European Journal of Pharmacology ∎ (∎∎∎∎) ∎∎∎–∎∎∎

Contents lists available at ScienceDirect

European Journal of Pharmacology

journal homepage: www.elsevier.com/locate/ejphar

Regulatory acceptance of animal models of disease to support clinical trials of medicines and advanced therapy medicinal products

Q1 Joy Cavagnaro [a,*], Beatriz Silva Lima [b]

[a] Access BIO, PO Box 254, Boyce, VA, USA
[b] iMED.ULisboa, Universidade de Lisboa, Portugal

ARTICLE INFO

Article history:
Received 18 February 2015
Received in revised form
26 February 2015
Accepted 12 March 2015

Key words:
In vitro
In vivo
Animal model
Species selection
Disease model
3Rs
Predictive value
Preclinical safety assessment
Regulatory guidance
Guidelines
ICH
Critical Path Initiative
Innovative Medicines Initiative
Induced pluripotent stem cells

ABSTRACT

The utility of animal models of disease for assessing the safety of novel therapeutic modalities has become an increasingly important topic of discussion as research and development efforts focus on improving the predictive value of animal studies to support accelerated clinical development. Medicines are approved for marketing based upon a determination that their benefits outweigh foreseeable risks in specific indications, specific populations, and at specific dosages and regimens. No medicine is 100% safe. A medicine is less safe if the actual risks are greater than the predicted risks. The purpose of preclinical safety assessment is to understand the potential risks to aid clinical decision-making. Ideally preclinical studies should identify potential adverse effects and design clinical studies that will minimize their occurrence. Most regulatory documents delineate the utilization of conventional "normal" animal species to evaluate the safety risk of new medicines (i.e., new chemical entities and new biological entities). Animal models of human disease are commonly utilized to gain insight into the pathogenesis of disease and to evaluate efficacy but less frequently utilized in preclinical safety assessment. An understanding of the limitations of the animal disease models together with a better understanding of the disease and how toxicity may be impacted by the disease condition should allow for a better prediction of risk in the intended patient population. Importantly, regulatory authorities are becoming more willing to accept and even recommend data from experimental animal disease models that combine efficacy and safety to support clinical development.

1. Introduction

Regulatory authorities play a major role in the interpretation of results from animal studies conducted to support clinical applications of novel therapeutic modalities. Regulators are tasked with simultaneously promoting innovations that can improve health while implementing policies that ensure that the benefits of new products will outweigh their risks. However, the regulatory environment is also increasingly challenged with a rapid growth in knowledge and technologies. In addition, when a product is withdrawn from the marketplace due to serious safety concerns; the regulatory authorities are under heightened public scrutiny and even criticized for approving an "unsafe" product.

Most developers and regulators concerned with assessing the safety of new medicines currently recognize the importance of applying the principles of the 3Rs (Replacement, Reduction and Refinement) for protecting animals used for scientific purposes (Directive 2010/63/EU). However, they also acknowledge that in most cases there are no established alternatives to testing in animals. More importantly, they are also challenged with an increasing imperative to enhance the predictability of the data from animal studies to ensure the safety in humans. While the current methods of safety assessment, mostly animal-based, have been successful in screening out compounds that might cause toxicity in a substantial proportion of patients, they have been less so at predicting serious adverse effects that occur only in a relatively small minority of patients. Some reasons given for why animal studies fail to detect these effects is that animal studies are not powered to detect rare events, and as they are mostly conducted in healthy animals, the impact of the disease on the biological activity of test compounds is not assessed. Arguably, patients enrolled in clinical trials also do not reflect the full range of the population or treatment situations that occur in practice. As a result, new safety issues are often identified only after medicines enter the market (Woodcock and Woosley, 2008).

Predictions of safety between species (e.g. rat, dog, monkey and human) are good but not perfect. Retrospective analyses conducted by industry has demonstrated that toxicity evaluation in healthy rodent and non-rodent species results in prediction of

* Corresponding author. Tel.: +1 540 837 9002.
E-mail addresses: jcavagnaro@accessbio.com (J. Cavagnaro), beatrizlima@netcabo.pt (B. Silva Lima).

http://dx.doi.org/10.1016/j.ejphar.2015.03.048
0014-2999/

human risk in approximately 71% instances (Olson et al., 2000). The present inability to show good concordance between some animal efficacy studies and human clinical outcomes is believed to be due in part to shortcomings in experimental design and conduct, as well as reporting results (Everitt, 2015). The various regulatory agencies house large repositories of in vitro and in vivo animal results that are linked with actual human outcomes data. Data mining efforts which effectively protect proprietary data provide the scientific basis for better predictive preclinical safety models.

The decision to utilize an animal model of human disease as part of a preclinical safety submission/dossier has historically been driven by a need to test a specific hypothesis typically generated after target organs have been identified in standard toxicity studies in healthy animals. Animal models of disease have not been used initially based on their inherent limitations e.g. inability to accurately recapitulate all the key aspects of the corresponding human disease and the limited historical data on general health and spontaneous disease pathology. This article specifically highlights current regulatory guidance published by US Food and Drug Administration (FDA) and the European Medicines Agency (EMA), and where appropriate, the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), encouraging the use of animal models of disease to support clinical development. It is acknowledged that other countries may have similar guidance.

2. Modernizing preclinical and clinical development

2.1. US initiatives

In 2004, the FDA launched the Critical Path Initiative (CPI), a project intended to improve the drug and medical device development processes, the quality of evidence generated during product development, and the outcomes of clinical use of these products (FDA CPI, 2004). In FDA's view, the applied sciences that are needed for medical product development have not kept pace with the tremendous advances in the basic sciences. The new science is not being used to guide the technology development process in the same way that it is accelerating the technology discovery process. Specifically, the sophisticated scientific tools used in drug discovery and lead optimization are not being used in the preclinical and clinical development stages. More importantly, insufficient applied scientific work has been done to create new tools to get fundamentally better answers about how the safety and effectiveness of new products can be demonstrated, in faster time frames, with more certainty, and at lower costs.

The “tools” identified for safety assessments include product testing, in vitro and animal toxicology studies, and human exposure studies. FDA acknowledged that despite efforts to develop better methods, most of the tools used for toxicology and human safety testing are decades old. In addition, although traditional animal toxicology has a good track record for ensuring the safety of clinical trial volunteers, it is resource intensive, time-consuming, requires large quantities of product, and may fail to predict the specific safety problem that ultimately halts development. Clinical testing, even if extensive, often fails to detect important safety problems, either because they are uncommon or because the tested population was not representative of eventual recipients (FDA CPI, 2004).

Propelled by CPI, the FDA agreed to form a partnership, together with the University of Arizona and SRI International, to create the Critical Path Institute (C-Path). Because of neutral funding and its mission to focus on process, not products, FDA is able to actively participate in the work of C-Path without concerns about conflicts of interest. The first consortium formed by C-Path was the Predictive Safety Testing Consortium. The goal of C-Path projects is to integrate new and advanced technologies into medical product development, especially those that accelerate pathways for innovative diagnostic tests and therapies. Currently most of the projects are focused on identification of translational biomarkers (e.g. nephrotoxicity, hepatoxicity, cardiotoxicity, vascular injury and muscle injury) (Woodcock and Woosley, 2008).

Recognizing the value of biomarkers, FDA's Center of Drug Evaluation and Research (CDER) has issued Letters of Support to submitters, briefly describing CDER's thoughts on the potential value of a biomarker thereby encouraging further evaluation. Although the letter does not connote qualification of a biomarker it is meant to enhance the visibility of the biomarker, encourage data sharing, and stimulate additional studies (Table 1)

2.2. EU initiatives

In Europe, an extensive long term consultation with stakeholders in the biomedical research and development process also commenced in October of 2004, organized by the European Commission (EC) in Brussels to address the causes of delay or bottlenecks associated with late attrition of investigational products as well as post marketing, safety – associated withdrawals. The research and development bottlenecks identified were (i) predicting safety, (ii) predicting efficacy, (iii) bridging gaps in knowledge management and (iv) bridging gaps in education and training. A Strategic Research Agenda was prepared describing the recommendations to address those bottlenecks and a plan for their implementation (The Innovative Medicines Initiative Research Agenda, 2008). It was concluded that, for improving the prediction of efficacy and safety of medicines, increased basic knowledge on several areas was needed including a better understanding of basic mechanisms of disease and involved targets, target biology and associated pathways, target cross talk and pathway interconnection would need to be explored. Furthermore, additional and/or alternative preclinical models beyond animal models would be needed. To address these concerns a partnership emerged, similar

Table 1
Example of current letters of support for biomarker development submitted to FDA.

Submitter	Biomarkers	Area(s) for further evaluation
Critical Path Institute's (CPI) Predictive Safety Testing Consortium (PSTC), Nephrotoxicity Working Group (NWG)	Urinary Biomarkers: Osteopontin and Neutrophil Gelatinase-associated Lipocalin (NGAL)	Early Clinical Drug Development
CPI, PSTC, Skeletal Muscle Working Group (SMWG)	Serum and Plasma Biomarkers: Myosin Light Chain 3 (Myl3), Skeletal Muscle Troponin I (sTNI), Fatty Acid Binding Protein 3 (FABP3), Creatine Kinase [Muscle Type (CK-M), Homodimer (CK-MM)]	Early Clinical Drug Development

adapted from http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm412833.htm.

Please cite this article as: Cavagnaro, J., Silva Lima, B., Regulatory acceptance of animal models of disease to support clinical trials of medicines and advanced therapy medicinal products. Eur J Pharmacol (2015), http://dx.doi.org/10.1016/j.ejphar.2015.03.048