Review of animal testing requirements in WHO guidelines and recommendations for biologics: a proposal to implement 3Rs principles

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Introduction

Many current *in vivo* testing methods for the assessment of potency and safety of vaccines and biological therapeutics were developed many years ago and use phenotypic rather than mechanistic endpoints. The transition away from using animal-based testing methods towards the use of non-animal technologies requires the development of product specific *in vitro* methodologies which allow potency and safety to be determined in a reliable and reproducible manner. International harmonisation of product specifications, based on clearly defined critical quality attributes, offers an opportunity to transition away from animal-based testing methodologies by focusing on specific, testable, mechanism-based product specifications which take advantage of the superior validity of *in vitro* testing methodologies.

This poster will highlight the opportunities for application of the 3Rs in quality control, batch and lot release testing of vaccines and biological therapeutics and how international harmonisation of product specifications, based on clearly defined critical quality attributes can facilitate transition away from animal-based testing.

The 3Rs in quality control, batch and lot release testing

Animals are used extensively in the development, production and quality control of biological products such as vaccines, cytokines, enzymes, and hormones. It has been estimated that more than 10 million animals a year are used worldwide for these purposes. The inherent variability of many of the animal methods used in batch release and quality control testing causes significant delays to the release of vaccines and biologics. For some vaccine products it is estimated that animal testing causes delays of up to one year in its manufacturing process.

The 3Rs (replacement, reduction and refinement) are increasingly being applied to support more humane and scientifically robust animal research and as a framework for the proper scientific justification on the choice of testing methods adopted in many fields of research across the biosciences. Harmonising international 3Rs approaches will reduce the rate of false negative findings and retesting requirements; reducing the time and costs required to release biologics products onto the market.

Harmonisation of product specifications and 3Rs opportunities

Global harmonisation of vaccine and biological therapeutics product specifications, based on clearly defined, patient-centric parameters is an important goal. Where these specifications are mechanistic in nature (e.g. derived from clinical biomarkers), there is an opportunity to use mechanistic *in vitro* assays, rather than phenotypic animal models, for the control of manufacturing consistency. Ideally, these models would be established during preclinical development and the detailed methodologies and reagents shared with the global biologics community to further support standardisation and harmonisation of quality control strategies. This approach aligns with Ph. Eur. chapter 5.2.14 [1] and the project detailed below.

Reviewing animal use requirements in WHO guidelines: an NC3Rs project

NC3Rs, facilitated by an expert working group, is systematically reviewing animal testing requirements within WHO guidelines for the post-licensure quality control and batch release testing of biologicals, and will recommend to WHO opportunities for the harmonised adoption of 3Rs approaches [2]. The recommendations will be presented to the Expert Committee on Biological Standardization in October 2023.

A subsequent project to implement the recommendations within WHO guidelines will be coordinated by WHO.

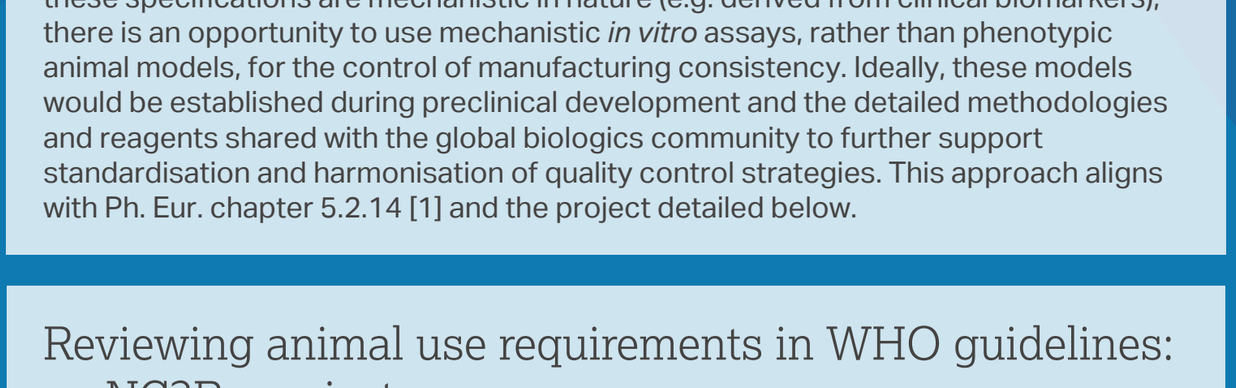

Figure 1. The stages of the project.

Figure 2. The countries represented on the working group (green).

Regulatory Agencies	Manufacturers	National Control Laboratories	Others
▪ MHRA ▪ FDA ▪ South Africa National Control Laboratory ▪ EDQM, France ▪ Health Canada ▪ ANMAT, Argentina	▪ GSK ▪ Janssen ▪ Merck ▪ Sanofi ▪ Serum Institute India ▪ IFPMA, DCVMN ▪ Finlay Institute, Cuba	▪ NIBSC, UK ▪ Paul Ehrlich Institute, Germany ▪ National Institute of Infectious Diseases, Japan ▪ National Institutes for Food & Drug Control, China ▪ Ministry of Public Health, Thailand ▪ RIVM, Netherlands ▪ National Control Laboratory Network	▪ WHO ▪ Seoul National University, South Korea ▪ European Commission Joint Research Centre ▪ IABS ▪ Expert Committee on Biological Standardization ▪ African Academy of Sciences

Figure 3. The organisations represented on the working group.

Guideline review

Eighty-one guidance documents have been reviewed with 63 found to contain reference to animal methods.

Based on the findings from this review, five focus groups (Adventitious agents, Neurovirulence, Potency, Pyrogenicity, and Toxicity) were established to review these methods and to propose alternative text/phrasing which better incorporate opportunities to apply the 3Rs.

Stakeholder engagement

There are several distinct communities that facilitate quality control, batch and lot release testing of vaccines and biological therapeutics. The key communities are manufacturers, national control laboratories (NCLs) and national regulatory authorities (NRAs) and each of these are likely to have subtle but important regional variations in current testing practice and engagement with the 3Rs. Regular stakeholder engagement with these communities is essential if the recommendations within this report are to be implemented by ECBS and welcomed and accepted by the end-users of WHO guidelines.

Two surveys were performed during the project – the first targeted at the manufacturers of vaccines and biological therapeutics and the second targeted at the regulatory community (both NCLs and NRAs). The output from the manufacturers survey has been published [3].

The regulatory survey output is currently being analysed and will be published in 2023. In addition to these surveys, the NC3Rs have hosted a series of regional workshops to better understand the potential impact of any proposed changes to WHO Technical Report Series documents on manufacturers and regulators globally. The output from these workshops will be published in 2023.

References

[1] Ph. Eur. (2016). Substitution of *in vivo* method(s) by *in vitro* method(s) for the quality control of vaccines. (5.2.14).

[2] World Health Organization. Expert Committee on Biological Standardization (2020). *Seventieth report. WHO Technical Report Series. 1024: Section 2.2.2.*

[3] Lilley ET *et al.* (2022). Integrating 3Rs approaches in WHO guidelines for the batch release testing of biologicals: Responses from a survey of vaccines and biological therapeutics manufacturers.

If you would like to know more about this project, please visit: www.nc3rs.org.uk/WHOproject
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