Clinical Requirements for the Development of Biosimilar Products

Part II*

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3.3 Product-specific annexes

The annexes to this guideline lay down the product specific non-clinical and clinical requirements. The sponsor is well advised to seek for scientific advice, i.e. for study design, duration, choice of doses, efficacy, PD endpoints and comparability margins.

With regard to pharmacovigilance and in addition to the requirements of EMEA/CHMP/42832/05 the risk management program should detail how risks will be addressed in post-marketing follow-up. Special attention should be paid to immunogenicity and potential rare serious adverse events. In order to further study the safety profile of the biosimilar product, particularly safety data from rare serious adverse events should be collected from a cohort of patients representing all approved therapeutic indications.

The Working Party on similar biological medicinal products (BMWP) has recommended that a further guideline be drafted on the non-clinical aspects of the development and assessment of similar biological medicinal products containing Low Molecular Weight Heparins (LMWH) [14].

* Part I see Pharm Ind. 2008 (70); 7: 825–829.

Table 1 (p. 927) gives a summary on the studies required for the various product types (modified; by Markgraf K. Biosimilars in the USA and the EU, Master Thesis, under preparation).

3.4 Immunogenicity Assessment of Biotechnology-derived Therapeutic Proteins (EMEA/CHMP/14327/06)

The guideline describes in detail the factors that may influence the development of an immune response against therapeutic proteins, the development of assays for measuring immune responses in humans, the potential clinical consequences, the clinical development regarding immunogenicity and pharmacovigilance aspects.

Therapeutic proteins show species differences in most cases. Human proteins will be recognized as foreign proteins by animals. Thus, the predictability of non-clinical studies for evaluation of immunogenicity is considered low. Non-clinical studies aiming at predicting immunogenicity in humans are normally not required.

A change in PK may be an early indication of antibody formation. If antibodies are detected during the clinical program, the impact on PK in the individual patient including binding characteristics (binding vs. neutralizing) should be evaluated.

Immunogenicity evaluation should be part of safety studies. The data should be systematically collected from a sufficiently large number of patients to characterize the variability in antibody response. For a clinical trial immunogenicity should be evaluated in all patients and not only in a symptom-driven manner. Since the comparative evaluation of immunogenicity both inter-product (i.e. biosimilar products or products in the same class) and intra-product (i.e. between different versions of the product, indications or different patient populations for a given product) is of relevance, a homogeneous patient population should be selected that allows for such comparisons.

The results of the immunological studies should be included in the relevant sections of the SmPC. The prescriber should be provided with data and guidance on how a patient with loss of efficacy should be handled over time, e.g. by an increase of dose or a reduced dosing interval or cessation of treatment.

Paediatric indications

Recombinant technology has allowed the development of proteins...
for use in genetic disorders where previous substitution treatment has not been available. Children are the most likely subjects exposed to these products and may be at high risk for antibody development. When studying the product in a paediatric indication, posology and treatment schedules should be selected and justified accordingly. Patients should be stratified by age and immunogenicity data should be evaluated and presented separately for each age stratum.

Post-marketing
Further systematic immunogenicity testing might become necessary after approval. The extent of immunogenicity data to be collected in the post-marketing setting will depend on various factors including:
- Disease-related factors like its prevalence, the vulnerability of the patients, availability of alternative therapies, duration of treatment;
- Pre-authorization immunogenicity findings including impact on efficacy and safety;
- Experience on immunogenicity with similar proteins or related members from that class of proteins, including proteins manufactured with similar production processes.

3.5 Comparability of Biotechnological Products after a change in the manufacturing process: Non-Clinical and Clinical Issues (EMEACHMP/BMWP/101695/06)
The guideline gives advice on the non-clinical and clinical requirements of the comparability exercise comparing post-change to pre-change product.

The need for non-clinical or clinical studies is a risk-based approach. If a manufacturer can provide evidence of comparability by physico-chemical and biological studies, non-clinical or clinical studies with the post-change product are not warranted. In cases, where an effect on efficacy or safety cannot be ruled out, additional non-clinical or clinical studies are necessary.

The strategy for comparability testing (i.e. regarding patient population, indication, endpoints, safety findings) should best predict or detect clinically relevant differences. The need, extent and nature of non-clinical or clinical comparability studies will be determined in consideration of various risk factors related to the process, the active substance, the product and the differences between pre- and post-change product. Data from non-clinical studies provide useful signals of potential therapeutic and safety differences.

Non-clinical and clinical data need to be available before marketing the new version of the product. Depending on the product and the indication, approval of the process change might be based on PD data. Additional clinical/safety data including immunogenicity data may be provided after approval.

Clinical data
The requirement for a clinical comparative efficacy and safety study depends on the stage of development, the type of change and the impact on quality attributes. The extent of the comparability studies will increase, if manufacturing changes are introduced at the later stages of clinical development.

Pharmacokinetic studies
A single-dose crossover study considering carry-over effects is acceptable. If the product can be administered by more than one route (e.g. s.c. and i.v.), it may become necessary to test all routes. The selected dose should be in the steep part of the dose-response curve. The choice of the population (healthy volunteers/patients) is primarily driven by the mode of action. The design of PK studies should not necessarily mimic that of the standard "clinical comparability" design [17], since similarity in terms of absorption/bioavailability is not the only parameter of interest.

Pharmacodynamic studies
PD studies should preferably be evaluated as part of the comparative PK study, since alterations in PD can sometimes be explained by altered kinetics. An endpoint should be selected that is sensitive enough to detect small differences, measurable with sufficient precision and clinically relevant for the target population. Studies at more than one dose level may be useful [27].

Efficacy studies
If no suitable marker exists, or if PD studies fail to establish comparability clearly, a double blind comparative equivalence clinical trial using
clinical endpoints will be required. The sample size should be based on considerations on clinical efficacy and on detection of differences in safety. It should be justified, if efficacy and safety results of the comparative study in one indication or population are extrapolated to other populations or indications.

**Clinical safety and pharmacovigilance requirements**

Safety data can be gathered as part of the efficacy study. Study duration and sample size calculation should consider frequency, severity and seriousness of expected adverse events. Specific safety endpoints should be selected taking into account the typical safety findings known for the product or the product class and potential other safety findings, which can be deduced from the mechanism of action, also unexpected ones. Immunogenicity should be integral part of the safety evaluation. Not only adverse events including the incidence but also possible differences in clinical presentation should be discussed.

The risk specification including a description of possible safety issues should be related to the changes in the manufacturing process. Within the authorization procedure a risk management plan or, after licensing of the product, an update of the existing one should be presented taking into account any specific safety monitoring imposed to the pre-change product and/or product class. In the PSURs any information

<table>
<thead>
<tr>
<th>Product</th>
<th>Characteristics</th>
<th>Non-clinical studies</th>
<th>Clinical studies</th>
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<tr>
<td></td>
<td></td>
<td>PD</td>
<td>Toxicology</td>
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<tr>
<td>Erythropoietins [15]</td>
<td>Recombinant erythropoietin produced in mammalian cells. Mainly used for the treatment of anaemia.</td>
<td>– a number of in vitro cell based bioassays</td>
<td>at least 1 repeat dose toxicity study for at least 4 weeks</td>
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<tr>
<td>Granulocyte-colony stimulating factor (G-CSF) [11]</td>
<td>Recombinant G-CSF produced in E. coli and CHO cells. Used for reduction or treatment of neutropenia.</td>
<td>– in vitro cell based bioassays or receptor-binding assays</td>
<td>at least 1 repeat dose toxicity study over at least 28 days</td>
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<tr>
<td>Recombinant human insulin [12]</td>
<td>Used for treat- ment of diabe- tes.</td>
<td>– comparative in vitro bioassays for affinity, in- sulin- and IGF-1-receptor binding assays</td>
<td>at least 1 repeat dose toxicity study over at least 4 weeks</td>
</tr>
<tr>
<td>Recombinant interferon alpha [9]</td>
<td>Used for treat- ment of viral hepatitis B and C, leukaemia, lymphoma, re- nal cell carci- noma and multiple myeloma.</td>
<td>– a number of comparative bioassays</td>
<td>at least 1 repeat dose toxicity study in relevant spe- cies over at least 4 weeks</td>
</tr>
<tr>
<td>Somatropin [16]</td>
<td>Recombinant human growth hormone produced in E. coli, mammalian or yeast cells. Anabolic, lipolytic and anti-insu- lin effects.</td>
<td>– a number of comparative bioassays</td>
<td>at least 1 repeat dose toxicity study over at least 4 weeks</td>
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1) Primary parameter: AUC, secondary parameter: $C_{\text{max}}$ and $T_{\text{max}}$.
on tolerability that might be related to a process change should be addressed. The cycle of submission of PSURs might be amended or restarted. Further post-licensing studies may be needed, e.g. pharmaco-epidemiological studies.

4. Outlook
Generic competition has started in the biosimilar market since a number of marketing authorizations have been granted for somatropin, epoetin and G-CSF. Several important recombinant proteins are already or will be coming off patent during the next few years. Thus, EMEA will probably extend the list of product specific guidelines for the clinical requirements for the development of biosimilars.

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References
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