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Editorial

Biologicals

Since the middle of the 20th century, medical science has found ways to prepare therapeutic products derived from human blood and plasma for the treatment of many life threatening diseases, as well as for complex surgical procedures. Two of the programmes and projects of WHO are called respectively *Biologicals* and *Blood Products and Related Biologicals* [5,6].

The informal portrayal of Biologicals given by WHO at their home page of Biologicals [5] is: biological medicines (i.e. Biologicals) such as blood products, vaccines, cell regulators and related *in vitro* diagnostic tests are life-saving components of every day medical practice worldwide. Thus it is clear that blood products fall under the umbrella of Biologicals.

More broadly, biologicals can be defined as medicinal preparations made from living organisms and their products, including serums, vaccines, antigens, antitoxins, etc. [2].

Over the last few years various therapeutic proteins, also called biologicals, have been brought on the market, including the monoclonal antibodies against TNFα (infliximab, adalimumab, etanercept) and CD20 (rituximab) [4]. Preferentially, the term biopharmaceuticals is nowadays used for these latter therapeutic proteins. Biopharmaceuticals are then defined as medical drugs produced using biotechnology. They are proteins (including antibodies), nucleic acids (DNA, RNA or antisense oligonucleotides) used for therapeutic or *in vivo* diagnostic purposes, and are produced by means other than direct extraction from a native (non-engineered) biological source [7].

Both the benefit but also the risks of biopharmaceuticals are becoming increasingly important. During the last years a substantial part of the FDA- and EMEA-approved compounds belong to this class of drugs. These remedies have a number of characteristics that set them aside from low molecular weight drugs. As Brennan and coworkers formulated it [1]:

> The unique and complex nature of biotechnology-derived pharmaceuticals has meant that it is often not possible to follow the conventional safety testing programs used for chemicals, and hence they are evaluated on a case-by-case basis. Nonclinical safety testing programs must be rationally designed with a strong scientific understanding of the product, including its method of manufacture, purity, sequence, structure, species specificity, pharmacological and immunological effects and intended clinical use.

And again and again in the literature concerns are expressed about safety [3]. Often their mechanisms of action are intimately related to their complicated shape and associated with secondary, tertiary and (sometimes) quaternary structures of the molecule. These structures cannot be fully defined with our present set of analytical techniques. Drug analysis is further complicated by the fact that the exogenous compounds often are the same as (or closely resemble) endogenous proteins. This implicates that the performance of biopharmaceuticals relies on strict production protocols and close monitoring of their activity in clinical situations. It also means that in safety testing and clinical test programs questions

have to be addressed regarding species-specific responses, selection of routes of administration and dosing schedules. The possible occurrence of immunogenicity is an other challenging issue. Toxicity problems associated with monoclonal antibodies have included lymphokine release syndrome, reactivation of tuberculosis and other infections, immunosuppression but also anaphylactic shock. More insidious, but nonetheless devastating, antibodies to a recombinant hormone or cytokine have been shown to neutralize not only the product, but also the endogenous factor.

It has to be noted that many of these novelties are highly effective and also that most often they are extremely expensive. Undoubtedly, as the usage of biopharmaceuticals will increase, the cost should come down. However this does not seem to be happening at an impressive rate and a new form of inequality between rich countries and low-income countries is a hazard. Academic leadership should persuade authorities to reduce customs duties and manufacturers to reduce prices for developing countries.

A special issue of *The International Journal of Risk & Safety in Medicine* on biologicals seemed warranted for two reasons. Firstly, WHO has always been deeply concerned about quality assurance and safety of blood products and related biologicals and the Organization has continuously stressed that only blood products of demonstrated quality, safety and efficacy should be used. However there is a fear that especially countries with limited resources have significant difficulties in fulfilling their responsibilities in this field [6]. Secondly, the ever increasing importance of biopharmaceuticals in medicine in itself was reason enough for such a special issue.

We recognize that the papers published here will not give final answers nor provide the ultimate solutions for existing problems. Towards the authors we emphasized that we did not expect lengthy review articles but just short opinion papers describing the situation and existing regulations in various parts of the world. The topic had to be biologicals, realizing that biopharmaceuticals and biosimilars form an important issue within that framework. Of course some duplication was to be expected. However, as there is still debate if the drug safety profile should be linked more to the product than to the substance quite some different opinions were also expected.

No further instructions nor any restrictions were formulated. Therefore subjects like the choice of suitable comparator/reference products, permitted indications, substitutability and interchangability, product names, immunogenicity and pharmacovigilance could all be discussed. Notwithstanding these liberties it becomes apparent from several of the contributions that there are considerable inconsistencies with respect to regulatory measures for small molecule generics and those for biosimilars. These inconsistencies seem to be inevitable but theoretically they could pose a serious threat. It is to hope that the reluctance of the US to go forward with the introduction of biosimilars will not prove to be justified prudence. Nevertheless, the reader of this special issue of the Journal will probably conclude with us that the appearance of biopharmaceuticals on the global market in the past decennia signifies an important milestone in the history of pharmaceutical medicine.

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