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Effective pharmaceutical regulation needs alignment with doctors

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Concerns emanating from the medical community about the safety and efficacy of biosimilars indicate an increasing distrust of the outcome of the drug regulatory process. To illustrate this, we analysed the creation of the European biosimilar regulatory framework, specifically focussing on the guidelines outlining approval criteria for biosimilar erythropoietins, which have been recently adopted. We observed an absence of the organised medical community in the public process of creating and updating the guidelines. In this article we argue that, to ensure that innovative medicines continue to find their way to the patients who might benefit from them, a closer collaboration between the organised medical community and regulators is needed.

Introduction

In October 2010, a revised European guideline came into effect outlining the approval criteria for biosimilar erythropoietins [1]. This was the first revision to the regulatory approval requirements for 'generic' biotechnology derived proteins, so-called 'biosimilars', which was established under the aegis of the European Medicines Agency (EMA). The biosimilar pathway has become an accepted regulatory route within Europe and both payers and governments expect this to be an effective way to contain drug costs in a time of increasing healthcare expenditures [2]. The first biosimilar was approved in 2006 and several others have subsequently reached clinical practice. However, healthcare professionals from various backgrounds have expressed their concerns about the safety and efficacy of biosimilars [3–5]. These concerns demonstrate the discordant views and expectations of regulators and clinicians of adequate approval requirements for these products. The creation and implementation of the European regulatory framework for biosimilar erythropoietins illustrates how a misalignment between regulatory and clinical worlds creates obstacles for the clinical uptake of medicinal products. In this article we argue that an active participation of relevant clinical stakeholders in the development of pharmaceutical regulation is needed to ensure that regulatory approval requirements meet the needs of prescribing physicians.

Building the biosimilar regulatory framework

In the past decade, the first generation of biotechnology-derived proteins lost patent protection and market exclusivity, including human interferons, insulin, growth hormone and erythropoietin. For conventional chemical entities (small molecules) that have lost patent protection and marketing exclusivity, marketing authorisation can be obtained based on an abbreviated application dossier demonstrating bioequivalence to a product already authorised on the European market [6]. This can generally be achieved through quality assessments and limited pharmacokinetic studies in healthy volunteers. However, the size and complexity of biotechnology-derived proteins and the inherent variability in their production process prevents the application of existing regulations. Therefore, in 1998, the EMA initiated a process to establish a regulatory pathway for the approval of competing versions of biotechnology-derived products. The term 'similar biological medicinal products', or 'biosimilars', was coined in European Legislation [7]. In essence, the European approach stipulates that for complex biological products, which cannot be adequately characterised, a 'comparability exercise' is required to demonstrate similarity to a reference product.

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The requirements for this comparability exercise were to be defined in a framework of guidelines developed by the scientific committee of the EMA, the Committee for Medical Products for Human Use (CHMP), and its working parties (European Medicines Agency: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000408.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac058002958c). The general guidelines lay down the need to provide an extensive non-clinical dossier and comparative clinical data; however, the exact requirements for each product are determined on a case-by-case basis. The first product specific guidelines were released for public consultation over a period of 5 months in 2005. Arguably, the fiercest debate centred on biosimilar erythropoietins and this article focuses on these products.

Pure red cell aplasia: a warning for biosimilars

As the regulatory framework for biosimilars was being developed, an adverse event was discovered that provoked major discussion of the approval criteria for biosimilar erythropoietins for pure red cell aplasia (PRCA) [8]. PRCA is characterised by severe anaemia, low levels of reticulocytes and a near complete absence of erythroid precursors in the bone marrow. A change in the manufacturing process and formulation of an innovator brand epoetin-α sold outside the USA (Eprex®) induced the formation of antierythropoietin antibodies and led to over 200 confirmed cases of PRCA. How this change induced the increase in immunogenicity, this issues remains a topic of scientific debate [9]. However, as a result of the occurrence of PRCA, most European countries contraindicated the use of subcutaneous Eprex® in 2002, but continued to allow its intravenous use.

Setting the norms for biosimilar erythropoietin

In June 2005, the first draft of the biosimilar erythropoietin guideline was circulated for public consultation. The occurrence of PRCA highlighted the complexity of manufacturing biotechnology-derived proteins and underscored the need for clinical studies to determine the immunogenicity of biosimilar erythropoietin. According to the draft guideline, clinical studies should be performed and should consist of a 'correction' phase, of at least 12 weeks, to correct haemoglobin levels in patients, followed by a 'maintenance' phase of at least 6 months. In addition, at least 12 months of comparative immunogenicity data in at least 300 patients would be required preauthorisation. Still, PRCA was expected to be a rare event that only occurred after prolonged subcutaneous erythropoietin treatment. Because subcutaneous Eprex® was contraindicated in patients with renal failure, no comparative studies could be done to establish comparability of subcutaneously administered biosimilars. Marketing authorisation would thus be possible only for the intravenous administration route. In addition, extensive pharmacovigilance activities would be mandatory for all biosimilars, including post approval observational studies to assess the incidence of PRCA. Furthermore, a demonstration of biosimilarity in renal anaemia would enable extrapolation to other indications of the reference medicinal product with the same route of administration.

Stakeholders that provided feedback on the draft version included representatives of regulatory agencies, innovator companies, generic companies, academia, and a patient organisation. However, none of the European medical associations offered feedback on the draft guidelines [10]. Following the release of the draft version, a joint workshop on the introduction of biosimilars was organised by the EMA and the Drug Information Association (DIA) at the end of 2005. Speakers came almost exclusively from regulatory agencies and industry (Drug Information Association, European Medicines Agency: http://www.ema.europa.eu/docs/en_GB/document_library/Agenda/2009/11/WC500012702.pdf). Following the public consultation period several changes had been made to the draft guidelines. Several amendments were made to the draft version. Because the incidence of PRCA was unknown, the guideline no longer mentioned a specific number of patients required in the comparative studies. Furthermore, the duration of the 'correction' phase was changed from a minimum of 12 weeks to a recommendation of 6 months. Much of the debate centred around the possibility to substitute innovator products with biosimilars. In general, decisions whether to substitute innovator products for biosimilars at the pharmacy or hospital level are made on a national level and thus were deemed to be beyond the scope of the guideline. In early 2006, the final versions of the guidelines were adopted by the CHMP.

When the first erythropoietin biosimilars entered the market, several European professional medical organisations expressed concerns about the safety of biosimilars, primarily about the possibility that biosimilars would induce immune responses [4,11]. Physicians would have to weigh this uncertainty against the expected cost savings of biosimilars. It was questioned whether biosimilars violated the prime medical ethic to 'first, do no harm', since innovator products with a well-established benefit/risk profile were available [12]. Thus far, the price savings of biosimilars have been modest in most European countries. This is partly owing to the fact that following the entry of biosimilars, several innovator brands also lowered their prices. In Germany, for example, the price of innovator erythropoietin was reduced by 13% [13].

Revising the erythropoietin guideline

By 2006, several changes had been made in the production and handling of prefilled syringes of Eprex® to prevent the reoccurrence of PRCA [14]. Follow-up measures were established to ensure that these changes had the desired effect, including prospective studies to document the incidence of PRCA and a registry to detect new cases [15]. When the contraindication for subcutaneous Eprex® was lifted in 2006, this opened the door to assess the biosimilarity of subcutaneously administered erythropoietin. In 2010, the biosimilar erythropoietin SB-309, was approved to be administered subcutaneously in chronic renal failure patients [16]. In 2009, a study that evaluated the subcutaneous safety and efficacy of the biosimilar HX575 (Binocrit®) was halted when two patients who received HX575 developed neutralising antierythropoietin antibodies [12]. The cases were identified before the product reached the clinic setting, but their occurrence reemphasized the need for continued vigilance for immunogenicity-related adverse events.

Meanwhile, European regulators questioned the need to perform two separate studies to demonstrate biosimilarity for erythropoietins. A revision to the approval criteria was released for public consultation in 2008 [17]. Again, only producers of innovator and biosimilar erythropoietins provided feedback and the occurrence of PRCA in the HX575 trial fuelled the guideline discussions. Opponents of the proposed change argued that, owing to the risk of PRCA, requirements should not be lowered, but rather extended, at least until more experience was gained with the biosimilars already on the market. The EMA argued that PRCA had only occurred in patients receiving SC epoetin and that the requirements of premarketing subcutaneous data would not be lowered. In addition, the EMA reiterated that extensive pharmacovigilance activities would remain mandatory. Following the consultation period, the revised guideline was adopted in March 2010, now

TABLE 1

Key clinical issues addressed in the current biosimilar erythropoietin guideline.

Clinical issue	Guideline
Which patients	Patients with renal anaemia are considered the most sensitive patient model
Number of studies	Two separate clinical trials for both routes of administration (IV and SC). Or one clinical trial for the subcutaneous route and providing adequate bridging data through a pharmacokinetic/pharmacodynamic study
Study characteristics	Each study should contain both a correction-phase and a maintenance phase
Number of patients in the studies	No minimum specified
Duration of study	Each study should (ideally) include a 6-month correction-phase and a 6-month maintenance phase
Immunogenicity	At least 12 months comparative immunogenicity data are required using validated assays
Extrapolation of indications	Demonstration of 'similarity' in renal anaemia will enable extrapolation to other indications of the reference medicinal product with the same route of administration.
Post marketing requirements	A pharmacovigilance plan should be submitted to address immunogenicity and potential rare events

stating that a single subcutaneous trial could provide adequate safety and efficacy data to demonstrate biosimilarity. Table 1 provides a summary of some key features of the adopted guideline.

To date, medical associations have not responded to the revised guideline, but it does not seem likely that it will change the views of physicians who are already concerned. The occurrence of PRCA in the development process of HX575 certainly impacted physicians' confidence in the safety of biosimilars [12]. The question remains if the current criteria for approval provide prescribing physicians sufficient guarantee and trust that biosimilar erythropoietins do not pose unnecessary risks to their patients.

Concluding remarks

The introduction of the biosimilar regulation is a telling example of the different 'worlds' in which regulators need to operate thereby balancing legal, scientific and public health considerations [18]. Although European biosimilar guidelines are primarily aimed to provide guidance for producers of medicinal products, regulators could benefit by actively involving the organised medical community in their activities. Clearly, the medical profession is represented in the CHMP by its members and an extensive array of expert scientific advice groups. In addition, competent authorities also comprise qualified members of the medical community. However, the absence of the major European medical associations in the regulatory process is a telltale of a misalignment of the clinical and regulatory communities. Physicians are increasingly confronted with measures that force them to consider the costs of clinical decision making, but they are reluctant to consider elements of cost saving when doubts remain about the safety and efficacy of medicines [19]. Regulatory guidelines are being developed for biosimilar versions of several widely used biotechnology derived proteins, such as interferon-β and monoclonal antibodies. If these products are to succeed on the market, trust in the regulatory system by prescribers and patients is crucial. An active role of medical associations could ensure that physicians' concerns are included early in the regulatory process and speed up the uptake of new medicines.

A public consultation period for regulatory guidelines is open to all interested parties and it could be argued that it is mainly the responsibility of the medical organisations to contribute to those guidelines that will affect the physicians they represent. Indeed, there are abundant examples of guidelines that have received feedback from the organised community, including the recently adopted guideline on biosimilar low-molecular-weight heparin [20]. Why physicians are absent in certain cases, but not in others, warrants further investigation. Clinical experts in the field of biotechnology might be more likely to have ties with the developers of innovator products and might not be actively included in the regulatory deliberations. It could be that perceptions of the regulatory system as a 'closed shop', is withholding medical associations from embarking on the guideline creation process. Perhaps most physicians are just more comfortable caring for patients than deliberating on regulatory guidelines, especially those guidelines considering issues that are not directly related to clinical practice. However, the criticism from physicians, expressed after the implementation of the biosimilars regulatory framework, suggests that doctors are engaged in regulatory matters, but are not reached or stimulated to act in a timely manner.

The US FDA is currently developing guidance for biosimilars, which might serve as an example for future doctor–regulator interactions. The public hearings included, besides representatives of innovative and generic manufacturers, speakers of patient organisations and representatives of medical associations [21]. Communicating and engaging with stakeholders and increasing the transparency of the agencies activities key focus points the EMA has set out for itself [22]. Establishing a platform to facilitate dialogue with European medical associations on issues of common interest could promote the acceptance of regulation. In the end, regulation not only aims to ensure that medicinal products have an appropriate benefit/risk balance, but also that promising products become available to patients. When regulators fail to involve doctors in their activities, this will impede the acceptance of the cost effective and innovative medicinal products of the future.

Conflict of interest

All declare no conflict of interest relevant to the subject matter or materials discussed in the manuscript.

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