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The safety, efficacy and regulatory triangle in drug development: Impact for animal models and the use of animals

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ABSTRACT

Nonclinical studies in animals are conducted to demonstrate proof-of-concept, mechanism of action and safety of new drugs. For a large part, in particular safety assessment, studies are done in compliance with international regulatory guidance. However, animal models supporting the initiation of clinical trials have their limitations, related to uncertainty regarding the predictive value for a clinical condition. The 3Rs principles (refinement, reduction and replacement) are better applied nowadays, with a more comprehensive application with respect to the original definition. This regards also regulatory guidance, so that opportunities exist to revise or reduce regulatory guidance with the perspective that the optimal balance between scientifically relevant data and animal wellbeing or a reduction in animal use can be achieved.

In this manuscript we review the connections in the triangle between nonclinical efficacy/safety studies and regulatory aspects, with focus on *in vivo* testing of drugs. These connections differ for different drugs (chemistry-based low molecular weight compounds, recombinant proteins, cell therapy or gene therapy products). Regarding animal models and their translational value we focus on regulatory aspects and indications where scientific outcomes warrant changes, reduction or replacement, like for, e.g., biosimilar evaluation and safety testing of monoclonal antibodies. On the other hand, we present applications where translational value has been clearly demonstrated, e.g., immunosuppressives in transplantation. Especially for drugs of more recent date like recombinant proteins, cell therapy products and gene therapy products, a regulatory approach that allows the possibility to conduct combined efficacy/safety testing in validated animal models should strengthen scientific outcomes and improve translational value, while reducing the numbers of animals necessary.

1. Introduction

The use of animal models in biomedical research and drug development is historically embedded in the scientific experiment as a model system from which we can translate findings to humans. The structural and physiological similarity between man and species used in mammalian animal models support their usefulness to demonstrate proof-of-concept of experimental medicines or procedures, unravel pathophysiological mechanisms and evaluate the safety of novel candidate therapies. This regards chemistry-based low molecular weight compounds, recombinant proteins, cell therapy products and gene therapy products: in the comprehensive approach described as "drugs". Fig. 1 presents these different types of drugs, in relation to their stage of implementation in health care.

Studies in animal models have been credited to be either at the basis of, or directly responsible for, countless medical advances that would otherwise have been impossible. In contrast, opponents of this notion put forward that despite the similarity in structure, physiology and pathology of disease, the differences between humans and animals weakens prediction to such an extent that medical progress is actually hindered. Can both opinions be correct?

We present penicillin as an example. The introduction and success of penicillin as an antibiotic have been attributed by its inventors to the lack of a toxicological response in mice, which then translated successfully to most other mammals and humans. In contrast, had guinea pigs or hamsters been used for toxicity evaluation, the severe toxicity of penicillin in those species would

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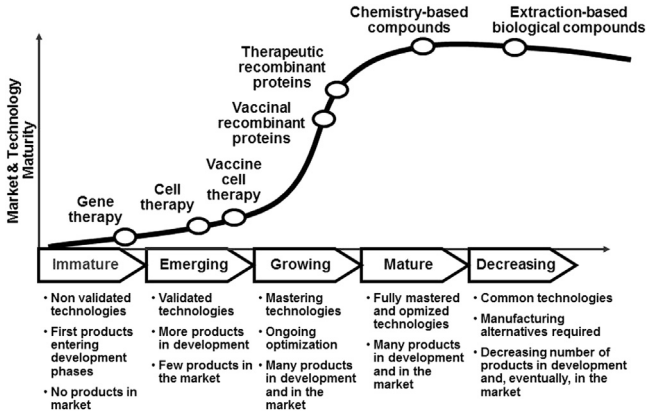

Fig. 1. Technology evolution in pharma industry. Various types of drugs are presented, together with their stage in implementation in health care. The characteristics of their maturity stage is also described. Picture modified from a slide provided by Dr Selçuk Özceada PhD, MBA, Managing Director, Bosfor Bioscience Partners Ltd Şti, Istanbul, Turkey.

have probably halted any further development. Nowadays we know that the toxicity in these species is related to species-specific adaptations of highly penicillin-susceptible gut flora. Fleming said about his experience with animal studies "*How fortunate we didn't have these animal tests in the 1940s, for penicillin we would probably never been granted a license, and possibly the whole field of antibiotics might never have been realized.*" (Greek and Hansen, 2013).

On the other hand, since the introduction in 1962 of the Kefauver–Harris amendment to the Federal Drug and Cosmetics Act that introduced additional animal studies to better predict human safety, there has, to date, not been a tragedy comparable to the thalidomide disaster in the mid 1950s. Nevertheless, there is continuous debate on the scientific basis of the predictability of animal studies, in other words its translational value, for the pharmacological and toxicological effects of drugs in man, and how and when animal studies should be conducted (Hackam, 2007; Hartung, 2013; Matthews, 2008).

There is nowadays a complex network of documents issued by competent regulatory authorities regarding drugs, i.e., regulations, directives, guidances and guidelines, that need to be addressed in drug development. In most cases, product-specific documents have been developed during the maturation and market entry of these products (Fig. 1); these documents are available on the websites of, e.g., the Food and Drug Administration (FDA) in the USA, the European Medicines Agency (EMA) in Europe, and in the world-wide approach the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). This guidance is well-established for low molecular weight chemical compounds, but less so for therapies of more recent date such as gene therapy products (see, e.g., EMA, 2014a). Regulatory documents include mainly safety aspects and nonclinical toxicology. Evidently, data on efficacy of a distinct drug have to be included in early regulatory filings during development, starting with the Clinical Trial Application or Investigational New Drug application, but the actual content including proof-of-concept is left to the sponsor of clinical trials or market authorization. This includes the choice of proper animal models for a given disease, i.e., the translational value for a given clinical condition.

The increased emphasis on animal welfare and animal well-being has brought this discussion in another perspective. For instance, there is a Directive in Europe addressing the protection of animals used for scientific purposes (European Union, 2010). With the content in this Directive, Europe is ahead of other continents in the world.

Since the introduction of the concept of 3Rs (Replacement, Reduction, Refinement) and humane treatment of animals in experimentation (Russell and Burch, 1959)., there is an increasing emphasis on model characterization contributing to greater awareness that there are limits to the utility of animal studies, and that data generated in animal models are only useful in specific circumstances. This is not only the case in academic laboratories and discourse, but this is also finding a voice in pharmaceutical companies and regulatory agencies. Noteworthy, there has been much achieved in harmonization of filings of (new) drugs to competent regulatory authorities worldwide, like the use of the Common Technical Document and the guidelines issued by the ICH (see ICH, 2014). As stated above, this regards mainly aspects like product manufacturing and safety requirements. There is little harmonization regarding pharmacology, including *in vivo* testing in relevant animal models.

In this manuscript we present more detailed considerations regarding the position of experimental animal models in the above-described triangle between safety, efficacy and regulatory aspects in drug development (Fig. 2). This is a quite broad theme, and we therefore limit these considerations to a number of relevant items, and, where possible, provide examples. The purpose of this manuscript is to bring the use of animal models in nonclinical safety and efficacy studies in the perspective of regulatory aspects and the perception of what is nowadays perceived as the best approach in drug development.

2. Opportunities to maximize the usefulness in routine regulatory animal studies

From a regulatory point of view, the entire process of safety testing of drugs in animals has been extensively documented in international and national legislation and guidance. In the European Union the reasoning behind the use and requirements for animal testing in the development of pharmaceuticals is set out in Directive 2001/83/EC Annex I (European Union, 2001). Animal welfare and the protection of animals used for experimental purposes, according to the principles of 3Rs are governed by Directive 2010/63/EU (European Union, 2010), which came into full effect in 2013. In addition, the use of nonhuman primates (NHPs) is only allowed if they are essential for the benefit of human beings and "*no other alternative replacement methods are available*" (paragraph 17 in this Directive). The 'no, unless' position of this directive is now also reflected in other European guidance documents (EMA, 2014b). Thus, the scientific justification of species selected for experimentation requires a careful consideration and explanation. Most (low molecular weight) drugs in the market today have been developed according to the guidance and

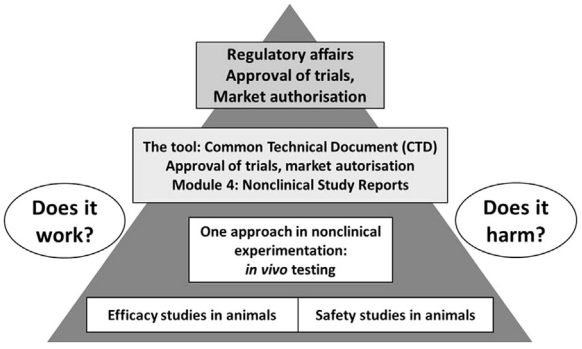

Fig. 2. Towards new treatments of diseases in humans: the triangle between nonclinical efficacy and safety studies and regulatory aspects, depicted for the case of studies in animal models.

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