NEWSLETTER

BIODEFENSE PRODUCTS

A NEW RENAISSANCE?

Since the start of the war in Ukraine in 2022, there has been a renewed interest in the development of drugs and vaccines that can counter the effects of dangerous pathogens used as bioweapons, as well as those aimed against chemical, radiological, and nuclear threats. Specific biological agents, such as those that cause anthrax, smallpox, botulism, plague, and tularemia, have received much attention regarding their potential use as bioweapons.

Introduction

Medical countermeasures (MCMs - (biologics, drugs, devices)) comprise drugs and vaccines developed to protect against or treat the symptoms caused by dangerous pathogens, as well as mitigating chemical, radiological, and nuclear threats.

Developing such products comes with a number of unique challenges, of which the most important potentially being the infeasibility of performing clinical trials against the active target (e.g. biological or chemical agents). This is due to both ethical reasons (dosing lethal or permanently disabling / debilitating toxic candidates) and, frequently, the limited prevalence of the pathogens of interest in the community,

environment or even biological research establishments. In 2002, the US Food and Drug Administration (FDA) issued the *Guidance for Industry - Product Development Under the Animal*, (the 'Animal Rule') to allow the approval of human drugs and biological products based on demonstration of safety in humans and efficacy in robust, well-controlled studies in animal models of disease.

FDA Animal Rule

The FDA *Guidance for Industry - Product Development Under the Animal Rule* is predicated on performing both appropriate and well-controlled animal models of the human disease or condition of interest. Under this guidance, companies developing new drugs and biological products must still demonstrate the product's safety in humans. Products can only be approved under the rule when all the following conditions have been met:

1. There is a reasonably well-understood physiological response to the toxicity of the substance and its prevention or measurable reduction by use of the product;
2. The effect is demonstrated in more than one animal species and can be used to predict the response in humans, unless the effect can be demonstrated in a single animal species sufficiently well to be used to predict the response in humans;
3. The animal study endpoint is clearly related to the desired benefit in humans, generally the enhancement of survival or prevention of major morbidity;
4. The data or information on the kinetics and pharmacodynamics of the product in animals or humans allows for selection of an effective dose in humans.

In addition, any novel products have to undergo a 'traditional' nonclinical and clinical toxicology program, similar to new chemical entities or biologics that do not fall under the Animal Rule.

Selection of relevant Animal Models

The key to translating preclinical efficacy findings in animal models is the selection of an appropriate strain or strains of the pathogen and relevant animal models that robustly recapitulate agent-typical disease in humans; such that efficacy can be adequately demonstrated.

The FDA guidance stipulates that the drug efficacy must be demonstrated in more than one animal species and is expected to promote or precipitate a response predictive for humans; unless the effect is fully demonstratable in a single animal species that represents a *'sufficiently well-characterised'* animal model for predicting the response in humans.

To translate efficacy from animals to humans, Pharmacokinetics (PK) and Pharmacodynamics (PD) in animals should be capable of extrapolation to PK in healthy humans. It is therefore important that suitable animal models should exhibit, where possible, similar PK behaviour relating to the investigated compound as compared to humans or at least PK properties that can be consistently translated.

Additionally the *'trigger to treat'* is an important clinical signal that provides unambiguous and discernable evidence to initiate treatment of an infected individual. Thus, the definition of trigger to treat can greatly impact efficacy assessments. For example, in most cases of infectious diseases in humans, trigger to treat is 'fever' accompanied by a clinical diagnosis and, where available, a confirmatory diagnostic test.

The development and selection of an animal model is often challenging because animals rarely fully recapitulate the changes in physiology, pathology and disease progression observed in humans. Lack of adequate knowledge, coupled with misinformation on the disease progression or condition in humans, exacerbates such difficulties along the development pathway.

Translation of Dose Level

The translation of the effective animal dose to an effective dose in humans is one such critical aspect. Different methods for selecting an effective human dose may be considered, based on the target of the investigational drug, prior human experience in related indications and/or the availability of a relevant biomarker.

The Animal Rule guidance states that methods for human dose selection supported only by comparing drug exposures can be used if no better alternative is available. In this case the assumption will be that the exposure-response (E-R) relationship in humans will be similar to the one in animals. Human dose determination well then be carried out by:

1. Establishing the E-R relationship in infected animal species (typically more than one animal model)
2. Identifying the fully effective dose (FED) in the animal models.
3. Extrapolation of efficacy at exposures that are higher in humans when compared with the exposure at FED in the animal models.
4.

This approach attempts to address the inherent uncertainty of the Animal Rule development paradigm in extrapolating the E-R relationship of a drug or biologic from animals to humans.

The integration of PK, PD, and safety data to define human dosing regimens can be challenging because of species-specific differences in PK, drug toxicity, disease progression, endpoint detection and host specificity of certain infections. Early preclinical, *in vitro* drug metabolism and toxicological screening assays can help characterise and address potential issues early-on in development. Furthermore, extensive application of pharmacometric approaches, including PK/PD modelling and simulation in the context of a model-informed drug development approach, is likely to facilitate an effective project progression under the Animal Rule pathway.

Conclusion

As discussed above, the challenges of developing a product under the 'Animal Rule' can be divided into two parts: the selection of an appropriate animal model for demonstration of efficacy, and the integration of PK, PD and safety data for translation to human dosing.

Early and continuous interaction with the FDA is primordial in ensuring a successful development.

In a next instalment of this newsletter we will discuss the European landscape for the development of biodefense products.

NEED EXPERT ADVICE DEVELOPING A BIODEFENSE PRODUCT? GET IN TOUCH!

Pathogenus Consulting Ltd.

30 High Street, Woking GU21 4UD, United Kingdom

Email: contact@pathogenus.com

Phone: 0044 (0) 7770 862571