Vaccine 31S (2013) B163–B175

Contents lists available at SciVerse ScienceDirect

Vaccine

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

Review

A global regulatory science agenda for vaccines

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ARTICLE INFO

Article history:
Received 8 August 2012
Received in revised form 22 October 2012
Accepted 31 October 2012

Keywords:
Vaccine regulation
Clinical trials
Post-marketing surveillance
Vaccine quality
Correlates of immunity
Vaccine standardization

ABSTRACT

The Decade of Vaccines Collaboration and development of the Global Vaccine Action Plan provides a catalyst and unique opportunity for regulators worldwide to develop and propose a global regulatory science agenda for vaccines. Regulatory oversight is critical to allow access to vaccines that are safe, effective, and of assured quality. Methods used by regulators need to constantly evolve so that scientific and technological advances are applied to address challenges such as new products and technologies, and also to provide an increased understanding of benefits and risks of existing products. Regulatory science builds on high-quality basic research, and encompasses at least two broad categories. First, there is laboratory-based regulatory science. Illustrative examples include development of correlates of immunity; or correlates of safety; or of improved product characterization and potency assays. Included in such science would be tools to standardize assays used for regulatory purposes. Second, there is science to develop regulatory processes. Illustrative examples include adaptive clinical trial designs; or tools to analyze the benefit-risk decision-making process of regulators; or novel pharmacovigilance methodologies. Included in such science would be initiatives to standardize regulatory processes (e.g., definitions of terms for adverse events [AEs] following immunization). The aim of a global regulatory science agenda is to transform current national efforts, mainly by well-resourced regulatory agencies, into a coordinated action plan to support global immunization goals. This article provides examples of how regulatory science has, in the past, contributed to improved access to vaccines, and identifies gaps that could be addressed through a global regulatory science agenda. The article also identifies challenges to implementing a regulatory science agenda and proposes strategies and actions to fill these gaps. A global regulatory science agenda will enable regulators, academics, and other stakeholders to converge around transformative actions for innovation in the regulatory process to support global immunization goals.

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http://dx.doi.org/10.1016/j.vaccine.2012.10.117

Contents

1. Introduction

Regulatory science is the foundation of regulatory decision-making and is used to assess the quality, safety, and efficacy of human and veterinary medicines throughout their life-span. The domains covered by regulatory science are considered to include both basic and applied biomedical sciences (such as microbiology, genetics, pharmacology, and biostatistics), clinical trial methodology and epidemiology, and social sciences (such as decision sciences, risk assessment, and communication). Regulatory science aims to contribute to the development of new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of regulated products.

2. How has regulatory science contributed to improved access to vaccines?

The impact of regulatory science on improved vaccine access can be illustrated through some recent examples.

2.1. New tests for evaluation of the live-attenuated oral poliovirus vaccine (OPV): Mutant analysis by PCR and restriction endonuclease cleavage (MAPREC) and transgenic mouse tests

The OPVs that have brought the Global Polio Eradication Initiative close to success were developed by Dr. Albert Sabin by passage and testing in non-human primates. Expensive, technically demanding tests in old-world monkeys [1] were the main safety tests initially used to assure against increased virulence of the vaccine on growth for production purposes. Two outcomes of regulatory science research have revolutionized testing for revertants: (1) a molecular-based assay that used knowledge gained from studies of mutations associated with attenuation in vaccine strains; and (2) a transgenic mouse model that expresses the human poliovirus receptor, allowing viral replication and pathogenesis, similar to non-human primates and humans.

In the 1980s, major efforts were made to understand the molecular basis of attenuation, and thus neurovirulence, in poliovirus vaccines. The molecular procedure termed MAPREC was developed to measure the proportion of revertants in vaccine bulks [2] and validated through an international collaborative study, to become an official method [3] which provides a more precise assessment of vaccine batch consistency than the monkey test, and is more easily performed.

At the same time that MAPREC was being developed, the cellular receptor for poliovirus was identified [4]. The poliovirus receptor cDNA was used to prepare transgenic mice which, unlike other mice, were sensitive to poliovirus infection and developed clinical signs of infection analogous to monkeys [5]. This alternative animal model to the monkey was validated using vaccines of varying degrees of virulence comparing results to those found in monkeys [6]. A standard operating procedure was developed, and the mouse