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Modern science for better quality control of medicinal products "Towards global harmonization of 3Rs in biologicals": The report of an EPAA workshop

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ABSTRACT

This article summarizes the outcome of an international workshop organized by the European Partnership for Alternative Approaches to Animal Testing (EPAA) *on Modern science for better quality control of medicinal products: Towards global harmonization of 3Rs in biologicals*. As regards the safety testing of biologicals, the workshop participants agreed to actively encourage the deletion of abnormal toxicity tests and target animal batch safety tests from all relevant legal requirements and guidance documents (country-specific guidelines, pharmacopoeia monographs, WHO recommendations). To facilitate the global regulatory acceptance of non-animal methods for the potency testing of, e.g., human diphtheria and tetanus vaccines and veterinary swine erysipelas vaccines, international convergence on the scientific principles of the use of appropriately validated *in vitro* assays for replacing *in vivo* methods was identified as an overarching goal. The establishment of scientific requirements for new assays was

List of abbreviations: 3Rs (principle), Replace, reduce, refine animal testing; ATT, Abnormal toxicity test; DT, D and T; Diphtheria and tetanus, ECBS; Expert Committee on Biological Standardization (WHO), EDQM; European Directorate for the Quality of Medicines and Health Care (Council of Europe), EFPIA; European Federation of Pharmaceutical Industries and Associations, ELISA; Enzyme-linked immunosorbent assay, EMA; European Medicines Agency, EPAA; European Partnership for Alternative Approaches to Animal Testing, EU; European Union, FDA; Food and Drug Administration (USA), GMP; Good manufacturing practice, GST; General safety test, ICH; International Conference on Harmonization, IFAH; International Federation for Animal Health, JEG 3Rs; Joint Committee for Medicinal Products for Veterinary Use/Committee for Medicinal Products for Human Use Ad-hoc Expert Group on the Application of the 3Rs in Regulatory Testing of Medicinal Products (EMA), NIBSC; National Institute for Biological Standards and Control (UK), OIE; Office International des Epizooties - World Organization for Animal Health, OMCL; Official Medicines Control Laboratories (EU), PAHO: Pan-American Health Organization; PEI, Paul-Ehrlich-Institut (Germany); *Ph. Eur.*, European Pharmacopoeia; QC, Quality control; SAM, Supplemental assay method; TABST, Target animal batch safety test; USDA, United States Department of Agriculture; VICH, Veterinary International Conference on Harmonization; WHO, World Health Organization.

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3Rs principle (replace - reduce - refine animal testing)
Regulatory acceptance

recognized as a further means to unify regulatory approaches in different jurisdictions. It was recommended to include key regulators and manufacturers early in the corresponding discussions. Manufacturers and responsible expert groups, e.g. at the European Directorate for the Quality of Medicines and Health Care of the Council of Europe or the European Medicines Agency, were invited to consider leadership for international collaboration.

1. Introduction

Established in 2005, the European Partnership for Alternative Approaches to Animal Testing (EPAA) is a public private collaboration between the European Union (EU) Commission, European trade associations, and companies from seven industry sectors. The partners are committed to pooling knowledge and resources to accelerate the development, validation and acceptance of alternative approaches to animal use in regulatory testing. The overall aim of activities is the replacement, reduction and refinement (3Rs) of animal use in regulatory testing. First defined by Russell and Burch in 1959 [1], the 3Rs principle became a firm legal requirement with *Directive 2010/63/EU on the protection of animals used for scientific purposes* [2].

In 2013, the EPAA launched the project *Harmonization of 3Rs in Biologicals.* Biologicals include a wide variety of products, such as hormones, immunoglobulins, blood products and vaccines. They are generally more complex pharmaceutical products as compared to their small molecule counterparts, and this is often reflected in the manufacturing processes for biological drugs. Strict quality control (QC) strategies are employed to ensure consistent batch-to-batch quality of, e.g., marketed human and veterinary vaccines. These QC strategies encompass validated production processes and analytical techniques that may include animal tests or non-animal *in vitro* methods and approaches. The regulatory requirements for the QC safety and potency batch release testing of vaccines and other biologicals are typically incorporated in pharmacopoeia monographs and guidelines. However, jurisdictions often differ in their legal requirements for batch release testing, just as they may differ in their requirements for marketing authorization (Fig. 1). In some jurisdictions, specific animal tests for the QC of vaccines and other biologicals have been deleted or replaced by non-animal approaches, whereas the same animal tests may still be required in other jurisdictions. Such regional regulatory differences may lead to the unnecessary continuance of scientifically unsupported animal testing if a product is intended for several international markets. Therefore, these regional regulatory differences merit evaluation to determine whether scientific evidence may facilitate the global regulatory acceptance of available non-animal methods or the deletion of no longer relevant tests. This may bring additional gains in resources and in timely patient access to medicines.

Against this background, the EPAA convened an international workshop *Modern science for better quality control of medicinal products: Towards global harmonization of 3Rs in biologicals,* organized by **Katrin Schutte** (EU Commission, Directorate General for the Environment, Belgium) and **Anna Szczepanska** (European Federation of Pharmaceutical Industries and Associations (EFPIA), Belgium), joint leaders of the EPAA Biologicals project team. The workshop focused mainly on vaccines, while addressing other biologicals as well, and took place on 15 and 16 September 2015 in Egmond aan Zee, The Netherlands. This report presents its outcome and the recommendations spelled out by the workshop participants.

The 45 invited participants of the workshop represented the World Health Organization (WHO), the World Organization for Animal Health (OIE; Office International des Epizooties), the European Directorate for the Quality of Medicines and Health Care (EDQM of the Council of Europe), the EU Commission and the European Medicines Agency (EMA), national regulators from different EU member states, Brazil, Canada, China, India, Japan, Mexico, and the USA as well as different human and veterinary vaccines, and pharmaceutical manufacturers and industry federations (Appendix I). The goals of the workshop encompassed a scientific evaluation of specific animal tests used for the QC of vaccines and other biologicals. The workshop aimed at addressing whether their deletion or replacement by non-animal methods, as applicable, might improve the scientific reliability of safety and potency testing. This included an exploration of the reasons for prevailing interregional differences in QC testing requirements. The workshop participants were invited to make concrete recommendations to overcome existing barriers to the global deletion of no longer relevant batch safety tests and global regulatory acceptance of specific non-animal methods identified in concrete areas.

Katrin Schutte (EU Commission, Directorate General for the Environment, Belgium, *Setting the scene)* opened the workshop. Subsequently, two introductory presentations served to exemplify challenges in meeting the scientific and legal obligation to implement the 3Rs principle in QC testing (**Catrina Stirling** (Zoetis, United Kingdom), *3Rs in product development and QC of biologicals: What do science and technology offer today?* and **Iwona Wilk-Zasadna** (GSK Vaccines), *Regulatory harmonization of 3Rs in QC testing requirements for biological products from the viewpoint of users).* These challenges fundamentally differ between general safety testing on the one hand and batch potency testing on the other hand: For abnormal toxicity tests (ATTs) or general safety tests (GSTs), deletion without replacement is being called for, whereas *in vivo* potency tests could be replaced by non-animal test methods. For many *in vivo* potency tests, that had been implemented for vaccine and other biological QC before the principles of *Good Manufacturing Practice (GMP) for ensuring the quality of biological products* had been established almost twenty-five years ago [3], non-animal methods have become available. As C. Stirling explained, modern analytical techniques are generally more appropriate for QC because they have the potential to enhance product characterization, and they are generally more consistent, rapid and cost effective. Most importantly, the 'consistency approach' has great potential to replace the need for *in vivo* testing. The consistency approach is founded upon a thorough characterization of the products during their development and the principle that the quality of subsequent batches is ensured by their consistent production following GMP principles and the strict application of an enforced quality system [4,5]. (Fig. 2 provides an overview of the principle steps of the research, development and marketing of biologicals (just as other pharmaceutical drugs.) Subsequently, I. Wilk-Zasadna described that, depending on the type of biological, non-animal methods may need to meet different specifications: For example, for well-established inactivated vaccines, such as inactivated rabies vaccines, generic tests may be suitable for all products