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## **Editorial: Biosimilars in rheumatology – the wind of change**

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The wind of change is blowing in rheumatology – rheumatologists may soon be exposed to “biosimilars” of the medicines they routinely use, since the European Medicines Agency (EMA) has recently issued its final guideline on biosimilar monoclonal antibodies (mAbs),[1] – a product class of utmost importance for rheumatologists – and a biosimilar infliximab is currently under evaluation for marketing authorisation in Europe,[2], and more will come. Rheumatologists, as it appears, are especially challenged these days since many of their patients are already successfully put on a long-term treatment with individualized drug regimens, including biologicals like for example Tumour Necrosis Factor (TNF)-alpha inhibitors. Apparently, introduction of “copy” versions of the medicines they already know may be seen as a critical issue, although economical considerations suggest major cost savings in healthcare,[3]. “Concerns”, “challenges” and “critical issues”: These are terms with which the term “biosimilar” is often combined in papers written by clinicians and discussions at conferences (see for example,[4-6]). We read about the “complexity” of biological medicines, and that it is difficult to replicate their exact structure. Also in clinical literature in rheumatology, we read about “small variations” that can impact the activity and function of a biosimilar, and “major safety and efficacy concerns“ that have to be addressed before clinicians can use biosimilars,[7].

In their review in this issue of the *Annals of the Rheumatic Diseases*, Thomas Dörner and colleagues report on a roundtable discussion on the advent of biosimilars in rheumatology recently held at the Charité in Berlin (Germany), [8]. I note at least one aspect in this review that is worth emphasizing – the paper puts scientific facts into perspective: For example, it reports about the complexities and

microheterogeneity of mAbs/cepts, but also puts it into perspective with the so-called “originator” mAbs/cepts that are likewise complex. As a regulator I have been deeply involved in the design of guidelines around biosimilars (including biosimilar monoclonal antibodies), and in discussions around public perception of biosimilars that I experienced it has been my impression that scientific facts are often discussed in isolation. For example, it is true that biologicals like mAbs and -cepts are complex, and that small changes in their manufacturing process can have a large impact on their function (although I have also seen a few cases where larger changes had only little impact). This has often had the connotation to implicitly assume that biosimilars therefore may have an undetected “inferior” quality as compared to the established originators, or that at least there is more uncertainty around them. The sentence “*biosimilar and biological reference medicines are similar but not identical*” (also used by Dörner *et al*) is maybe one of the most frequently misunderstood sentences in the history of biosimilars and has almost become a mantra when raising concerns around biosimilars. It comes from a previous version of the EMA “Questions and Answers” document on biosimilars, [9] (the document has meanwhile been updated, so the sentence can no longer be found there), and its intention had rather been to clarify that due to inherent complexity and inherent variability of biologicals any biosimilar can never be “identical” to its reference product (and therefore the “generic pathway” is not possible). One would have to add that also no batch of any reference product is “identical” to the previous one – “non-identity” is a normal feature of biotechnology that has to be controlled by tight specifications of critical product attributes, within current technical and scientific limitations (inherent variability). The „art“ for a biosimilar is to demonstrate that the biosimilar is as close as possible to its reference product in all relevant functional and structural aspects, again within current technical and scientific possibilities and its inherent variability. What is often not mentioned (but mentioned by Dörner *et al*; this is also acknowledged by other papers like for example by Scheinberg and Kay,[7]) is that originator mAbs/-cepts have undergone changes after their approval – this is what regulators call the “life cycle” of a medicine. This is normal, manufacturing processes are updated during the life cycle of any medicine, and this is welcome, since these are often improvements. A recent publication suggested that licensed biologics undergo changes in relevant molecular attributes over time,[10]. In fact, the seminal regulatory guideline ICH Q5E, issued by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH),[11], an internationally agreed standard that sets the data requirements for changes to the manufacturing process for biotechnological and biological products, stipulates that “*The demonstration of comparability does not necessarily mean that the quality attributes of the pre-change and post-change product are identical, but that they are highly similar and that the existing knowledge is sufficiently predictive to ensure that any differences in quality attributes have no adverse impact upon safety or efficacy of the drug product.*” This is called the „comparability exercise“,[12], and the determination of comparability is usually based on a combination of physico-chemical and analytical testing, biological assays, and, in some cases, non-clinical and clinical data. In other words, clinical

data (especially from new randomized controlled clinical studies) have not always been part of a dossier for a biological medicine that underwent changes in its manufacturing process, because such data was in many cases not necessary to demonstrate that the pre- and post-change product are comparable. Such changes in manufacturing can be seemingly small changes like change in the supplier of cell culture media, and range to major ones like introducing new purification steps or implementing new manufacturing sites. It is true that even small changes can have a large impact. But this would certainly be picked up in the comparability exercise and regulatory assessment, and via implementation of correct regulatory measures for post-approval surveillance. In fact, all of the licensed mAbs and –cept fusion proteins used in rheumatology have had changes in their manufacturing processes after their initial approval (see upper part of Figure). Since several years, EMA publishes a regularly updated list of “steps taken after approval”, [13] for any medicine. These can be as simple as a change in the address of the marketing authorisation holder (which obviously does not have any impact on the product at all), and range to complex changes such as new clinical indications or changes in the manufacturing process. One can see from the upper part of the Figure that virtually any medicine has undergone numerous changes of their manufacturing processes, and some people go so far as to say that the medicine that a clinician administers to a patient today is not anymore “identical” (but comparable) to the medicine authorised years ago. Any of such changes in the manufacturing process (ranging from a change in the supplier of cell culture media up to new purification methods or new manufacturing sites) was substantiated with appropriate data and was approved by EMA.

The scientific principles of a change in manufacturing process of an originator mAb/cept molecule and the generation of a biosimilar are the same, [14, 15]. A “true” biosimilar, as developed along the principles in the EMA guidelines, was recently proposed as a “*copy version of an already authorized biological medicinal product with demonstrated similarity in physicochemical characteristics, efficacy and safety, based on a comprehensive comparability exercise.*”, [15]. Regulators require an as close as possible resemblance of the biosimilar to its originator, as exemplified by data recently published for some of the authorised biosimilars, [16, 17]. “Non-innovator” products that are copies of authorised products, [18] are not necessarily “biosimilars” according to the current definition. The current concept of development of biosimilar mAbs/cepts follows the principle that an extensive state-of-the-art physicochemical, analytical and functional *comparison* of the molecules is complemented by *comparative* non-clinical and clinical data that establish equivalent efficacy and safety in a clinical “model” indication that is most sensitive to detect any minor differences (if these exist) between biosimilar and its reference mAb also on a clinical level, [19]. This “model” indication has to be scientifically duly justified by the Applicant, and any extrapolation to other indications not specifically studied is based on an in-depth scientific review process. As such, a biosimilar development is therefore not so much “abridged” but rather “tailored” towards a distinct scientific objective; that is to

establish biosimilarity, not to re-establish benefit for the patient (this is, by the way, also nicely described in the review by Dörner *et al.*). Like most biologicals, biosimilar mAbs/-cepts will have to be licensed via the centralised marketing authorisation route, that is via the European Medicines Agency,[20], and one could say that only upon scientific assessment and positive recommendation by the EMA's Committee for Medicinal Products for Human Use (CHMP) can it be considered that the comparability between a proposed biosimilar and its reference product is established and the criteria for naming the medicine as "biosimilar" have been fulfilled. It needs to be pointed out that the approval process for a biosimilar is critical, stringent, and no step in this process is "automatic" and without scientific assessment by experts from regulatory authorities. The CHMP appoints two "Rapporteurs" amongst its members whose expert teams perform an independent critical assessment on a biosimilar candidate's quality, non-clinical and clinical data,[21]. In the regulatory review procedure for a marketing authorisation, dedicated experts in analytical, physicochemical and biological characterisation prepare an assessment report, and the CHMP's Biologics Working Party (BWP),[22] discusses the assessment report in depth to adopt a list of questions to the Applicant. The BWP is composed of European experts selected according to their specific expertise (one member per Member State). An important part of the scientific assessment of a biosimilar is to put microheterogeneity (often mentioned in connection to "concerns" around biosimilars) into perspective with the very same microheterogeneity found in batch-to-batch variability of the reference biological: As already mentioned, microheterogeneity is not specific to biosimilars; it is a "normal" feature of any biological medicine. In parallel, non-clinical and clinical experts in the Rapporteurs' teams prepare separate assessment reports of the respective data and raise relevant questions in their field of expertise. The CHMP will then integrate these recommendations into a multidisciplinary list of questions for the Applicant that needs to be addressed before a positive recommendation for marketing authorisation can be issued. Any impact of any "small differences", would they be present, would be picked up and discussed. This holistic assessment of quality, non-clinical and clinical data puts any minor differences between the biosimilar candidate and its reference mAb into the perspective of their clinical relevance (N.B.: More than only "minor" differences would not be in line with a biosimilar, and authorisation as a biosimilar may not be possible,[1]).

When comparing the overall number of questions asked in these lists of questions for licensed biosimilars to those asked for mAbs/cepts authorised in rheumatological indications, one easily recognizes that the review process for a biosimilar is as critical as for an originator biological: The median overall number of questions asked for currently authorised biosimilars was 119, as compared to 121 for authorised mAbs/cepts used in rheumatology (analysis from confidential data on file), thus not different at all. Obviously, these questions have been resolved with adequate responses, since all of these products have subsequently been recommended for marketing authorisation. A high number of questions is not necessarily a measure of the quality of a dossier, but these data show that regulatory

review for biosimilars is indeed as critical as for a new-in-class compound. Certainly the aforementioned figures suffer from the low number of procedures (eleven biologics authorised in rheumatological indications, and seven distinct biosimilar molecules), and it is scientifically not absolutely correct to compare the currently licensed biosimilars to mAbs/-cepts, since the biosimilars authorised so far are less complex biologics like growth hormone, filgrastim, or erythropoietins. However, upcoming biosimilar mAb/cept applications may not be expected to have fewer questions, since these are more complex molecules, so the conclusion that regulatory review is as critical as for originator mAbs/cepts will very likely remain valid. It can also not be said that biosimilars undergo an “abridged” or “accelerated” approval, since the time from start of the regulatory review procedure to a positive opinion issued by the CHMP was apparently not shorter for the biosimilars authorised so far as compared to mAbs/cepts used in rheumatology (see lower part of Figure) – biosimilars undergo a full review, and every word in the Summary of Product Characteristics (SmPC) that informs the prescriber has been actively assessed and approved, including the indications granted for a biosimilar.

Obviously, regulatory review and approval sets a high entry bar for any biological medicine, including biosimilars – this is also acknowledged by Dörner *et al.* Regulators evaluate biosimilars cautiously, and a biosimilar is only registered if the Applicant has demonstrated in sufficient detail that the biosimilar is of good quality and equivalent in efficacy and safety to its reference medicinal product. Authorised biosimilars are as good, safe and efficacious as originator biologicals. Dörner *et al* make another valid, even vital, point that the role of biosimilars in rheumatic diseases will be determined by the confidence placed in them by rheumatologists,[8]. Closer communication and interaction between regulators (explaining their framework,[24]) and clinicians (explaining what they need to know about it to alleviate concerns) will become increasingly important. Having this in mind, the paper published in this issue of the journal by an international group of clinicians is, from my perspective, a further step along this road, since it provides a balanced clinical view – is the “wind of change” finally blowing also in this respect? Numerous biosimilar mAbs/-cepts are under development,[25], and thus a clear understanding of what a biosimilar is (and what it is not) is of critical importance. Clinicians and regulators and maybe also other stakeholders may have to join forces to come to a balanced, objective, and well-informed decision-making that puts medical decisions on science, in the best interest of doctors and patients – on whose behalf we regulate.

### **Disclaimer**

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### **Competing interests**

None

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### Figure legend:

Number of changes in the manufacturing process after approval for mAbs/-cepts authorised in rheumatological indications (**upper part A of figure**). Products in the order of date of approval in Europe (from MabThera®, authorised on 02-06-1998 for the initial authorisation in oncology, to Benlysta®, licensed on 13-07-2011). Such changes range from change in the supplier of a cell culture media up to new purification methods or new manufacturing sites. **Lower part B of figure:** mAb/cept products authorised in rheumatological indications, currently licensed biosimilars (both sorted by date of licensing in the EU) (left), and time to positive opinion issued by the European Medicines Agency (including clock-stop periods where the Applicants address the issues raised by EMA) (right). A positive opinion is a pre-requisite for authorisation by the European Commission.

All information taken and analyses made from data published in the EPAR,[21] (European Public Assessment Report; document type: “EPAR - Procedural steps taken and scientific information after authorisation”,[12] or “EPAR - Procedural steps taken before authorisation”,[23]). N.B. for lower part B of figure: MabThera® calculated for the RA indication, granted in 2006, not for the initial approval process in 1998 in oncology. Remicade cited for the Crohn’s disease indication; RA indication granted a year later (27 June 2000).