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Blockbusters, Biotechnological Drugs And Biosimilars

Present Situation and Perspectives

Background

Nowadays, available drugs cannot adequately treat all patients: side effects without clinical improvements or clinical improvement associated with relevant side effects can occur, as well as benefits and adverse events. The expectations for new drugs are, therefore, very high, both from the healthcare system and the public. However, the development process of new drugs requires a huge amount of research. As a matter of fact, out of 5,000-10,000 molecules designed, only 250 reach the preclinical phase; among them about 10 are tested in phase I, II and III trials and only one is approved and launched on the market.

This process, due to its costs, is becoming more and more difficult to be maintained by pharmaceutical industry. That is why, in the recent past, a decreasing number of chemical drugs addressed to large consumption and relevant sales (blockbusters), have been placed on the market. In the future, a closer partnership between the pharmaceutical companies and academic research will be necessary to develop a new business model for “health industry”.

Moreover, we are experiencing a shift from “traditional medicine” to “targeted/personalised medicine”. This new model will imply the development of molecules tailored on a genetic and phenotypic pattern, increasing the number of potentially treatable patients and maximising the therapeutical efficacy and reducing side effects. Simultaneously, the development of drugs targeted to a broad segment of patients is bound to decrease.

Biotech drugs (citokines, hormones, clotting factors, monoclonal antibodies, vaccines) represent an essential part of modern pharmacotherapy: a total of 174 biological medicinal products obtained approval between 1995 and 2007 by EMA and FDA, and, at present more than 450 organic products are under development. The percentage of sales from biotechnology products (bioengineered vaccines and biologics), within the world's top 100 drugs, is set to increase from 11% in 2000 and 31% in 2009 to 48% by 2016. Moreover, taking into account the broader market, sales from biotechnology products are set to gain 23% of the world pharmaceutical market by 2016, versus its share of 17% in 2009. The estimated market of biosimilars for 2015 is 1 to 3.5 billion dollars depending on the molecule.

For some biologics, patent has already expired (three expired in 2012, while 32 will expire from 2013 to 2015); on the basis of these observations, in next years all treatment areas will be involved in this process, although, some of them, such as respiratory medicine, not immediately. New biologic drugs, in addition to the increasing number of generic chemical drugs, represent the new therapeutic perspective in the future.

Biosimilars

The term “biosimilars” refers to biopharmaceuticals which are manufactured by non originator pharmaceutical companies following expiration of patent period. They are similar in terms of quality, safety and efficacy to an already licensed reference product, whose similarity is defined as ‘the absence of a relevant difference in the parameter of interest’. They will be marketed by an independent application, following expiry of patent and regulatory data/market exclusivity periods of the reference product. Creating an identical copy of a biologic drug is nearly impossible; even when the DNA coding sequence is known, the complexity of postranslational modification (eg. glycosylation and methylation) and of manufacturing processes, makes the replication of the original structure very difficult . As a matter of fact, they are defined “similars” and not “equivalents”, as it happens instead for chemical drugs. “The process is the product”: this characteristic defines biotecnology products.

The development of a biosimilar from a biopharmaceutical previously registered drug avoids the costly step of drug discovery. As a matter of fact the production of a new biotech drug implies a 8-12-year project project with an investment ranging from
500 million to 1 billion dollars, with a probability of success of the overall project around 5%; on the contrary, biosimilar development requires shorter times (7-8 years) with a cost of about 100-150 million dollars and probability of success of around 50%. It is realistic to believe that this process will involve especially large pharma companies or large producers of generics who have sufficient resources, clinical development expertise, distribution network and marketing skills. Small biotech companies and players in emerging markets will be involved in the process, although not alone.

In the last years, several documents concerning both the production and the marketing of biomolecules have been published: EMA guidelines and documents regarding key concepts and principles (CHMP/437/04), clinical (EMEA/CHMP/89249/04), non-clinical (EMEA/CHMP/BMWP/42832/2005) and quality (EMEA/CHMP/49348/05) details and expectations of biosimilars. In the US the BPCI Act (Biologics Price Competition and Innovation Act), defines an abbreviated licensure pathway for biological products that are demonstrated to be “biosimilar” to or “interchangeable” with an FDA-licensed biological product; a biological product may be defined “biosimilar” if data show that the

product is “highly similar” to an already-approved biological product. These guidelines focus on common issues raised by sponsors interested in developing proposed biosimilar products, biologics license application (BLA) holders, and other interested parties regarding FDA’s interpretation of the Biologics Price Competition and Innovation Act of 2009. Moreover, these guidances describe the Agency’s current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited .

In the EU, fourteen biosimilars of somatotropin, epoietin-alpha, epoietin-zeta and filgrastin have been approved until 2011. No differences have been detected among these biosimilars and reference products in terms of composition and primary structure, higher order structure conformation, post translational modifications, polarity, charge, isoforms, size, detection of aggregates, binding and biological activity. On the contrary, due to significant biophysical and clinical variation in terms of efficacy, tolerability and side effects, other biosimilars have not been approved (for instance interferon-alpha-2a pegylated thrombopoietin - treatment-associated- thrombocytopenia).

Clear guidelines and tight control are necessary to guarantee efficacy and safety. For instance, Isoform distribution among eleven different epoietin-alpha products from four extra European different countries (Korea, Argentina, China and India) showed important variations of bioactivity in vivo (from 71 to 226%); for this reason, five products failed to fulfill their own specification. If for this kind of therapy, with adequate haemoglobin monitoring, a variance in potency may not represent a critical issue, such variability would not be acceptable for monoclonal antibody therapy, treathing transplant rejection, etc). Since current analytical techniques and preclinical experimental studies cannot detect or predict all the biological and clinical differences between the biosimilar and the original brand, EMA requires more rigorous clinical trials before approving biosimilars than would typically apply to a small molecule drug. Although lab tests (radio immune precipitation and double antigen bridging ELISA assay) are sensitive for detecting high affinity antibodies, the immunological safety can only be demonstrated in clinical trials and post marketing surveillance.

Great attention should also be paid in drugs storage and handling. Moreover, a strict control on adverse event occurrence, data about drug such as dosage given and brand name, international nonproprietary name (INN) is fundamental. As regards biosimilars, a unique INN should be necessary, in order to facilitate prescribing and dispensing of biopharmaceuticals and the pharmacovigilance process. For each biosimilar deviation from reference product, safety and efficacy data should be known. Implicit in the characteristics of biosimilars should be their interchangeability.

As for the equivalent drugs (generic), biosimilars availability could represent a cost-saving for healthcare providers (over 2 billion USD). For example, the introduction of a biosimilar of erythropoietin in Germany with a significant lower price than reference drug has determined an overall 33% price reduction of the initial price of the drug. As expected by German SHI system analysis, the decrease of drug prices will lead to savings of over one billion USD per yearby 2017. We are at the beginning of a revolution in patient care and physician practice.

Asthma

Asthma is a chronic inflammatory disease which presents multiple phenotypes and underlying endotypes. For this reason, the objective of target therapy are the different molecules involved in Th2 pathway (IgE, IL-4R-alfa receptor, IL-13 IL5). Omalizumab (anti IgE), as demonstrated in several randomised trials and meta-analyses, has shown its clinical efficacy and its ability to reduce airways remodelling, while anti IL-5 (Mepolizumab and Reslizumab) showed its efficacy in eosinophilic asthma. The introduction of Lebrikizumab, an anti IL-13 antibody, and the discovery of a biomarker (periostin) related to the action of IL-13 has made it possible to divide patients into responders and nonresponders, according to this biomarker.

Several biotech approaches are currently under investigation in asthma treatment. While new molecules appear on the horizon, old biotech products for asthma treatment (such as Omalizumab) will soon be available as biosimilars. The use of these molecules will result in a reduction of the costs for treatment, while the identification of specific subsets of patients will help the provision of effective therapy, maximizing the effectiveness and minimizing side effects.

Clinical immunology and allergy treatment will therefore change in the next future, since biological allergen immunotherapy products are likely to become biosimilars, and some of these products have already been registered by EMA.

Conclusions

A targeted approach is increasingly replacing mass therapy in clinical and pharmaceutical research. In this scenario, new biotech products are appearing while others are gradually approaching patent expiration. This approach will enable the availability of new tailored treatments for well selected patient populations and the reduction of treatment costs. Specific research and updated knowledge for an appropriate and safe use of these products is necessary.

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