Original Article

Biotechnology-derived medicines: What are they? A pharmacological and a historical perspective

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ABSTRACT Biologicals, that is, medicines obtained from living organisms, are not new. History provides many examples of animal or human extracts being used to prevent or treat human diseases. Physicians have thus been aware for centuries of the therapeutic value of our own molecules. The difficulty laid many times in how to obtain these self or self-like compounds. Biotechnology – a technology by which manipulated living organisms are utilized to generate useful products such as drugs – provided a revolutionary answer. We know how to genetically engineer bacteria, yeast, insect or mammalian cells to synthesize human molecules, the so-called human recombinant therapeutic proteins. Murine and humanized monoclonal antibodies against human antigens are also biotechnological products. The number of biotechnological drugs being marketed, and those in clinical trials or awaiting authorization, is growing exponentially. We are now still on the beginnings of a new era in pharmacotherapy of which it is impossible to see the end. Pharmacologists need to keep pace with these changes and develop new skills. They may even have to challenge old assumptions in order to investigate new molecules. Using an easy and comprehensible approach, this review article revisits 'bio-concepts', and underlines the real dimension of the challenge.

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WHAT ARE BIOLOGICALS?

The search for new drugs has led humans to explore the tropical rain forests and the seabed, and to design new molecules, more or less successfully, but often quite blindly. However, for many of the targeted diseases or syndromes, we may not have had to make such a huge effort to discover active drugs, as the solution was well within reach, inside our own body, in the form of molecules with a known function that can be converted

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into medicines. The idea is not new. In fact, recent history provides many examples. For instance, since the 1940s, it is known that the glucocorticoids that we generate, when administered as drugs, have an anti-inflammatory and an immunosuppressive effect that has proven to be beneficial in autoimmune, allergic and inflammatory processes, as well as in preventing rejection of organ transplants.[1] The mystery to be solved, in addition to identifying a potential therapeutic benefit for endogenous molecules, was how to obtain and purify them. In the case of steroids, we learnt to produce them by chemical synthesis, and today we have a wide range of agents that more or less mimic their natural counterparts. The case of proteic hormones proved more difficult, and it was often necessary to turn to the human or animal tissues and organs in which they originate. A well-documented trial with hormone replacement therapy dates back to 1896, when a woman was efficaciously treated with oral bovine ovarian tissue extract loaded with estrogens.[2,3] However, perhaps the most shattering example of the therapeutic use of animal tissue was insulin.[4] In 1922, insulin extracted from bovine pancreas was shown to regulate the concentration of blood glucose in a diabetic patient who could not synthesize the hormone (subsequently, given its greater similarity to human hormone, porcine's became the main source of insulin until the end of the last century). Agents of this type are known as biologicals. Yet in pharmacology originally the term biologic applied basically to blood-derivatives and vaccines, it is now used as synonym of biological medicine (or biological for that matter) and biomedicine, to define, according to the European Medicines Agency (EMA),[5] a drug or medication obtained from a living organism, which is understood to range from humans to bacteria, and even viruses. This establishes a fundamental distinction between biological medicines and currently most frequently used medicines, that is, those small products manufactured by chemical synthesis and already known as classic, traditional or conventional, drugs, whose production does not involve organisms or cells, either as intermediary or source. Technically, biological medicines thus included well-known agents such as gammaglobulins[6] (γ-globulins) – that is, antibodies or immunoglobulins isolated from human blood to prevent or combat infections – antibiotics[7] (when they were directly obtained from bacteria or fungi), vaccines made from extracts of attenuated microorganisms or, more recently, low-molecular-weight heparins (LMWH)[8] (obtained from bovine lung tissue or porcine gastric mucosa), and clotting factor VIII when extracted from human plasma.[9]

What, therefore, is novel about biological medicines? The novelty, at least in terms of the agenda for scientific advances, is that we now have access to more refined and efficient techniques that enable more reliable production of specific biologics in the laboratory in sufficient quantity, as we shall see immediately. In addition, increased knowledge of the endogenous activity of some of these products has led the pharmaceutical industry to carry out an enormous amount of research, development and/or innovation (R&D&i) projects, thus helping to forge the beginnings of a truly new era in pharmacology: the era of biomedicines (or biopharmaceuticals; a term coined in 1980, albeit with a slightly different meaning). The psychotherapist's desire to 'know thyself' has never been as fruitful for medicine; such desire places us in a privileged position to expand the frontiers of pharmacological therapy.

BIOTECHNOLOGICAL MEDICINE: A TYPE OF BIOLOGICAL MEDICINE

A biological medicine is somewhat more than managing to obtain an endogenous molecule in the laboratory. The broad group of biological medicines includes

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a subgroup – drugs derived from biotechnological processes – that is expanding exponentially. These drugs form the subject of the present article, and we prefer to simplify by calling them biotechnological products. Biotechnology, that is, technology based on living organisms or biological molecules (enzymes or antibodies) that are purposely used or manipulated to obtain useful products,[10] had opened up a new area in pharmacology. Biotechnological agents are hence produced from living organisms, as are biologics, but to generate the former, organisms have had to be manipulated somehow. For example, the genetic material of an entity such as *Escherichia coli* can be altered in such a way that, amazingly, a human protein can be produced. This is known as recombinant DNA (rDNA) technology, which is part of genetic engineering, or gene manipulation, which in turn belongs to the wider field of molecular biology. Although a certain similarity always exists in their chemical structure and composition, the products obtained using biotechnological techniques are not always intended to be exact copies of endogenous human molecules. Thus, monoclonal antibodies against self-antigens produced in mice that have been bred for research purposes (manipulated) and that have been previously treated (manipulated) are also biotechnological agents.[11] These are two clear examples of biotechnological techniques that serve pharmacology and, hence, medicine.

The first company to produce a commercially viable therapeutic molecule using biotechnology was Genentech, founded by Robert Swanson and Herbert Boyer in 1976. Since then, with the launch of recombinant human (abbreviated as rHu or rh) insulin (1982), recombinant human growth hormone or rhGH (that is, recombinant somatotropin) (1985), and recombinant human erythropoietin, also known as EPO or epoetin (1989), an unstoppable race has been in progress in the biopharmaceuticals field. It is worth remembering that, by definition, biotechnology also includes the process of fermentation used to produce foods and drinks such as beer, wine and cheese; however, we shall not discuss this application here.

From the above, it can be inferred that, as they are generated in living organisms, all drugs that are biotechnological in origin are biological medicines, but not all biological medicines are biotechnological drugs. This duality between a biotechnological drug and a biological medicine is clearly seen in clotting factor VIII. Human factor VIII, given to hemophiliacs to restore hemostasis, can be obtained in at least two ways. One involves extraction from human plasma (9); the drug is then known as a blood derivative and is considered by definition a biological medicine, but not a biotechnological one. However, if the same factor VIII is produced using rDNA technology,[12] it is described as a biotechnological drug. In fact, AIDS, which appeared at the beginning of the 1980s (and whose transmission was attributed to blood transfusion and, therefore, to therapy involving blood derivatives), was one of the greatest boosts to research into the biotechnological production of human blood proteins instead of isolating them from blood. Yet, although it had been assumed that there would be a shift from blood extraction procedures to recombinant processes to generate blood derivatives such as factor VIII and others, a few companies still successfully market products isolated from plasma.[13]

RECOMBINANT DNA: PAST, PRESENT AND FUTURE

Undoubtedly, the potential of biotechnology in pharmacology is limitless. We are now on the threshold of an era of which it is impossible to see the end, while already second and third generation agents are making their way into the market. Today, although biotechnological drugs have not been socially 'integrated', not even by many health professionals, new-generation

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biotechnological drugs are being developed and will be broadly used by the students of today and tomorrow. One area of biotechnology involves obtaining small fragments of nucleic acids (oligonucleotides), which, by acting on the genome, can curb or boost the expression of specific genes to make up what has come to be known as gene therapy.[14] This area also includes the use of stem cells for therapeutic purposes (the so-called regenerative medicine).[15,16] Experiments are already being carried out in the fields of basic science and clinical research so that biotechnology can provide even more creative therapeutic options.

Although biotechnological drugs vary widely in terms of their chemical structure, most are proteins, or at least molecules with a considerable peptidic component. These therapeutic proteins are expected to dominate the market for biotechnological drugs in the coming years. Monoclonal antibodies are proteins, irrespective of how they are produced; however, the driving force behind advances in biotechnological drugs is the rDNA technique, which makes it possible to manufacture extremely pure human peptides and proteins (recombinant proteins) for therapeutic purposes more efficiently. The advances made in this field since the 1970s led to the introduction in 1982 by Eli Lilly of the recombinant human insulin produced by Genentech. This was the first recombinant molecule to be launched as a drug, and it replaced insulin isolated from porcine pancreas, the most widely used until then.[17]

The advantages of rDNA include its ability to overcome many of the dangers involved in administering molecules extracted from human and non-human tissues. One example can be seen in the treatment of children with congenital dwarfism, which, until the 1980s was treated with cadaver hypophysis – derived growth hormone (somatotropin or somatropin). This sometimes led to Creutzfeldt-Jacob disease (spongiform encephalopathy),[18] a drawback that was overcome with the development of recombinant human somatotropin. The therapeutic suitability of recombinant proteins against severe diseases is beyond doubt. Take, for example, the advantages offered by rhEPO in the treatment of anemic patients with chronic renal failure,[19] the success of recombinant filgrastim (granulocyte-colony stimulating factor, or G-CSF) in cancer patients receiving chemotherapy,[20] and the usefulness of engineered interferon (INF)-α in the treatment of hepatitis.[21] Also in use are other cytokines (for example, IFN-β or interleukin [IL]-2), biotechnological vaccines such as the recent human papillomavirus vaccine, monoclonal antibodies that require this technology in their production process, clotting factors, enzymes, and other proteins and peptides (often hormonal), such as insulin and somatotropin as already mentioned. The increasing interest in these drugs by researchers and clinicians means that they also receive the attention of regulatory bodies and health authorities.

As is always the case in biomedicine, the state of the art in biotechnological pharmacology is the result of decades, even centuries, of efforts by many investigators. The principal landmarks became obvious during the twentieth century, with the award of several Nobel Prizes. The controversial award of the Nobel Prize in Medicine and Physiology in 1923 to Banting and McLeod for their discovery of insulin[22] was followed by the recognition of important findings that, in many ways, were the forerunners of today's biotechnology. In 1945, Fleming, Florey and Chain were awarded the Nobel Prize for discovering that antibiotics could be obtained from microorganisms.[23] This was a revolutionary glimpse of how biotechnology could grow to serve pharmacologic therapy. In 1955, Vincent du Vigneaud was awarded the Nobel Prize in Chemistry for synthesizing the first peptides using biochemical techniques (oxytocin and vasopressin).[24] This revealed the interest in, and need for, laboratory techniques that could be used to synthesize proteins. In 1959, Severo Ochoa

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and his disciple Arthur Kornberg were awarded the Nobel Prize in Medicine and Physiology for the discovery of the synthesis mechanisms of the nucleic acids RNA and DNA,[25] a fundamental event that was to have decisive consequences for the subsequent development of genetic engineering. A fitting salute to pharmacologists, Dr Ochoa held the Chair of Pharmacology at the Medical School of New York University. In 1978 Arber, Nathans and Smith were awarded the Nobel Prize in Medicine and Physiology for the discovery of restriction enzymes[26] and, in 1980, Berg, Gilbert, and Sanger received the Nobel Prize in Chemistry for leading the field in the development of rDNA technology.[27] Sanger's achievement was particularly praiseworthy, because he had already received the Nobel Prize in 1958 for clarifying the structure of insulin. Other achievements also deserve recognition, for example, the discovery of the molecular structure of DNA by Watson, Crick, and the often forgotten Wilkins,[28] Nobel Prize winners in Medicine and Physiology in 1962. If we review the list of prizewinners in Medicine and Physiology or Chemistry, beyond the production of protein using rDNA procedures, we can see how many other findings are also directly related to modern biotechnology. A clear example can be seen in Köhler, Milstein and Jerne, who obtained the Nobel Prize in Medicine and Physiology in 1984 for proposing and developing the monoclonal antibody production technique.[29] However, protein synthesis using the rDNA of different species has become the basic technique for producing proteic drugs. Let us examine this technique in more detail (Figure 1).

Genetic engineering really took off at the beginning of the 1970s, with the discovery of restriction enzymes (or endonucleases), 'molecular scissors' that make it possible to obtain a specific fragment of human DNA that codes for the protein to be produced.[10,30,31] The rDNA technique

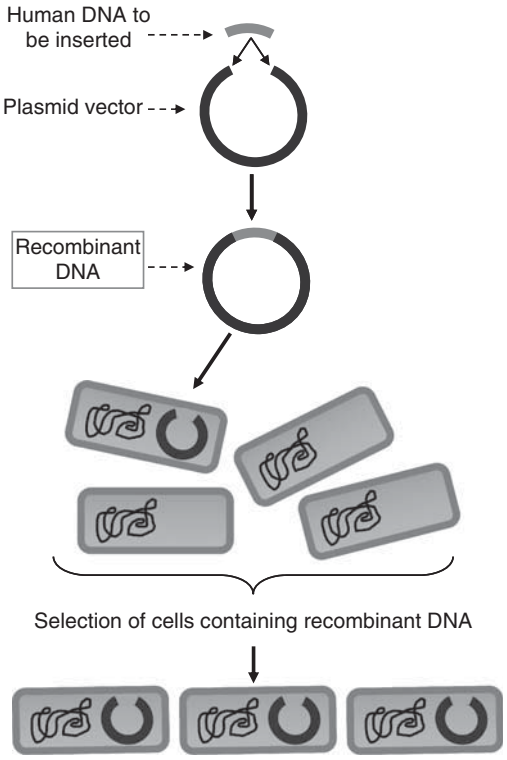


Figure 1: This diagram summarizes the recombinant DNA technique, which is used in the production of recombinant therapeutic proteins. Once the protein of interest has been identified, endonucleases are used to isolate the DNA fragment coding for it (in orange). This fragment is inserted into a plasmid that serves as a transfer vector; in other words, it is recombined with the plasmid (this is the engineered vector). The plasmid is then inoculated into the bacteria (for example, *Escherichia coli*) or other producing cell. Some of the bacteria will accept the new gene and produce the protein, others (most), will not. Those that contain the recombinant DNA molecule will be selected.

flourished because the classic procedures for obtaining proteins were many times unproductive, limited to a few specific molecules, and often unsafe. Recombinant DNA technology is based on the insertion, by viral vector, of a known human protein – coding gene into the genome of a prokaryotic (bacteria) or a eukaryotic cell (mammal, insect or yeast). The receptor cell population of

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the human gene is known as the expression system. The human gene 'recombines' with the genetic material of that system, which then produces human protein as if it were their own. What is relevant is that it produces protein in large quantities, quickly, and in a form that is analogous to the natural protein, if so desired. In 1977, Eugene Goldwasser, a reputable molecular biologist and biochemist from the University of Chicago, famous for his decisive contribution to the isolation and characterization of erythropoietin, expressed how revolutionary the technology was by stating that 10 mg of erythropoietin, the dose needed to treat a dialysis patient for one year, would have required 2550 l of urine from anemic patients. EPO produced by rDNA could finally be obtained without the need for so much urine.

Producing recombinant molecules is both difficult and expensive. Identification of the gene, choice of the protein-expressing cell population, and purification of the protein produced are only some of the complex steps necessary for the biosynthesis of recombinant therapeutic proteins, which also requires monitoring throughout the process.[32] In general, this is infinitely longer and more complex than the production of drugs by chemical synthesis. For example, a traditional chemical product requires from 100 to 200 quality control assays, whereas a biotechnological drug can require more than 2000 (including *in-process* control and product analysis).[33] This complexity is extremely relevant: seemingly insignificant variations in the production process can lead to structural changes in the final molecule that can have a huge impact on the pharmacological behavior of the product. In the case of biotechnological drugs, it is said that 'the process is the product', because the structure, conformation, and, therefore, the pharmacologic properties of the final product are closely linked to the procedures applied during manufacture.[34] This is understandable since living organisms behavior is tightly linked to environmental changes, far more than chemistry-derived compounds. This shows just how different biotechnological drugs are from synthetic drugs, which admit greater flexibility in their production process.

A well-discussed example that illustrates the relevance of the production protocol of biotechnological agents is the choice of the system for the expression of the human recombinant protein. Prokaryotic cells (bacteria) enable more rapid protein production, since, as a single bacterium is assumed to divide every 20 min, a billion cells will form in little more than half a day (they are cultured in tanks capable of holding thousands of liters). Seemingly, this is an advantage of prokaryotic systems. On the other hand, mammal eukaryote cells such as Chinese Hamster Ovary (CHO) grow more slowly and, therefore, take considerably longer to produce a similar amount of the biodrug. The resulting protein amino acid sequence in both expression vectors is the same, although we know that bacteria cannot glycosylate proteins[35] (that is, cannot add carbohydrates – or sugars – from the Greek *glycos*, meaning 'sweet'), whereas mammal cells can. For some proteins, glycosylation is essential for them to be active.[35–37] This is an extreme example of the importance of choosing the production process. Other changes, although seemingly insignificant, are sometimes even more decisive for the therapeutic viability of recombinant biological medicines, especially in terms of safety. For instance the formulation of the final product will determine stability, conformation, and hence biological activity.[38,39]

Despite the fact that pharmacologists are in general still not familiar with this methodology, we are about to develop more sophisticated recombinant proteins, or at least proteins requiring more sophisticated production processes. Proteins which are created by joining parts of two or more different genes which originally coded for separate proteins (fusion proteins) are already in the market,[40] and toxins linked to an

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antibody directed to a specific cell-surface tumor-associated-antigen (immunotoxin) or chimeric toxins[41,42] already exist. The situation becomes more complicated, because genetic recombination to obtain proteins can be carried out in plants[43] and farm animals that thus become transgenic (the so-called 'farm pharmacy'). For example, in 2006, the EMA approved an anti-thrombin-α produced in the milk of goats into which the corresponding gene had been inserted.[44]

To conclude on this, compared with traditional techniques for obtaining proteic molecules, recombinant DNA methodology enables products to be obtained more rapidly and in greater quantities. These products are purer, less susceptible to contamination, and more similar to the endogenous molecule if desired. The success of this technique has an unavoidable 'arithmetic' consequence: the exponential growth in the number of protein drugs produced and expected to reach the market. If we take currently authorized recombinant biotechnological drugs, those waiting for authorization and those in the pipeline, the expected market size is almost unimaginable.[45] In 5 years, from 2003 to 2008, the global market for biotech drugs has more than doubled from US$38 billion to $83 billion. This, despite market share for conventional medicines is progressively decreasing in favor of biomedicines. This is a particularly relevant warn for pharmacologists. But, how does the protein nature of a drug affect its pharmacologic behavior?

PHARMACOLOGY OF RECOMBINANT THERAPEUTIC PROTEINS: IMMUNOGENICITY AND OTHER ASPECTS

Other than in the production process, recombinant proteins differ from traditional chemically synthesized drugs in two basic ways: in their chemical structure (obviously proteic) and in the structural and functional similarity between the recombinant proteins and endogenous molecules. These aspects of biotechnological protein drugs considerably affect their pharmacological behavior and the methodology necessary for their research and development.

The complexity involved in the development and study of therapeutic proteins, and the impact of this complexity on pharmacokinetics compared with traditional chemical products, is illustrated for example by size differences. EPO, for instance, is approximately 170 times greater than acetylsalicylic acid (other molecules are up to 1000 and even 10 000 times smaller when compared to monoclonal antibodies). Size matters in pharmacology. Furthermore, although forms that resist degradation at the administration sites have been developed,[46] the bioavailability of these drugs is usually low and their distribution in, and penetration of tissue, is quite limited.[47–49] In addition, the fact that the drugs often copy endogenous molecules means that the patient's pathophysiological status has a considerable effect on their activity.[47] Not only do pharmacologists require in-depth knowledge of the pharmacokinetics and pharmacodynamics of therapeutic proteins for research and development, but the technology surrounding these compounds is also considerably different from that which is habitually used in chemically synthesized drugs. Manufacturers often have to design techniques to evaluate protein molecules, ensuring that these methods discriminate between the biological medicine and its endogenous counterpart,[50] and to develop methods of detecting antibodies against the biological medicine. Pharmacologists, for their part, require new technical knowledge in order to be able to investigate biotechnological drugs. Pharmacology should include education of preclinical or clinical 'biopharmacologists', because the introduction of these drugs will challenge some of the traditional concepts of pharmacology. This can be seen particularly clearly in the concern raised over adverse effects resulting from the immune reactions

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that these new compounds generate, that is, their immunogenicity; anecdotic to date in the pharmacology of small molecules.

Why has immunogenicity suddenly become a cause for concern? It is easy to understand that large, complex and often-unstable molecules such as therapeutic proteins and peptides are more likely to express regions that behave like epitopes (structures against which the immune system reacts). The ability of these protein drugs to initiate the immune response is known as immunogenicity.
It is even easier to understand the tendency of proteins to become immunogenic if, as is sometimes the case, these protein molecules are not exclusively of human nature.
This is why the potential therapeutic benefit of the administration of murine monoclonal antibodies was shadowed by the immune reaction they generated when identified as foreign. These antibodies are known as human antimouse antibodies (HAMA).
This, triggered the development of chimeric human-mouse monoclonal antibodies (with the suffix – ximab, for example, rituximab), followed by 'humanized' antibodies with a greater human content (with the suffix – zumab, for example, trastuzumab), and even the currently available fully human antibodies (suffix – umab, for example, adalimumab). Although these agents go a long way towards reducing immunogenicity, they do not solve the problem completely.[51] This should come as no surprise, because even recombinant therapeutic proteins with an amino acid sequence that is identical to that of a natural counterpart, are not exempt from carrying antigenic determinants.
It is not easy to explain why a recombinant therapeutic protein can be immunogenic, despite such primary structure similarity. Nevertheless, some comments can be made.[52,53] Recombinant therapeutic proteins are three-dimensional compounds and sometimes-complex quaternaries whose folding generates a spatial form that may be suboptimal and often unstable.[54] Its instability during storage may occasionally be sufficient to generate new structures, such as protein aggregates or products resulting from chemical degradation, which behave like epitopes. In addition, the protein purification process during production often carries impurities from the expression vectors (for example, portions of DNA from bacterial genes), and these impurities may cause immunogenicity.[53]

Immunogenicity would not be perceived as an element to be avoided if it had no clinical consequences. Biological medicines may, and commonly do, generate antidrug antibodies that do not have a clinical impact, but these same antibodies could cause therapy to fail or severe adverse reactions to develop.[55,56] Although severe adverse reactions are not common, an episode that occurred at the end of last century and beginning of this, forewarned us about the need to evaluate the potential clinical consequences of a hypothetical case of immunogenicity. As stated above, rhEPO was a revolutionary molecule that was marketed in the 1980s. It has prevented many transfusions, increased the quality of life of patients with chronic renal failure, and minimized many of the adverse effects of chemotherapy in cancer patients.[19,57]
One of the companies that launched rhEPO introduced an apparently insignificant variation – switching albumin for polysorbate 80 – in its formulation. From there, very severe and sometimes, yet scarce, fatal adverse reactions began to be observed in patients treated with a specific type of pre-filled syringe.[58] Several hypotheses have been put forward to explain these reactions.[59]
The most plausible seem to be aggregate formation or leachates potentiating the production of neutralizing anti-EPO antibodies that recognized not only the drug, but also the patient's own erythropoietin.[60]
The antibodies that reacted with the endogenous erythropoietin, thus breaking its immune tolerance, caused a type of sudden-onset anemia known as pure red cell aplasia (PRCA), which had fatal consequences.

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Although the problems highlighted by this case appear to have now been overcome, the EMA has strengthened its safety requirements for the approval of biological medicines. A similar situation was observed with recombinant thrombopoietin,[61] although luckily this was detected during clinical development.

Finally, regardless of the severity of adverse reactions, immunogenicity can cause failures in therapy because the antibodies that interact with external protein drugs neutralize them by attenuating or blocking their activity;[62] a phenomenon observed for instance in IFN and Factor VIII preparations.[63] Demonstrating the existence of neutralizing antibodies during the development of a biological medicine is an important warning for the pharmaceutical company or regulatory bodies, sometimes against further development. In April 2008, the EMA, the agency in charge of biotechnological drugs authorization in Europe, published the definitive guidelines with recommendations that pharmaceutical laboratories must adopt to evaluate immunogenicity.[64]

BIOSIMILARS, NOT BIOGENERICS

The general requirements for the preclinical and clinical development of an innovative biotechnological medicine are fundamentally the same as those of a synthetic drug, in spite of the fact that, on average, the necessary investment is much higher for the biodrug. Although we could focus on specific aspects of drug development (for example, the need to evaluate immunogenicity in the case of biological medicines), here we examine why is it more demanding to make a copy of a biological medicine than of a chemically synthesized (small) drug, a so-called generic.

We have already seen how even a slight variation in the production process of a biological medicine can modify the chemical characteristics of the final product (that is, 'the process is the product'), and that this could in turn lead to changes in the biological behavior of the molecule[65] and, consequently, to changes in its safety and/or efficacy.[66] These consequences must be taken into account, for example, when a company aims to modify the production protocol of an innovative drug that has already been launched,[67] but, they also need to be considered when attempting to produce a copy of a biotechnological medicine whose patent has expired.[68,69] The complexity of therapeutic proteins and their production techniques based on living organisms, and the confidentiality requirements of the pharmaceutical companies make it impossible for another company to produce a structurally identical copy of the innovative drug.[70] Slight differences in composition could compromise the drug's safety and efficacy, since it is not sufficient for the amino acid sequence of the copy to be the same. As it is neither possible to generate two identical biodrugs nor to completely guarantee their molecular three-dimensional structure due among other things to post-translational modifications that lead to microheterogeneity of those medicines, the development criteria for a biotechnological drug must be stricter than those required for a generic, for which only pharmacokinetic bioequivalence is generally enough to prove identical therapeutic behavior.[71] Thus, to make them equivalent, the copy of a biotechnological medicine must be shown to be as efficacious and safe as the innovative reference drug in comparative clinical trials that evaluate both aspects. Preclinical comparisons must also be made and post-marketing safety data of the copy are mandatory. Again, as for the EMA regulation, biopharmaceutical laboratories producing innovative biotech therapeutics need also to demonstrate no changes in efficacy and safety when a major change of the manufacturing process is applied to the innovator product.

The EMA uses the term 'biosimilar' or 'similar biological medicine' for the authorized copy of a biological, hence biotechnological, medicine produced in accordance with specific requirements of

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quality, efficacy and safety.[72] In order to avoid confusion, the term biogeneric should not be used since their corresponding regulatory pathways to reach authorization are different. In 2005, the EMA issued guidelines on biosimilars,[73,74] thus making it the only regulatory body to date that has proposed an abridged pathway for their development (Japan and Canada are on the way). We shall see what the position of the FDA towards biosimilars, or follow-on biologicals (FOB) as they would presumably be called in the United States, will be. Since the approval in Europe of two biosimilars of somatotropin in 2006, the EMA has granted authorization to 13 biosimilars (in fact really six different molecules). Before guidelines were issued one copy of a biotech product had been rejected, and at least another one was withdrawn from EMA assessment by the promoter later on. The demanding exercise of comparing a biosimilar with the innovative drug requires more time and effort, as well as a considerably greater investment (between 5 and 100 times) than that required for the development of a generic medicine. Although biosimilars price is expected to also lead innovators to apply a discount on their products, the demanding regulations will presumably not allow discounts near those reached on generics. The biosimilars market is expected to grow in the next few years. Luckily, because they cover a 'social' need in a world where health-care expenses are growing at an exponential rate. However, the investment necessary has generated apprehension and doubts concerning the financial viability of these agents. It only remains to be seen, therefore, how fast the biosimilars industry will develop in Europe and the rest of the world. The growing uncertainty in many companies over the possibility of recouping the original investment is aggravated by the fact that, in some countries, national laws prevent biotechnological drugs from automatic substitution by pharmacists (unlike innovative synthetic drugs and generics).[75] It is important to highlight that this 'non-automatic substitution' policy does apply in some countries to any biotech drug, also innovative products, not specifically to biosimilars. This means for instance that the pharmacist cannot dispense one innovative EPO if the physician prescribes another innovator one (there is more than one original EPO in the market). The same would apply to the two original IFNβ-1a currently in the market for multiple sclerosis.

It is therefore to say that biosimilars are drugs that are therapeutically as guaranteed as the corresponding original biomedicines in terms of quality, efficacy and safety, and that once the molecule has been approved by the EMA it is no longer a copy, but rather another biotech medicine. Some argue that even a biobetter can be produced in some instances in which modern techniques are used for their production. Let us finally not forget that a copy of a biomedicine that has not entered the EMA pathway for authorization, and yet has been launched in non-European markets, should not be called biosimilar.

CONCLUSION. BIOTECHNOLOGICAL MEDICINES (BOTH INNOVATORS AND BIOSIMILARS): BOTH A NEED AND A CHALLENGE

From what has been discussed above, it is clear that biological medicines are not simply a new drug family, as were for instance angiotensin-converting enzyme inhibitors, proton pump inhibitors, or leukotriene receptor antagonists in their day. This new generation of therapeutic molecules heralds a new era in pharmacology, one that will require pharmacologists to acquire new skills to develop and manage these molecules. These new drugs have opened up at least one whole new branch of pharmacology. Perhaps it is time to begin to use the old term biopharmacology, now in disuse, with a different meaning. We could go even further. If we accept, as some thinkers have

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proposed, that a science uses its own resources to explain itself, biopharmacology could become an emerging science at the intersection of several other disciplines.

More than a promising development for the future, biotechnological agents are a tangible reality. However, like most new products, their development and commercialization pose many questions. It is up to manufacturers, researchers, physicians, pharmacists and regulators to coordinate efforts to help answer these questions, in order to ensure that treatments are both safe and efficacious. Guaranteing drug's safety and patients' access to these important drugs should be the ultimate goal of all those actors. Partisan interests mean that many questions are directed towards specific areas of the relevant regulations. Fortunately, the nature of these regulations in Europe acts as a guarantee for patients. This is a desirable approach from the EMA in the face of the uncertainty over, and the ignorance of, a lot of the underlying scientific and medical rationale of many of these drugs. Is it justified for the pharmacist not to be able to automatically substitute biotechnological agents in some countries? Do the few cases of fatal immunogenicity justify such strict regulations? Given these requirements, will the market share of biosimilars reach that of the generic market. Will the Food and Drug Administration (FDA) develop a similar set of regulations to that of the EMA concerning FOB? Will biosimilars compete only on price? Will efficacious enteral administration of therapeutic proteins be possible? Will plants (albeit transgenic) again be used as the main source of drugs? Only time will provide answers to these and other questions. For now, only the horizon is visible. But we know that something, probably almost everything, lies beyond it.

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