



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.

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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.

3.1. Discrepancy between industry and regulator expectations

Although considerable refinement in animal testing for vaccine batch release has taken place, reduction in animal testing and application of the consistency approach have not been implemented on a significant scale in vaccine marketing authorization documents (MA). Industry is reluctant to submit variations to their MA, since they are apprehensive that these variations will not be satisfactory to regulators. Regulators, on the other hand, cannot approve variations that have not been submitted. While regulators try to accommodate 3R alternatives by providing guidance documents, these documents are as yet mainly theoretical exercises. Moreover, these documents can have the unintended side effect of obstruction: they are sometimes seen by industry as binding, and block the case-by-case approach that is believed to be more promising.

If industry would submit proposals (introducing 3R methods or based on the consistency approach) for changes to their MA, first steps could be made towards implementation of the consistency approach. While it may not be possible to switch the entire production process to the consistency approach at once, a step-by-step approach that implements the easier goals first may be used. The possibility to implement (part of) the consistency approach will most likely depend on the combination of product, manufacturer and regulatory body. By providing cases, it is expected that mutual confidence as well as understanding the factors essential to the consistency approach will increase and further steps will be taken more easily.

In order to increase confidence, during the workshop suggestions were made to organize informal discussions between industry and regulators based on cases submitted. This may be enabled by site visits by regulators to industry and by creating forums in which industry and regulators can discuss (for instance within EMA). Discussion in an early phase may allow expectations to be harmonized.

3.2. International harmonization

Ideally, best practices for 3R alternatives are shared on a global scale, and manufacturers making the effort to reduce animal testing or apply the consistency approach are getting global acceptance. In reality, replacing an animal test needs to be pursued in Europe, America, China, India, Brazil, and other parts of the world individually. During the workshop the perception was that, in the field of vaccines there is no international body, acting on a global scale, which moves the consistency approach forward. In contrast to the observation at the workshop, in the field of veterinary vaccines, VICH¹ actively moves the consistency approach forward on a global scale; and has already published internationally harmonized criteria to waive target animal batch safety testing (TABST) [5]. Both VICH GL 50 (TABST Inactivated Vaccines for Veterinary Use) and VICH GL 55 (TABST Live Vaccines for Veterinary Use) were adopted by the VICH Steering Committee in May 2017 for implementation by May 2018. The ICH² would be the other ideal candidate to setup such a body. The top priority of this international body should be to introduce the consistency approach for one specific product (this may still be a combination vaccine). This however, is in contrast to the current policies of ICH and VICH not to provide product specific guidance. Based on future case-by-case experience more detailed road maps for implementing consistency approaches can be developed. In a later phase, WHO may take the lead through the Technical Report Series.

Apart from harmonization on a global scale, some companies experience problems with having animal tests replaced/deleted only in specific countries. The primary initiative to resolve these

situations lies with industry. Regulators and legislators of countries granting 3R alternatives could however help in persuading the competent authorities of objecting countries. This would require manufacturers to share information on problems they experience in these specific countries with their regulators. As stated above, such information could be shared during informal contacts between industry and regulators.

¹VICH, International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products. ²ICH, International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. The VICH guidelines apply to vaccines for veterinary use, and the ICH guidelines apply to vaccines for use in humans.

3.3. Economic motives

Economic motives are also a factor that has acted as a negative incentive for the implementation of the consistency approach. While a clear driver exists that can influence the economic barrier associated with that approach, that is, the potential reduction of lead time and associated costs of some of the new *in vitro* tests as opposed to the animal tests, a series of other considerations strongly mitigates its allure. Many old vaccines, e.g. tetanus, diphtheria and many veterinary vaccines, are generally made using methods that are not fully characterised, and that historically rely mainly in final batch release testing on animals, a procedure whose underlying mechanisms are still largely unknown. And yet, despite the aforementioned shortcomings, the process for their production is very well-established, and has already safely brought to market millions of doses. In such a landscape, the key point to stress is the following: a successful implementation of the consistency approach to those vaccines would necessarily revolve around a) a comprehensive knowledge of the entire production process, and b) a clear definition and subsequent monitoring of the critical quality parameters occurring in the course of all the production phases, so that such parameters could be safely relied upon to replace the final *in vivo* testing with in-process control testing. The costs associated to such a transformation are unfortunately very relevant, and they would weigh on what are essentially product lines with limited financial margins. Economic considerations aside, such change carries along another source of apprehension, in the form of the regulator's reaction to the transformation. The increased amount of information provided by the companies on internal processes could trigger ever changing information requirements – thus imposing yet other costs – from the regulatory side, imposing new burdens on vaccines that are, to all intents and purposes, already well established products with decades old history of safety and efficacy. So, besides the reduction in costs potentially associated with the aforementioned reduction in lead time and the other drivers related to the corporate social responsibility, there are no remaining motives for manufacturers to invest in 3R alternatives. Incentives could be considered such as price reductions for vaccines that are tested using 3R methods or through legal phase-outs, analogous to the ban on animal testing of cosmetics in Europe. Manufacturers, however, indicate that legal phase-out could mean ceasing production, and this may result in shortages of vaccines on the market.

3.4. Scientific needs

Whereas most barriers and drivers are shared between the industry and regulatory perspectives, the barriers highlighted by the scientific perspective during the workshop tended to focus on a single issue: the identification of alternatives to the *in vivo* final batch release testing (understandable, as this is the most widely

known aspect of the overall production process). This unilaterality has strengthened our conviction that science initiatives should be initiated in platforms that see the presence of all stakeholders, such as the Innovative Medicines Initiative (IMI)-funded VAC2VAC project [6]. A setup like this may also ensure that also knowledge on the production processes be shared, thus prioritizing production-relevant research topics. Furthermore, access to relevant materials (products, failed batches, reagents) is improved, and data sharing with industry facilitated. The involvement of regulators also helps to get them acquainted with tests that will later on be presented in registration files. One of the major obstacles identified, however, is the absence of 'real' failed batches. Most studies are therefore performed on batches that have been artificially degraded. Close cooperation with industry may solve this problem. To ensure that the knowledge obtained by sharing these batches does not backfire to the manufacturers, a safe harbour principle is available in the EU.

The lack of predictive value of animal models is accepted; this provides an incentive to move to alternative assays. However, results obtained from *in vitro* tests are often difficult to link to those obtained *in vivo*, or the human situation. It is regarded as difficult to mimic an *in vivo* immune response to all vaccine antigens/epitopes in *in vitro* assays. In addition, investigating adjuvanted vaccines *in vitro* is seen as a major challenge, although, the ability to detect a pertussis toxin spike in adjuvanted acellular pertussis vaccine [7] is encouraging. Moreover, as stated above, most animal tests are performed on vaccine products that have been introduced long ago, implicating limited production characterization and a lack of knowledge on critical product characteristics and correlates of protection.

4. Discussion

An issue that did not come out of the workshop but that may be regarded important is the lack of knowledge by scientists on the vaccine production process. This may have to do with the academic (and not so much industry) background of the scientists involved in the workshop. Whereas final product testing is detailed in publicly available sources (e.g. European Pharmacopeia), production details and in process testing requirements are mostly proprietary and product specific. A consequence of this lack of knowledge is that there is limited possibility for scientific improvement of individual steps along the production chain, but only for the final product. Improvement of these individual steps is deemed to be highly important in the consistency approach. An opportunity to improve this situation would be that industry discloses these steps with regulators and scientists: if a certain step is robust and can be well-monitored regulators may not be inclined to raise a concern and scientists will not invest time to improve such a step. An example of such an opportunity is the IMI-funded VAC2VAC project in which industry, regulators and scientists are joined on specific products.

The drivers and barriers identified in our study may be compared to the ones observed in two earlier studies [4,8]. The first study investigated mechanisms underlying the (lack of) implementation of the 3Rs in vaccine testing by interviewing stakeholders (in Canada) based on two case studies: diphtheria potency testing and acellular pertussis safety testing [8]. In this paper, barriers and drivers are denoted challenges and opportunities. Major challenges to implementation were identified to be: inconsistent regulatory testing requirements, lack of biological functionality of some *in vitro* methods, benchmarking *in vitro* against fundamentally different and often variable *in vivo* assays, and high caution towards method changes. Opportunities to implementation were also identified: harmonization of test methods between countries, collaborations on new method development, poor

performance of traditional animal methods, the domino effect of one regulatory authority accepting a method after another, and stakeholder concerns for ethical care and use of animals used in vaccine testing. Although the study was different in setup, the challenges largely overlap with the barriers found during our workshop, and opportunities overlap with the drivers; for example, the societal "protection of healthy children" in practice comes down to "nobody wants to be responsible for releasing bad batches" that was characterized as a driver during the workshop (Supplementary Table 1).

The second study identified which factors influence the regulatory acceptance and use of available 3R models to replace, reduce and/or refine the NIH challenge test for rabies vaccine potency testing [4]. The study was done by a combination of literature review, interviews and a survey among 50 rabies vaccine experts from regulatory authorities and industry. These barriers and drivers were identified for three stages of regulatory acceptance and use, i.e. (A) the stage of formal incorporation into regulatory requirements, (B) the stage of actual acceptance by regulatory authorities and (C) the stage of use by industry for regulatory purposes. Again, the barriers and drivers found, largely overlap with those identified during the workshop. Due to the setup of our workshop, a more in-depth analysis of the reported drivers and barriers was not possible. Most of the drivers and barriers identified during the workshop were aimed at the stage of formal incorporation into regulatory requirements. The subsequent stages of regulatory acceptance that are addressed in the paper by Schiffelers et al. were not identified in our workshop.

In conclusion, the workshop resulted in a lively discussion between participants with an industry, regulatory and scientific affiliation. Barriers and drivers from industry and regulatory perspectives often overlap, whereas from a science perspective the perceived barriers and drivers differ. The main barriers for successful implementation of the consistency approach, (1) discrepancy between industry and regulator expectations, (2) international harmonization, (3) economic motives and (4) scientific needs, are similar to the ones identified during other inventories made earlier. The same holds for the drivers, which (most often) still appear to be too weak to overcome these barriers. In that respect, new viewpoints were not obtained. However, one of the main conclusions from the workshop was that unfamiliarity between all stakeholder groups forms a critical barrier. The discussions held during the workshop, the contacts made and the resulting awareness of each other's viewpoints may contribute to overcome this barrier, and work towards the consistency approach in closer cooperation.

Conflict of interest

Laura Viviani was an employee of the GSK group of companies at the time of the study.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.biologicals.2017.06.006>.

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