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Marketing Authorization for Recombinant Products in Europe

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Rules and procedures affecting our daily life are increasingly derived of European rather than of national origin. While there is certainly room for criticism on certain aspects of European legislation its aim to remove undue (national) legal hurdles inhibiting the principle of a common market is widely supported. This strong focus is particularly evident in the field of regulation of medicinal products and medical devices.

The history of the rules governing medicinal products in Europe dates back to the mid 1960ies. Since that time the system has evolved continuously and, most importantly, also successfully. As a main achievement, European drug legislation as it is implemented today is unanimously accepted by both, individual Member States and industry.

The legal framework to authorize medicinal products in the European Union was originally restricted to products produced by means of genetic engineering and to those derived from complex biotechnological processes as well as to new active substances. The majority of products remained, however, eligible also for Mutual Recognition (MR) or national licensing procedures.

Options for both, MR and national procedures have been restricted constantly during the recent years. This is best but not only reflected by the fact that whenever a product is going to be licensed in more than one Member State (MS) a harmonized procedure must be applied in order to achieve a single scientific conclusion on a particular product. Any option to deviate from that concept has now been abolished. Recently revised European drug legislation has put the European Medicines Agency (EMA) in London and its Committee for Medicinal Products for Human Use (CHMP) in a very strong position to ensure that any of the European procedures for licensing medicinal products will follow these new rules.

In parallel, the newly created Committee for Mutual and Decentralized Procedures for Human Medicinal Products (CMDh) – the former Mutual Recognition Facilita-

tion Group (MRFG) – has been equipped with appropriate legal instruments in order to serve as a mediator between the interests of MS and the European Commission (EC).

The European drug regulatory system as it stands now is complex but is generally considered to be superior compared the individual rules laid down in all MS legislations. This is particularly acknowledged by the pharmaceutical industry whose access to a common market is facilitated due to common rules and principles.

Although complex the legal principles of current European drug legislation are not understood to be dogmatic. They allow a high degree of flexibility in order to respond rapidly to immediate public health threats and well address the needs of patients. All actions related to medicinal products are publicly available and information related to products is provided in formats which are understandable for both, medical/scientific communities as well as patients and patients organizations.

European drug legislation also recognizes that drug development is a common undertaking requiring shared responsibilities of regulatory agencies and the industry. This is particularly emphasized by the principle of CHMP's scientific advice to industry which has become a frequently used and powerful instrument to straightforward pharmaceutical development processes. Along the same line the recently introduced legal requirement for assessing and approving clinical trial applications will help to minimize discrepant positions between industry and agencies regarding the clinical development of new drugs, ultimately resulting in a more streamlined evaluation of Marketing Authorization Applications.

Specific aspects related to medicinal products for children and for treatment of rare diseases (orphan drugs) are addressed in detail by latest European drug legislation and strong incentives are offered to accelerate development of such products. Beyond that, advanced technology based medicinal products such as gene and cell therapy medicinal products are covered. A concept for products derived from tissue engineering will follow in short time.

Generic medicinal products are an important aspect to facilitate equal access to highly effective medicinal products in all MS, to foster competition and to strengthen the concept of a common market. While generics have a long tradition at least with respect to the well characterized pharmaceuticals, it is generally accepted that biological medicinal products are more difficult to regulate via that route. To address this need, the concept of biosimilar medicinal products was integrated into European legislation only recently, and, for the first time provides opportunity to industry specialised on those products to specifically file for a Marketing Authorization. It remains open to what range of biological medicinal products the biosimilarity strategy can be applied on.

Overall, the implementation of common principles to regulate medicinal products is a success story. Although mostly called a centralized system it is widely accepted amongst Member States and industry primarily due to the fact that an environment

has been created allowing all parties involved to feel as a “primus inter pares” through providing equal opportunities. This is the main reason why we can be confident that current and future challenges to the health and welfare of the European population will best be responded to by commonly agreed principles rather than by individual member state legislation.

Discussion

Frost: Do you think this procedure, similar to the approach you just described, could be applied to allergens?

Pfleiderer: That depends on the complexity of the molecules. As a virologist, I do not know how complicated allergens could be, but if you have a very simply-structured recombinant allergen, I could well imagine that it works. Where functionality is not dependent on complex three-dimensional structures, which cannot be assessed by physicochemical means, I would clearly say yes: It is possible. When you think about interferons as biological substances and compare them to recombinant allergens, it is clearly possible. And that makes it much easier to get allergens licensed.

Frost: But one principle of biosimilars is the demonstration of comparative immunogenicity. And immunogenicity is actually the aim, the principal of allergens. So how can one show a similarity of immunogenicity? That may be very difficult.

Pfleiderer: You have to convince the authority. So you need a decent set of clinical data. You have to show that with a group of related or similar antigens, you get the desired amount of immunogenicity. This is nothing that you can solve today or tomorrow. It is an option for the future, but the option is there, which is important. But my understanding is that clinical data on recombinant allergens are very sparse, they are still under development. From that perspective it is not yet possible, you need to have a solid data base related to clinical efficacy and safety.

