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A response from the scientific and regulatory perspective in support of the EU biosimilar framework

To the editor:

The commentary by Schellekens and Moors on clinical comparability and the European biosimilar regulations in the January 2010 issue¹ questions the value of the comparability exercise mandated in the European Union (EU) regulatory guidance. Their argument is based for the most part on the assertion that the comparability exercise is superseded by clinical data. Schellekens and Moors claim not only that requiring a comparability assessment of a brand and biosimilar product will inhibit the development of complex biologicals as biosimilars where (non-relevant) differences are often anticipated, but also that the biosimilar framework should be extended to cover complex non-biological products. Conversely, we propose that data on both analytical comparability and clinical comparability are needed to facilitate the proper development of biosimilars. Although we welcome Schellekens and Moors' comments as part of the ongoing debate concerning biosimilar regulatory oversight, we nonetheless consider their arguments misleading—even incorrect—from a scientific perspective. In the following article, we respond from quality, non-clinical and clinical points of view.

Here we systematically discuss (i) the need for a quality-based comparability exercise as a prerequisite for pursuing the biosimilar pathway, (ii) the rationale for pharmacokinetic and pharmacodynamic comparability, (iii) the value of clinical comparability and benefit-risk assessments as the basis for approval of biosimilar products, (iv) whether a biosimilar product can be “better” than a reference medicinal product, (v) the applicability of the biosimilar pathway to more complex biological medicinal products, and (vi) extension of the biosimilar pathway to encompass non-biological medicinal products.

Regarding the need for a quality-based comparability exercise as a prerequisite for pursuing the biosimilar pathway, Schellekens and Moors suggest that the identification and verification of quality attributes of the biosimilar product should be sufficient for approval of a biosimilar product, without comparison with a reference product. Aside from the fact that it is an integral part of the approval process from a legal perspective, the stepwise comparability exercise, starting with quality comparison, is the crucial element in ensuring the safety and efficacy of a biosimilar. Schellekens and Moors highlight quality differences (related to aspects such as formulation, glycosylation and the presence of impurities) observed for several biosimilars approved in the EU. As stated elsewhere², it is not expected that the quality attributes of the biosimilar and reference medicinal products will be identical. However, any differences noted must be properly justified and shown to have no impact on

the safety and efficacy profile of the biosimilar, either by relevant scientific investigation, or by non-clinical and/or clinical studies. The decision on whether the biosimilar is sufficiently similar to the reference product is made on a case-by-case basis, and biosimilar applications could be refused because of differences noted at the quality level.

A comparability exercise at the quality level should facilitate overall development of a biosimilar more than hindering the process. It should reduce the total development cost by making most non-clinical animal studies as well as usual dose-finding and at least phase 2 activity studies unnecessary. Using this approach, the developer may avoid repeating time-consuming and costly parts of product development, as well as undue clinical testing. Furthermore, in the situation where slight clinical differences are observed in the pivotal clinical comparative study, a comprehensive comparability exercise including analyses of relevant physicochemical and biological attributes (including functional assays), may provide valuable arguments that the (slight) clinical differences observed are compatible with the inherent variability of both the reference medicinal product and the biosimilar and not attributable to a 'real' difference. As such, this first part of the comparability exercise will potentially become more important for more complex biosimilars. Schellekens and Moors mention a failed biosimilar version of interferon (IFN)- α -2a; indeed, the European Public Assessment Report³ delineates that differences in the clinical outcome counting against the product were not counterbalanced by a sufficiently firm reassurance on analytical, physicochemical and biological grounds supporting biosimilarity.

Conducting a comparability exercise starting at the quality level is important during early development for a new biosimilar candidate. If relevant differences are detected at an early stage, a developer could reconsider the feasibility and applicability of the biosimilar route, as compared with a stand-alone development programme, which requires an entirely different development strategy. Indeed, if relevant differences to the reference product are detected at the quality level, the reduced non-clinical and clinical development programme, as described in current CHMP guidelines⁴, may no longer be sufficient to ensure safety and efficacy of the new candidate, and in some cases, such differences will even disqualify the molecule for entering the biosimilar route. Such knowledge and understanding of the candidate product could facilitate a 'go/no-go' decision in early development and thus will potentially save a considerable amount of money.

As discussed below, the comparability exercise on quality attributes also forms the basis for extrapolation between clinical indications. In this respect, it will promote the development of more complex biosimilars, such as monoclonal antibodies⁵. Where a reference product is licensed for more than one indication, the efficacy and safety in any indication will have to be demonstrated separately—except when a thorough comparability exercise has been successfully undertaken. If such a comparability exercise has not been performed, it cannot be demonstrated that the biosimilar molecule has a similar potency and specificity profile and thus be similar in its clinical activities in comparison to the reference product.

A second key consideration concerns the rationale for pharmacokinetic and pharmacodynamic comparability. Schellekens and Moors question why comparative pharmacokinetic (PK) data should be required at all if clinical efficacy and safety data in the end appear to prevail and drive the regulatory decision for approval of biosimilars. The reason, quite simply, is that PK is normally a very sensitive parameter for establishing biosimilarity. Pharmacokinetic studies complement the preceding physico-chemical and *in vitro* biological comparison of the biosimilar and the reference product and provide the first evidence that both have similar absorption, distribution, metabolism, and excretion *in vivo*. Pharmacokinetic behavior is also mechanistically linked to biological function (i.e., pharmacodynamics via exposure to the biotherapeutic) and thus consequentially to clinical efficacy and safety. In some cases, comprehensive studies using pharmacokinetic endpoints combined with pharmacodynamic endpoints alone may even provide the pivotal data on comparable efficacy, for example for biosimilar insulin⁶ or G-CSF (granulocyte-colony stimulating factor⁷). It should be noted, however, that a clinical trial would normally still be required, given the importance of comparative safety. Again, similar PK provides, together with the quality comparability exercise, the basis for extrapolation between different clinical indications. If similar efficacy and safety is established in one clinical indication, and the pharmacokinetics are likewise similar, it may be scientifically more easily justified to extrapolate efficacy and safety to other indications that were not (or have been to a lesser extent) studied. Relevant differences in PK could raise concerns about the extent to which clinical efficacy can be generalized, or even bring biosimilarity into question. The reason for the classic 80–125% acceptance range for some PK assessments of biosimilars can be explained simply by the fact that these products were under development in parallel to the establishment of the EU biosimilar framework, and the developers could not anticipate future regulatory considerations. Now, after more experience has been gained, the proposed range is still deemed relevant and in agreement with the expected clinical variability.

Schellekens and Moors mention some difficulties with PK study design that may be limiting. For instance, sometimes imprecise assays are used to determine product levels, or the relationship between pharmacokinetic parameters and clinical effects is unclear, or a bell-shaped dose-response curve is observed (i.e., widely differing protein levels have the same clinical effect), or difficulties are experienced in prospectively predefining and justifying the acceptance range for pharmacokinetic parameters. Nevertheless, it has in most cases been possible to meet these challenges, e.g. by selecting a dose in the linear ascending part of the dose-response curve, or by surveying relevant literature for the reference medicinal products as regards linkage of plasma levels and therapeutic effect, variability of clinical outcome measures etc. Moreover, on a case-by-case basis, regulators accept appropriate scientific justification when limitations are unavoidable.

A third area where we disagree with Schellekens and Moors concerns the value of clinical comparability and benefit-risk assessments as the basis for approval of biosimilar products. Schellekens and Moors argue that only the evaluation of what the CHMP accepts or rejects will define

what a biosimilar is, and that there is no definition of acceptable differences in quality, safety and efficacy. However, considering the wide range of biologicals potentially eligible as biosimilars, it is virtually impossible to *a priori* define ranges or lists of acceptable differences. An objective viewpoint would consider that “acceptable differences” can only be determined on a case-by-case basis. Furthermore, it could be unnecessarily restrictive for developers if regulators specifically require clear-cut figures for equivalence margins based on knowledge acquired at a given time, which may change, on a product-specific basis, as more experience with this is gained.

Regarding deviations from the guidelines for biosimilars of the overall development program for the first licensed biosimilars in the EU, the need to design and initiate clinical developments before or in parallel with the drafting of the guidelines prevented developers from anticipating subsequent regulatory requirements. To reject such dossiers solely on non-compliance with the guidelines would not have been scientifically appropriate, as the applicants had sound scientific justifications for their chosen development programmes. The CHMP agreed on a positive recommendation for marketing authorization based on the overall data from the comparability exercise conducted at the levels of quality, safety and efficacy. It could be speculated that some licensing procedures would have been much more straightforward (and cheaper) had they been performed according to the biosimilar framework. Also in some cases other external factors were drivers for deviations from the biosimilar guidelines (e.g., a temporary contraindication for subcutaneous use for one of the reference products adopted that made it impossible for biosimilar developers to perform a subcutaneous route clinical comparison during development). In practice, such limitations have not hindered a reasonable ‘biosimilarity’ exercise and deviations from guidelines may be justifiable under certain circumstances, notwithstanding the fact that direct clinical comparison remains essential.

In the final instance, the CHMP must recommend approval or refusal of a marketing authorization application for any medicinal product, whether innovative or biosimilar, based on the benefit-risk assessment, which is based on scientific principles. Thus, the fact that it is the CHMP who defines whether a product can be considered biosimilar, based on a pre-set, although flexible, series of criteria for quality, safety and efficacy data that has to be provided by the sponsor, is not a weakness of the biosimilar legislation or guidelines, but the actual mandate of the Committee. In the case of a stand-alone product dossier, this is established by performing clinical studies with the relevant product. In contrast, for biosimilars, this is established by demonstrating that the biosimilar product is 'similar' to an already existing product with a known benefit/risk profile. This principle is stipulated in more recent guidelines on biosimilars (IFN beta⁸⁾ and monoclonal antibodies⁹⁾) which state that the focus of the biosimilarity exercise is to demonstrate similar efficacy and safety compared to the reference product, not patient benefit per se, since that has already been shown for the reference product.

A fourth area of concern to Schellekens and Moors involves whether a biosimilar product can be "better" than a reference medicinal product. Schellekens and Moors argue that companies

developing biosimilars often use more state-of-the-art technologies than originator companies, and that the quality of a biosimilar can therefore be “better” than the originator product. They conclude that this implies that regulators should therefore expect biosimilars to be produced using the best available technology rather than being of comparable quality to the originator’s products which are “locked into old technologies”. It has already been stressed that the comparability exercise is the foundation for accepting reductions in the non-clinical and clinical studies. The requirement for a biosimilar to be comparable to the reference medicinal product should not necessarily be a hurdle for innovation. The general regulatory requirement is that state-of-the-art technology should be used². Thus, a better quality as such should not be a reason for disproving comparability and improved production methods leading to a superior quality (e.g., lower levels of impurities) will not prohibit approval of a biosimilar. In this respect, regulators do not require replication of the manufacturing process used for the reference medicinal product. It should however be remembered that the manufacturers of originator products have a long and detailed experience with their manufacturing processes, which are usually highly optimized and operating under tight specifications. They also have the regulatory obligation to update their dossier and use state of the art techniques for quality control. Therefore, the implication that reference products are inferior in quality to biosimilars is not necessarily correct. Likewise, a product claimed to be “better” than the reference medicinal product would have to be tested to prove this hypothesis, in order to verify this claim, and any such claim would have to be substantiated with appropriate data. For example, a higher degree of purity achieved for a biosimilar product does not inherently mean that it will be clinically “better” in terms of efficacy and/or safety (which would then also contradict biosimilarity).

A fifth issue raised by Schellekens and Moors concerns applicability of the biosimilar pathway to more complex biological medicinal products. Schellekens and Moors argue that there is, in the EU guidelines, the implicit assumption that the pathway does not apply to “more poorly” purified biologics that are more complex and difficult to characterize than a highly purified recombinant DNA derived biologic like erythropoietin or filgrastim. This is not necessarily correct, as the biosimilar framework is, in principle, applicable to any biological¹⁰. It is instead the lack of sensitive analytical techniques to detect differences, or lack of knowledge or experience concerning the possible consequences on *in vivo* behaviour of such differences detected in some quality attributes with sensitive analytical techniques, that complicate development of more complex biologicals as biosimilars. Guidance on more complex biologicals such as low molecular weight heparins has been published¹¹, and a new guideline for a more complex class of biologicals (monoclonal antibodies) was already announced in 2009 (Ref. 12). Thus, in our view it has already been demonstrated that the biosimilar framework can be expanded, based on scientific progress in relevant fields. A significant number of monoclonal antibodies are already under development as biosimilars, and scientific advice has been provided to sponsors of such products by the CHMP. However, it may just not be *feasible* to develop some complex biologicals as a biosimilar, e.g. because a clinical equivalence trial would be

much larger than a placebo-controlled trial (and be much more expensive) or it is technically not feasible to compare certain quality aspects of the biosimilar with the reference product. Some structurally complex vaccines could serve as an example of this. Given that vaccine antigens are sometimes very complex, a demonstration of “similarity in molecular and biological terms” would on an analytical level currently not be possible. For many vaccines, commonly accepted immunogenicity read-outs exist that correlate with efficacy, for example a rise in post-vaccination antibody titres and this must be demonstrated for a new vaccine. This could make a “stand-alone” development programme (i.e., not comparative to another vaccine) more feasible and less cumbersome than a very large equivalence trial against a reference vaccine as required for the biosimilar approach.

The sixth and final issue that we wish to address here concerns the extension of the biosimilar pathway for complex non-biological medicinal products. Schellekens and Moors propose extending the scope of “biosimilar” legislation to cover complex non-biological products. They argue that such products are excluded from the generic pathway (Articles 10(1) and 10(2)(b) of Directive 2001/83/EC as amended, Ref. 13) owing to their complexity. It is agreed that there is a need to consider scientific aspects of the “biosimilar philosophy” for more complex non-biologicals and in certain cases, e.g. liposomal formulations of chemical substances. This has already occurred within the framework for generics. For cases where demonstration of bioequivalence is not sufficient for approval and additional non-clinical and/or clinical data is needed, another provision exists in Article 10(3) of that Directive, which requires additional non-clinical and/or clinical data to establish that the safety and efficacy profile is not modified as compared to the original product. Therefore, there is no need to amend Article 10(4) of Directive 2001/83/EC, which specifically addresses Similar Biological Medicinal Products.

In conclusion, we see no sound scientific rationale to drop the requirement for a three-level comparability exercise, which has already proven its value in the marketing authorisation of appropriately developed biosimilar products. The proposal of Schellekens and Moors would compromise demonstration of similar clinical efficacy and safety for a biosimilar when a reduced non-clinical and clinical development programme is applied. We acknowledge that European regulators adopted a conservative approach to biosimilarity as they were the first regulators to create a regulatory pathway for the abbreviated development of biologicals. We appreciate the need to regularly re-evaluate and update regulatory guidelines on the basis of accumulated experience – indeed, this has been recently undertaken with a major revision of the guideline on biosimilar erythropoietin¹⁴, and is also planned for the general biosimilar guidelines^{15, 16, 17}. Considering the complexity of biomolecules, the limitations at present in analytical characterisation and in clinical trials (like defining sensitive and feasible endpoints to detect differences), it is necessary that the biosimilar concept relies on demonstrating comparability at all three levels, i.e. quality, pre-clinical and clinical to ensure as complete a picture as possible on the features of such complex molecules. A relaxation of these requirements is not justified.

Christian K. Schneider ^{a)p)}, John J. Borg ^{b)s)}, Falk Ehmann ^{c)}, Niklas Ekman ^{d) r)}, Esa Heinonen ^{d)e)r)}, Kowid Ho ^{f) r)s)}, Marcel H Hoefnagel ^{g)s)}, Roeland Martijn van der Plas ^{g)s)}, Sol Ruiz ^{h)s)}, Antonius J van der Stappen ^{g)s)}, Robin Thorpe ^{i) r)}, Klara Tiitso ^{c)}, Asterios S. Tsiftoglou ^{j) q)}, Camille Vleminckx ^{c)}, Guenter Waxenecker ^{k)s)}, Mats Welin ^{l)s)}, Martina Weise ^{m)r)} & Jean-Hugues Trouvin ^{f)o)q)} on behalf of the Working Party on Similar Biological (Biosimilar) Medicinal Products (BMWP) and the Biologicals Working Party (BWP) of the Committee for Medicinal Products for Human Use (CHMP)

^{a)} Danish Health and Medicines Authority, Denmark, and Twincore Centre for Experimental and Clinical Infection Research, Germany;

^{b)} Medicines Authority, Malta;

^{c)} European Medicines Agency (EMA), UK;

^{d)} Finnish Medicines Agency (FIMEA), Finland;

^{e)} Swissmedic, Switzerland

^{f)} Agence française de sécurité sanitaire des produits de santé (Afssaps), France;

^{g)} Medicines Evaluation Board (CBG-MEB), The Netherlands;

^{h)} Spanish Medicines Agency (AEMPS), Spain;

ⁱ⁾ National Institute for Biological Standards and Control (NIBSC), UK;

^{j)} Aristotle University of Thessaloniki, Greece;

^{k)} Austrian Medicines and Medical Devices Agency (AGES), Austria;

^{l)} Medical Products Agency (MPA), Sweden;

^{m)} Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM), Germany;

^{o)} University Paris Descartes, France.

^{p)} Chair of the Working Party on Similar Biological (Biosimilar) Medicinal Products (BMWP), EMA, UK;

^{q)} Chair of the Biologics Working Party (BWP), EMA, UK;

^{r)} Member or expert of the BMWP, EMA, UK;

^{s)} Member or expert of the BWP, EMA, UK;

Correspondence should be addressed to C.K.S.: E-mail: c_schneid@web.de

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