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## Setting the stage for biosimilar monoclonal antibodies

With the first marketing authorization application for a biosimilar monoclonal antibody now under consideration at the European Medicines Agency (EMA), what are the critical issues for regulators?

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Recently, the EMA received the first marketing authorization application (MAA) for the biosimilar monoclonal antibody (mAb) infliximab<sup>1</sup> and its Committee for Medicinal Products for Human Use (CHMP) adopted the final guideline on biosimilar mAbs<sup>2</sup>. In this article, we summarize the experience of CHMP with biosimilar mAbs and focus on remaining questions regarding the registration and ongoing oversight of such products. Such questions include the extent to one can ‘extrapolate’ biosimilar product uses to indications outside that where clinical comparability was originally evaluated? In addition, discussion continues concerning the impact of changes to manufacturing of a biosimilar or its reference product on biosimilar regulatory oversight. Above and beyond these scientific challenges, it is clear that improved communication to physicians, payers and patients about the labeling and rigor of oversight for biosimilar mAbs—or any

biosimilar for that matter—will clearly be instrumental in improving the uptake of what remains a new type of biological product unfamiliar to many in medical practice.

### **Setting the scientific stage**

In July 2009, following publication of an initial discussion on the pros and cons of biosimilar mAbs<sup>3</sup>, the EMA convened a closed meeting between regulators and stakeholders, including representatives from ‘originator’ companies, ‘biosimilars’ companies, academia and scientific journals<sup>4</sup>. Participants at this workshop discussed basic ideas on how to develop a biosimilar mAb; in particular, whether a biosimilar of such a complex molecule would even be possible, given that the biosimilar pathway had until that time been applied to far less complex therapeutic proteins, such as growth hormone and erythropoietin. The philosophy was not to come to specific conclusions on what would be required, but to collect ideas that would enable the CHMP’s Working Party on Biosimilar Medicinal Products (BMWP) to conclude if the scientific field had evolved sufficiently to propose drafting a guideline. Indeed, BMWP was given the mandate by CHMP to work on such guideline and published a concept paper in October 2009 (ref. 5) officially announcing the drafting of this guideline, which was later published<sup>3</sup>. This triggered numerous EMA Scientific Advice procedures (**Fig. 1**) where applicants requested answers on specific questions, such as clinical trial design or selection of analytical technologies for comparing biosimilar mAbs to their reference mAb.

Two years later, a second EMA workshop<sup>7</sup> on biosimilar mAbs was convened to assist in the revision of the then draft guideline, which published shortly after<sup>6</sup>. This further boosted the number of Scientific Advice requests for biosimilar mAbs and IgG fusion proteins (which are considered by EMA to be related molecules where the principles for biosimilar mAbs apply). Indeed, from 2009, biosimilar mAbs have become the largest class of candidate biosimilars (**Fig. 1**), quickly superseding granulocyte colony stimulating factor (G-CSF; filgrastim) as the ‘number one’ product class in Scientific Advice procedures. Between 2003 and the end of 2011, around 40% of all requests for Scientific Advice on biosimilars directed to the EMA were for biosimilar mAbs.

The reasons for the popularity of biosimilar mAbs may be attributable to the potential size of the market and approaching patent expiry for several blockbuster products. Thirty-five biosimilar mAb products were reviewed in 43 procedures (some companies requested Scientific

Advice more than once). It is interesting to note that the scope of questions in these confidential Scientific Advice procedures for mAbs has shifted over time (**Box 1**).

## Development of a biosimilar framework

The current concept of development of biosimilar mAbs follows the principle that any analysis that compares the biosimilar mAb with its reference mAb aims to detect differences using state of the art technology, thus excluding to the best possible extent that there are any relevant differences (see **Table 1** for a summary of the basic concepts). Slight differences, within known and controlled ranges, are a given fact for biologicals—including innovative mAbs in their batch-to-batch micro-heterogeneity and variability—and thus do not preclude the conclusion that a given mAb is a ‘true’ biosimilar, as recently defined<sup>8</sup>.

The highest burden for a biosimilar development program is on the physicochemical and biological characterization (in regulatory jargon the ‘quality programme’) with various state-of-the-art methodologies. First, the biosimilar mAb has to fulfil all relevant requirements for a mAb of the concerned class (stand alone properties); second, it has to be comparable with the reference mAb. In other words, the analytical package for a biosimilar mAb submission is considerably larger than for a ‘stand-alone’ mAb (blue plus orange segment in quality portion shown in **Fig. 2a**). Since the objective of a biosimilar development is to establish biosimilarity, not to re-establish benefit, the non-clinical and clinical development program is more focused and ‘tailored’ toward this objective<sup>8–10</sup> (**Fig. 2a**), making in part reference to the already licensed original mAb. We have provided a comparison of regulatory reviews of (non-mAb) biosimilars to those of stand-alone biotechnological medicinal products, as this may throw light on issues that will be important for biosimilar mAbs (**Box 2**).

The current concepts for biosimilar mAbs have evolved over time; indeed, several previous guidelines on specific product classes of biosimilars<sup>11</sup> introduced important milestones on non-clinical and clinical aspects that paved the way for more complex biosimilars, including mAbs (see **Table 2** for an overview of the relevant guidelines). One area that illustrates this evolution is EMA stance on whether evidence from a clinical trial in one particular clinical condition can be considered sufficient for a biosimilar to be equally effective and safe in another clinical condition. This ‘extrapolation’ of indications was first applied to a wider extent to biosimilar low-molecular weight heparin<sup>12</sup>, where the question arose whether clinical data on venous thromboembolism could

provide the basis for use in the prevention of arterial thromboembolism. Several guidelines introduced concepts around pharmacodynamic markers that are usually more sensitive as clinical endpoints; for example, the guidelines on biosimilar insulins or G-CSF<sup>13,14</sup>. As such, the current European regulatory approach to biosimilar mAbs is a synthesis and maturation of ideas previously published and publicly consulted, melded with new approaches.

### **Scientific challenges ahead**

The principles proposed for the regulatory oversight of biosimilar mAbs were open for a public consultation for six months until May 2011 (ref. 6). Over 20 stakeholders contributed more than 400 pages of written comments. Although there was largely an agreement on most of the principles proposed, some common themes emerged as to scientific aspects that require further refinement or clarification<sup>15</sup>. By and large, these reflect current challenges around biosimilars in general rather than being specific to biosimilar mAbs.

One frequently raised concern was whether it should be permissible to extrapolate efficacy data from one clinical condition, specifically studied, to another or others, not specifically studied (e.g. could clinical data on biosimilar versions of anti-tumor necrosis factor (TNF)-alpha antibodies in rheumatoid arthritis (if suitable as a model) be extrapolated to their use in psoriasis, Crohn's disease or other licensed indications?). As expected, there has been considerable controversy around such a proposal. Several stakeholders, including clinical organizations, have urged caution or even requested that regulators disallow this without clinical data in each additional indication. For previous biosimilar applications, the criteria for extrapolation have included clinical experience gained with the reference medicinal product plus available literature data, and whether or not the same mechanism(s) of action or the same receptor(s) were involved in all indications<sup>16</sup>. Apart from feasibility considerations (comparative equivalence trials in all indications would make a biosimilar mAb development much more costly than a stand-alone approach), the regulatory thinking around this has evolved in that extrapolation of scientific evidence could be seen as a logical consequence of the comparability exercise principle. As mentioned previously, physicochemical and biological characterization ('form and function' of the mAb) generates the foundation of biosimilarity; remaining uncertainties (e.g., large variability in results using certain analytical methods or detection of slight differences with unknown relevance for clinical performance) would be solved by comparative clinical data in the most sensitive model to establish

biosimilarity. If the totality of evidence, to be assessed individually for each new biosimilar mAb, allows, then extrapolation will most probably be permitted—not as a ‘bonus’ for biosimilar companies, but based on solid scientific evidence compiled by the Applicant.

An important consideration is knowledge gained with handling of manufacturing changes of already marketed (non-biosimilar) biologicals and changes in their analytical attributes over time. A recent analysis<sup>17</sup> compared quality profiles of batches of several marketed biologicals over time and found abruptly occurring changes of certain important quality attributes like glycoform patterns. The authors suggested that such alterations could stem from changes in the manufacturing process.

In fact, there is virtually no biological product where the manufacturing process has remained unchanged after initial approval. As such, over the 20 year or so history of biotech, regulators have gained substantial experience in handling comparability exercises with biologicals. Indeed, the principle for a comparability exercise following changes in a manufacturing process<sup>18</sup> is that Applicants must provide sufficient reassurance that the changes do not adversely impact product safety and efficacy. This can be achieved by the provision either of physicochemical and biological characterization data alone (which is all that is required in the majority of cases) or of additional non-clinical or clinical data. One could argue that extrapolation of evidence was already applied because the data packages in the majority of cases of biological products did not include efficacy and safety data from several clinical indications. We are patently aware that the situation for biosimilars may not be the same because the biosimilar manufacturer has their own manufacturing process and no access to data generated with the reference biological product, apart from Applicant data generated during the development of the biosimilar when analyzing batches of the reference mAb. Therefore, the extrapolation of indications for biosimilar mAbs will likely remain a case-by-case decision based on the totality of evidence provided.

Post-approval changes of the manufacturing process of licensed ‘stand-alone’ biologicals, including mAbs, and perhaps also for licensed biosimilar mAbs in the future, raises interesting questions for regulators. Abrupt changes to the manufacturing process of any mAb following approval will need to be addressed, especially given the aforementioned debate on whether biosimilar approvals on the basis of clinical data from one indication can be extrapolated to others. The question is whether such changes in manufacturing processes for approved biosimilar mAbs should be handled more strictly than for reference mAbs, taking fully into account requests of stakeholders that extrapolation should only be allowed when there is clinical evidence that the

product still performs in all licensed indications. One could argue that the experience gained with the product before the change becomes less relevant when a major change is introduced. In our view, whatever the change, regulatory oversight should not depart from a flexible and science-based case-by-case approach. Applicants should still have the possibility to optimize their manufacturing process after approval in a feasible and efficient way, whether the product is a ‘stand-alone’ mAbs or a biosimilar mAb. Certainly, regulatory demands should not stifle the modernization and optimization of medicines.

Another question currently under debate is how to handle the oversight of a biosimilar mAb if its reference mAb undergoes changes in its quality profile (or vice versa, if a biosimilar undergoes changes). In other words, is a biosimilar mAb a ‘biosimilar forever’ or a ‘biosimilar for licensing purposes’ that has a lifecycle on its own after approval? In the latter scenario, any post-authorization change to either the biosimilar or the reference mAb would then likely require only a comparison between pre-change and post-change product, but not a comparison of the biosimilar mAb with the reference mAb. However, this implies at least a theoretical possibility that a reference mAb and a biosimilar mAb could become dissimilar in relevant quality attributes in their on-going respective life cycles. Would such products then be considered interchangeable in patients?

Although the decision on interchangeability of biosimilar medicines in Europe lies with the national authorities in the Member States, it is nevertheless a scientific issue under constant debate. Industry and regulators may have to join forces to establish a comprehensive surveillance system for adverse events associated with either original mAbs or biosimilar mAbs, which is required in any case by the new European pharmacovigilance legislation<sup>19</sup>. In fact, pharmacovigilance of a class of mAbs (which includes the reference mAb and one or more of its biosimilars) may become a practical challenge. A marketing authorization application focuses on the assessment of quality, safety and efficacy of a biosimilar mAb on its own. Such applications will most probably not be able to foresee all situations in this respect, like the generation of data of switching from a reference mAb to a biosimilar mAb, from a biosimilar mAb to a reference mAb, or from a biosimilar mAb to another biosimilar mAb of the same product ‘class.’ Whether or not this is a problem remains to be determined.

### **Non-scientific challenges ahead**

Several responses to the published draft guideline on biosimilar mAbs<sup>15</sup> were non-scientific in nature. One of the most common themes was the need for prescribers to be transparently and adequately informed about which studies were provided for regulatory review of a biosimilar mAb. In fact, the information provided to the prescriber is one of the most crucial elements in any licensing procedure. We are aware of critical attitudes to biosimilars in the clinical community, which, in our view, often arise from lack of understanding of the biosimilar principles, including use of incorrect terminology around the term biosimilar<sup>8</sup>. Prescribers, payers, patients and other stakeholders appear to make increasing use of publicly available documents provided by regulators, including the product label (Summary of Product Characteristics) and the European Public Assessment Report (EPAR)<sup>20</sup>.

To explore ‘real-world’ uptake of biosimilars and impact of regulatory communication, we made use of the Danish Register of Medicinal Products Statistics. This register, established in 1993, systematically collects and analyzes the sales of medicines in both primary and hospital care settings and thus allows a comprehensive analysis of real-world use of any medicine<sup>21</sup>. Denmark therefore may serve as a paradigm. Using register data, we analyzed the uptake of biosimilars in Denmark from 2008 to 2010 (**Fig. 2c**). One of the most striking observations is that the uptake of biosimilar erythropoietin and biosimilar filgrastim has been so low, never exceeding 10% for filgrastim or even 1% for erythropoietin. Only biosimilar somatropin has experienced increased uptake in 2011, which may be based on a sudden shortage of originator somatropin and physicians requiring an immediate alternative. We are fully aware that the situation may be or may become different in other European Union (EU; Brussels) member states, but the analysis is in line with our experience from dialog with stakeholders. Interviews with the doctors in Denmark suggested that the main reason for not recommending for example biosimilar G-CSF is an “expression of uncertainty” in regulatory communication and also the lack of a ‘real’ phase 3 study.

The European Public Assessment Report for some biosimilar G-CSFs<sup>22</sup> states that the “only area of uncertainty is the mobilisation of peripheral blood progenitor cells because it is not known whether the efficacy in oncology can be fully extrapolated to this area of use. The uncertainty is due to the lack of complete understanding of the mechanism of peripheral blood progenitor cell mobilisation from the bone marrow. This issue has now been satisfactorily addressed by the RMP [Risk Management Plan].” Scientific uncertainties regarding the mechanism of action in stem cell mobilization were solved by inclusion of this indication into the post-authorization risk management, thus generating further evidence post approval. It should be emphasized though that



already at the time of biosimilar G-CSF licensing, the overall evidence provided on biosimilarity was considered sufficient. The indication “mobilisation of peripheral blood progenitor cells” was granted, as one can read in the product label<sup>22</sup>, and clearly any indication granted by the CHMP is based on solid scientific evidence.

It is therefore apparent that doctors are not aware that the EPAR document that they are referring to only reflects the situation at the time of approval (thus to be found in the category “Initial marketing-authorisation documents”); the document itself is not updated, but is complemented by additional documents like summaries called “Procedural steps taken and scientific information after authorisation” (found at the same place on the EMA EPAR website). Moreover, regulatory authorities routinely review all medical products, including biologicals and biosimilars, after approval on an ongoing basis. Apparently, the concept on how a biosimilar is developed (see **Tables 1,2**) is poorly understood by prescribers; for example, why what physicians termed a ‘real’ phase 3 study was not considered necessary by EMA as part of a biosimilarity exercise.

We consider that provision of an adequate level of relevant and scientifically valid information for biosimilars is necessary. The most crucial element in such information provision to the prescriber is the product label. It is not only a document that is regularly updated, thus reflecting for example the indications for which a biosimilar mAb is licensed, but is also a powerful instrument to provide information on evidence that was generated with a particular medicine. Several scenarios are possible for a biosimilar mAb (**Table 3**), ranging from having an identical product label for the reference mAb and the biosimilar mAb to having completely different labels where only the information is provided that was actually generated with the biosimilar. All scenarios have their pros and cons. It remains to be seen how best to handle this issue and discussions are ongoing.

## Conclusions

The implementation of regulatory oversight of biosimilar mAbs in Europe has been an evolution of a basic concept: similarity to a reference mAb in terms of safety and efficacy profile is established to the best extent possible through a multidisciplinary comparability exercise—not through the re-establishment of benefit *per se*. It is clear from evidence in Denmark at least that evolution of regulatory principles will have to go hand in hand with evolution of physician education and public

understanding of these concepts to appreciate how biosimilars are developed and on what grounds they are authorized.

We note that better communication to prescribers, payers and the public of the relevant and unbiased information about biosimilars is essential<sup>23</sup>; after all, biosimilars and biosimilar mAbs remains a relatively new and unfamiliar class of therapeutic products to many. This communication exercise should clarify that biosimilars—recently defined via their strict adherence to the comparability exercise paradigm<sup>8</sup>—are high quality medicines that undergo critical regulatory review. One could say that the CHMP ‘brands’ a medicine as ‘biosimilar’ upon successful regulatory review. As of this time, there is no MAA for a biosimilar mAb, but the stage is set.

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### **Disclaimer**

The views expressed in this article are the personal views of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of the European Medicines Agency or one of its committees or working parties.

### **Competing interests**

The authors declare that they have no competing interests as defined by Nature Publishing Group, or other interests that might be perceived to influence the results and/or discussion reported in this article.

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#### **24. Box 1. Q&As during Scientific Advice procedures**

Until recently, applicants typically requested advice on the need or otherwise for *in vivo* studies in non-human primates for a biosimilar mAb or on endorsement of their proposal regarding the most sensitive clinical ‘model’ (see main text) to detect differences between a biosimilar mAb and its reference. As time has progressed, however, other questions have arisen. For example, can a biosimilar mAb have reduced immunogenicity or would this contradict the biosimilar principle that efficacy and safety should be equivalent? Also, are more ‘exotic’ expression systems possible where for example the glycosylation is not only quantitatively different (e.g., when comparing several mammalian expression systems that still have a common core glycan structure but cultivated under different conditions), but also qualitatively different (e.g., when using insect cells or other expression systems)?

The short answer to the first question about immunogenicity is yes it can. For the second question, the response is more equivocal. Such expression systems may be possible, but considerable data on the lack of relevant impact of such changes on the clinical efficacy and safety profile would be needed, and it could well be that differences identified at the structural level are too far removed from the reference product to be compatible with the biosimilar approach.

## Box 2. Biologicals versus biosimilars

In a preliminary exploratory analysis, we compared several questions asked by the CHMP for 11 biosimilar applications (filed between 2004 and 2012) with those asked for 48 biologicals filed in the past five years (where systematic electronic data is on file; see **Fig. 2b**). We analyzed the outcome of the first regulatory review for both a range of biologicals and non-mAb biosimilars after filing of a MAA (i.e., day 120 of the centralized procedure, where the two ‘Rapporteurs,’ who are in charge of the scientific assessment, provide their first evaluation)<sup>10</sup>. More questions were asked for biosimilars regarding quality (median number 96 questions for biosimilars versus 66 questions for ‘stand-alone’ biologicals), whereas fewer questions were asked on non-clinical (median four for biosimilars versus eight for biologicals, respectively) and clinical issues (median 23 for biosimilars and 62 for biologicals, respectively). This could be interpreted as reflecting the aforementioned predominance of the quality program for biosimilars, and narrower focus on non-clinical and clinical issues.

Notably, the number of ‘Major Objections’ was higher for biosimilars than for stand-alone biologicals in both quality *and* clinical assessments (**Fig. 2b**). Major Objections are defined as critical issues that, if not resolved by the ‘Applicant’ with an adequate response, would prevent a positive outcome of a MAA. Readers should note that our analysis only involved the first regulatory review; in the majority of these procedures all issues were solved so that the majority of products in both categories were finally approved.

There are some caveats to the above analysis. First, it is not clear whether the trends observed for these biosimilars will apply to biosimilar mAbs. What’s more, the stand-alone biologicals which are used in this analysis include more complex biological molecules (there were 18 mAbs/fusion proteins, six advanced therapy medicinal products (defined as gene therapy medicinal products and cell-based medicinal products, including tissue engineered products), five enzymes, 12 blood or plasma-derived medicinal products (including their recombinant variants) and seven other biologicals). The biosimilars reviewed included erythropoietins, G-CSF, growth hormones, alpha-interferon and insulins. We could not include the brand biologicals for these biosimilars in the analysis (which would have been the optimal comparators) because these products are older and were not licensed in the centralized procedure (which only became mandatory for recombinant biologicals in 1995). For this reason, no direct comparison is possible due to different review processes. Nevertheless, we consider that our comparison is useful and conservative because it compares less complex proteins (biosimilars) with, in the majority of cases,

considerably more complex biological molecules; even in this comparison, the review of the Quality dossier resulted in more questions for biosimilars, suggesting a rigorous review. We are also aware that the timeframes of our analysis are not identical (2004 to 2012 for biosimilars; 2007 to 2012 for biologicals) for reasons of availability of documents to the authors. However, we consider that the number of biologicals is large enough to justify such comparison on an exploratory level, and the timeframes reasonably overlap. Our analysis shows that biosimilars are, when recommended for approval by the CHMP, high-quality medicines that underwent critical review. We also note, when looking at the confidential details of the issues raised, that the CHMP followed the common scientific principles around biosimilars and focused on the comparability exercise. Thus, the regulatory review stage is also well set for biosimilar mAbs.



**Table 1. Basic concepts around development of biosimilar mAbs<sup>2,6</sup>.**

Concept	Comment
<p>Various analytical techniques, including biological assays, have been established in the past years that allow more in-depth characterization of complex proteins, both on a physicochemical and a functional level (e.g., potency assays) and there is experience in the identification and assessment of minor quality differences due to changes in manufacturing processes for mAbs.</p>	<p>An extensive comparability exercise, first at quality level, employing such methods is the mainstay for a biosimilar mAb development.</p> <p>Non-clinical or clinical studies are meant to fill gaps of knowledge left by identification of any physicochemical and biological differences.</p>
<p>Step-wise non-clinical development. <i>In vitro</i> studies should be conducted first (including binding to target antigen(s), binding to representative isoforms of the relevant three Fc gamma receptors, FcRn and complement (C1q, and Fab- and Fc-associated functions), followed by a decision on the extent of what <i>in vivo</i> work, if any, will be required.</p>	<p>This decision is based on a risk-based approach, taking into account for example the expression system used and the glycosylation profile measured.</p>
<p>The design of the clinical program: patients are normally enrolled commensurate with the level of evidence obtained from preceding steps which support comparability. The clinical strategy includes the following principles: first, comparison of pharmacokinetics, combined with pharmacodynamics, is normally the first step; second, pharmacodynamic parameters may substantially contribute to the comparability exercise for certain mAbs and in certain indications; third, similar clinical efficacy is usually demonstrated in (at least) one adequately powered, randomized, parallel group comparative clinical trial, preferably double-blinded, and normally as an equivalence trial; fourth, the objective of this trial is to establish biosimilarity, not to establish clinical benefit (which is already considered established by the reference mAb); fifth, the clinical trial normally enrolls a homogeneous patient population and compares the efficacy (or activity) and safety of a biosimilar mAb to its reference in a clinical condition that is most sensitive to detect differences in the molecules, should they occur.</p>	<p>Extrapolation of efficacy (i.e., acceptance of other indications licensed for the reference mAb and not specifically studied) is in many cases possible based on the overall evidence on biosimilarity provided, and thus a logical scientific consequence of the biosimilar concept.</p>

**Table 2. EMA product-specific guidelines on biosimilars relevant for biosimilar mAbs<sup>11</sup>.**

<b>Guideline</b>	<b>What it introduced relevant for biosimilar mAbs</b>
Similar biological medicinal products containing low-molecular-weight-heparins. EMA/CHMP/BMWP/118264/2007 (original version from 2007)	Extrapolation of efficacy data. Prevention of venous thromboembolism by a biosimilar LMWH will allow for indication in the prevention of arterial thromboembolism if well justified.
Non-clinical and clinical development of similar medicinal products containing recombinant interferon alpha EMA/CHMP/BMWP/102046/2006	Introduction of the ‘pharmacodynamic fingerprint approach’: Use of one or more biological markers like expression of serum proteins where the relation to the mechanism of action is unknown, but which are nevertheless used as sensitive parameters to establish biosimilarity to provide “another piece of the puzzle”.
Similar biological medicinal products containing interferon beta CHMP/BMWP/652000/2010	Acceptance of a surrogate pharmacodynamic endpoint (e.g., magnetic resonance imaging) instead of a clinical endpoint due to its sensitivity, thus not requesting the endpoint that is required for a new-in-class substance according to EMA guidelines.  No specific requirement for equivalence testing in clinical outcomes.  Confirmation of the ‘pharmacodynamic marker fingerprint approach’.
Similar biological medicinal products containing recombinant erythropoietins EMA/CHMP/BMWP/301636/08 (revised version)	Use of the most sensitive patient population as a model indication (renal anaemia).  Alternative demonstration of biosimilarity for the intravenous and subcutaneous route by a bridging concept: show comparable efficacy for one route of administration in a comparative clinical trial and provide comparative single dose and multiple dose pharmacokinetic/pharmacodynamic bridging data in an epoetin-sensitive population for the other route of administration.
Non-clinical and clinical Issues - Guidance on biosimilar medicinal products containing recombinant granulocyte-colony stimulating factor (G-CSF) EMA/CHMP/BMWP/31329/2005  Non-clinical and clinical issues -	Acceptance of a pharmacodynamic marker as proof of equivalent efficacy if well justified. For example, absolute neutrophil count in healthy volunteers for a biosimilar G-CSF or time-effect profile of hypoglycemic response induced by biosimilar insulin.

Guidance on similar medicinal products  
containing recombinant human insulin  
EMA/CHMP/BMWP/32775/2005

**Table 3: Pros and cons regarding the product label of a biosimilar mAb**

Option	Pros	Cons
Product label is an identical copy of the reference mAb label	In line with the ‘generic approach’ (chemical generics usually have identical product labels).	<p>Prone to misunderstanding regarding information specifically generated with the reference mAb, in particular results from pivotal clinical studies: The reader would assume that the studies were made with the biosimilar.</p> <p>Results obtained from the biosimilarity exercise are not included.</p>
Product label only gives information obtained with the biosimilar mAb	<p>Transparent regarding which studies were performed with the biosimilar</p> <p>Could allow putting more specific messages like the need for monitoring of switching of products within a class (likely to be part of the label of all products of that class, including the originator).</p>	<p>Prone to misperception by prescribers who could falsely conclude that the level of evidence created is not according to “usually expected” standards as for a novel mAb if the concept of biosimilars is not known (or not explained in the label).</p> <p>Misses important information generated from the long-term use of the reference mAb, such as safety information.</p> <p>Not in line with “generic approach”; implicitly suggests a difference between the biosimilar and the reference mAb, although such differences were excluded when licensing the biosimilar.</p>
Product label is a combination of information (e.g. studies performed with the biosimilar mAb) and relevant safety and/or efficacy data from the reference mAb	<p>Could be seen as a balanced approach.</p> <p>Gives relevant information to prescriber.</p> <p>Could allow putting more specific messages like the need for monitoring of switching of products within a class (likely to be part of the label of all products of that class, including the originator).</p>	<p>Not in line with ‘generic approach’; implicitly suggests a difference between the biosimilar and the reference mAb, although such differences were excluded when licensing the biosimilar.</p> <p>Prone to misperception by prescribers who could falsely conclude that the level of evidence created is not according to “usually expected” standards as for a novel mAb if the concept of biosimilars is not known (or not</p>

explained in the label).