatotropin
(EMA/CHMP/BMWP/94528/2005)

Annex: recombinant human soluble insulin
(EMA/CHMP/BMWP/32775/2005)

PREREQUISITES AND POINTS TO CONSIDER FOR CLINICAL DEVELOPMENT

The SAME reference product (authorised in the community) should be used throughout development for quality, safety and efficacy.

CAVE: batch to batch variability of the reference compound

deviation from the labelled strength with the reference compound

The European Pharmacopoeia monograph for epoetin allows a potency range of 80 - 125%

Differences in impurity profiles between the "biosimilar" and the reference compound need to be justified; may have impact on non clinical and clinical data package

LOOK FOR DIFFERENCES!

This is important for a pivotal "Comparability Exercise": adequate characterization of the "biosimilar" vs. the reference (*not per se*),

e.g. receptor binding studies, cell proliferation assay (e.g. from quality-related bioassays); animal PD in an appropriate model (e.g. as documented in the European Pharmacopoeia); repeat dose toxicity in a relevant species

WHAT NEEDS NOT TO BE DONE?

No full data package for non clinical and clinical data

Distribution, metabolism, (elimination), interactions,
PK in special populations not required

Not all approved clinical indications of the reference
compound need necessarily to be investigated

EXTENSION OF INDICATION

"Appropriate demonstration of efficacy and safety in the most sensitive clinical model (renal failure), may allow extension to other indications of the reference product if the mode of action is the same and if appropriately justified by current scientific knowledge."

(EMA/CHMP/94526/2005)

"Demonstration of efficacy and safety in renal anaemia may allow extrapolation to other indications of the reference medicinal product if appropriately justified by the applicant."

(EMA/CHMP/BMWP/94526/2005 Corr.)

CORE CLINICAL DEVELOPMENT PROGRAMME FOR BIOTECHNOLOGY-DERIVED PROTEINS

(EMA/CHMP/BMWP/42832/2005)

The "Comparability Exercise" is based on:

PHARMACOKINETICS: "The design of comparative PK studies should not necessarily mimic that of the standard "clinical comparability" design (CHMP/EWP/QWP/1401/98), since similarity in terms of absorption/bioavailability is not the only parameter of interest. In fact, differences in elimination characteristics between products e.g clearance and elimination half-life should be explored.

The choice of the design for single dose studies, steady-state studies should be justified by the applicant.

The acceptance range to conclude clinical comparability with respect to any pharmacokinetic parameter should be based on clinical judgement,

.... clinical comparability limits should be defined and justified prior to conducting the study."

Example epoetin:

s.c. and i.v. administration required

single dose cross-over

healthy volunteers acceptable

primary endpoint: AUC

secondary endpoint: C_{max} and T_{1/2} or C_{1/F}

CORE CLINICAL DEVELOPMENT PROGRAMME FOR BIOTECHNOLOGY-DERIVED PROTEINS

(EMA/CHMP/BMWP/42832/2005)

The "Comparability Exercise" is based on: *(continued)*

PHARMACODYNAMICS: "PD markers should be selected on the basis of their relevance to demonstrate therapeutic efficacy....in a population where the possible differences can best be observed.

Combined PK / PD studies may provide useful information on the relationship between exposure and effect.

The selected dose should be in the steep part of the dose-response curve.

Studies at more than one dose level may be useful."

Example epoetin:

"Pharmacodynamics ... evaluated as part of the comparative pharmacokinetic studies.

In single dose studies, reticulocyte count is the most relevant and therefore recommended pharmacodynamic marker...

On the other hand, reticulocyte count is not an established surrogate marker for efficacy of epoetin and therefore no suitable endpoint in clinical trials."

CORE CLINICAL DEVELOPMENT PROGRAMME FOR BIOTECHNOLOGY-DERIVED PROTEINS

(EMA/CHMP/BMWP/42832/2005)

The "Comparability Exercise" is based on: *(continued)*

EFFICACY TRIALS: "Usually comparative clinical trials will be necessary to demonstrate clinical comparability...

Clinical comparability margins should be pre-specified and justified, primarily on clinical grounds.... assay sensitivity (see ICH topic E10) has to be ensured".

Example epoetin:

"...at least two adequately powered, randomised, parallel group clinical trials.

Confirmatory studies should be double-blind...

... Patients with renal anaemia are ... recommended as the target study population as this would provide the most sensitive model.

... correction phase study in a pre-dialysis population using s.c. epoetin

... maintenance phase study in a haemodialysis population using i.v. epoetin"

Preferred primary endpoint:

"haemoglobin responder rate" correction phase study

"haemoglobin maintenance rate" maintenance phase study

THE GUIDELINE DOES NOT INDICATE
THE DIFFERENCE THAT IS CLINICALLY NOT MEANINGFUL.

CORE CLINICAL DEVELOPMENT PROGRAMME FOR BIOTECHNOLOGY-DERIVED PROTEINS

(EMA/CHMP/BMWP/42832/2005)

The "Comparability Exercise" is based on: *(continued)*

SAFETY AND PHARMACOVIGILANCE REQUIREMENTS:

"Prelicensing safety data should be obtained in a number of patients sufficient to address the adverse effect profiles...

...clinical safety... must be monitored closely on an ongoing basis during the post-approval phase including continued benefit-risk assessment.

The applicant should give a risk specification in the application dossier...

...the applicant should present a risk management programme / pharmacovigilance plan...

PASS / RMP

IMMUNOGENICITY:

"In case of chronic administration, one-year follow up data will be required pre-licensing."

POTENTIAL ROLE OF CLINICAL PHARMACOLOGY

(EMA/CHMP/BMWP/42832/2005)

Confirmatory PK/PD studies may be sufficient to demonstrate clinical comparability, provided that all the following conditions are met:

- PK of the reference medicinal product well characterised
- sufficient knowledge of PD properties
- therapeutic "concentration-response" curve sufficiently characterised
- at least one PD marker accepted as a surrogate marker for efficacy; relationship dose/exposure to the product and the surrogate marker well known

Examples:

ANC & G-CSF

early viral load reduction in chronic hepatitis C
& alpha interferons