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Drivers and barriers in the consistency approach for vaccine batch release testing: Report of an international workshop

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ABSTRACT

Safety and potency assessment for batch release testing of established vaccines still relies partly on animal tests. An important avenue to move to batch release without animal testing is the consistency approach. This approach is based on thorough characterization of the vaccine, and the principle that the quality of subsequent batches is the consequence of the application of consistent production of batches monitored by a GMP quality system. Efforts to implement the consistency approach are supported by several drivers from industry, government, and research, but there are also several barriers that must be overcome. A workshop entitled "Consistency Approach, Drivers and Barriers" was organized, which aimed to discuss and identify drivers and barriers for the implementation of the 3Rs in the consistency approach from three different perspectives/domains (industry, regulatory and science frameworks). The workshop contributed to a better understanding of these drivers and barriers and resulted in recommendations to improve the overall regulatory processes for the consistency approach. With this report, we summarise the outcome of this workshop and intend to offer a constructive contribution to the international discussion on regulatory acceptance of the consistency approach.

1. Introduction

Vaccines are a highly efficient tool for the protection against many infectious diseases. They are biological products composed of protective antigens derived from whole microorganisms or components thereof and as such, batches may have minor variations in composition. The variability of vaccines is complicated by the fact that many are produced as combinations of antigens from different microorganisms (such as diphtheria, tetanus, pertussis, polio), and may also have excipients and adjuvants added. The complex nature of vaccines renders them unique compared to other pharmaceuticals. As a result, while new generation vaccines (e.g. virus-like particles of human papilloma virus, and polysaccharide conjugate vaccines such as *Haemophilus influenzae* b, *Pneumococcus* and *Meningococcus* vaccines) tend to be well characterized, there are still knowledge gaps on the structure and *in vivo* activity of some of the established vaccines (e.g. diphtheria, tetanus, acellular pertussis and rabies vaccines).

In order to minimize potential risks to vaccine recipients, each batch must undergo extensive quality control testing. Although manufacturers perform many tests at various stages throughout

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vaccine production, regulators require that the final formulation of every vaccine batch be tested for potency and, if applicable, safety before the lots may be released onto the market.

Safety tests are performed to detect contaminants or active toxins, which may cause adverse reactions after immunization, while potency tests are performed to evaluate the ability of vaccines to induce the same amount of protective immune response as was found in the initial batches of vaccine used in the clinical trials. Once a final formulation has passed manufacturer tests, which are laid down in a registration file, vaccine batches and the data from manufacturer testing are submitted for review. For established vaccines, batch release testing often relies on animal models for safety and potency, requiring large numbers of laboratory animals. These animals experience severe pain and distress, which cannot be relieved because this might interfere with the test results.

The consistency approach considers each batch to be one of a series; the focus for testing is shifted from the final batch to the overall production process [1,2]. The consistency approach promotes the use of production methods that are well-characterised and analytical tools and *in vitro* assays to create a product profile. It assesses the quality of vaccine batches by demonstrating the similarity of their profiles to a manufacturer-specific reference vaccine of proven clinical safety and efficacy. Establishing a product profile requires the measurement of relevant antigen characteristics during production such as quantity, identity, antigenicity, purity, configuration, size and functionality. This can be achieved using a battery of tests with the ability to discriminate between batches of standard and substandard quality. The consistency approach requires that products need to be well-characterized using relevant analytical tools and agreed crucial product-specific parameters have to be monitored.

The way in which the consistency approach may be further developed for application to established vaccines with an emphasis on the continuing need for co-ordination and harmonization, has been laid down in a meeting report [3]. In the report, also recommendations are also given on how to encourage acceptance and implementation of the consistency approach.

Efforts to implement the consistency approach are supported by several drivers from industry, government, and research, but there are also several barriers that must be overcome. To identify these drivers and barriers, a workshop was organised by the Dutch National Institute of Public Health and the Environment (RIVM), entitled “Consistency Approach, Drivers and Barriers”. This workshop was part of the IABS conference on “3Rs alternatives and consistency testing in vaccine lot release testing” (Egmond aan Zee, The Netherlands; September 16–18, 2015). The workshop aimed to discuss and identify drivers and barriers for the implementation of the 3Rs in the consistency approach from the perspective of three different stakeholder groups: industry, regulatory and science frameworks. The choice for these three stakeholder groups was based on the assumption that these are the central partners for regulatory acceptance of the 3Rs [4] and therefore also for the regulatory acceptance of the consistency approach. The workshop contributed to a better understanding of these drivers and barriers and resulted in recommendations to improve the overall regulatory processes for the consistency approach. With this report, we summarise the outcome of this workshop and intend to offer a constructive contribution to the international discussion on regulatory acceptance of the consistency approach.

2. Methodology

2.1. Participants

Before the workshop, six individuals (two from each stakeholder group: industry, regulatory and science frameworks) who had registered for the IABS conference were invited by the workshop organisers to act as expert or moderator during the workshop. Next to them, 39 participants (17 from industry, 18 from organizations with regulatory roles, 2 from academia and 2 others) and 4 organizers (RIVM) attended the workshop. The experts and moderators were involved in the preparation of the workshop and in the guidance of the discussions within their own stakeholder group. The participants were divided in sections in such a way that each section was of similar size and similarly represented the three stakeholder groups.

2.2. Workshop outline

The workshop started with a short presentation by each of the designated experts. The experts were asked to give a short introduction on their professional stakeholder group, and their personal perspective on the main drivers and barriers within their stakeholder group. After these presentations, the discussion started in sections envisioning the drivers and barriers of each stakeholder group, guided by the designated moderator of the respective stakeholder group. The experts were asked to participate in the discussion of their own stakeholder group. The sections rotated so that each participant could give input in the discussion of each stakeholder group. In this report, drivers are defined as intrinsically stimulating factors as well as solutions to barriers.

The barriers and drivers that were presented by the experts on the final slide of their presentations were used as a starting point for the discussion. In each round of discussion, participants were asked to individually define additional barriers on sticky notes. After this, the moderator clustered the sticky notes, looking for overlapping subjects. Thereafter, the drivers were further defined through discussions for which each participant was asked to contribute. This was repeated in the subsequent rounds of discussion.

2.3. Representation of the barriers and drivers, and their analysis

To create an overview of the workshop output, the barriers and corresponding drivers as obtained during the workshop were numbered and categorised per stakeholder group (Supplementary Tables 1, 2 and 3). The order in which the barriers are indicated in the Tables is neither a reflection of the number of times the barrier was mentioned, nor does it represent prioritisation. If no driver is indicated, no solutions to the barrier were indicated during the workshop. Next to this, the primary (P) and (if necessary) secondary (S) actors, were defined and listed in the Tables (in the column “Actor”). An actor is a stakeholder group, (funding) source or platform that is the most likely candidate to take the initiative to move the driver forward. Possible actors that were defined are legislators, regulators, industry, science, regulatory bodies, or funding agencies. The actors were mostly defined after the workshop. The drivers and barriers as defined during the workshop constitute the workshop output. The barriers identified across the three stakeholder perspectives are depicted in Supplementary Tables 1, 2 and 3. Subsequently, the barriers are clustered into themes, with the aim to identify the main barriers for successful implementation of the consistency approach.

3. Results

The 29 barriers identified across the three stakeholder perspectives perceived can be divided in four themes: (1) discrepancy between industry and regulator expectations, (2) international harmonization, (3) economic motives and (4) scientific needs.