Validation, acceptance and implementation of 3Rs opportunities.

Special 3Rs considerations for a COVID19 vaccine

Laura Viviani

28 April 2020

E-workshop on Regulatory Pathways and changes in Vaccine Testing

Agenda

1. Validation of 3Rs opportunities – where we are
2. Acceptance of 3Rs opportunities – global perspective
3. Implementation of 3Rs opportunities – hurdles and possible solutions
4. Special 3Rs consideration for COVID19 vaccines

Validation of 3Rs opportunities

In general terms, validation is a process which should demonstrate that **a method is relevant and reliable for the given purpose**.

WHO TRS937 Annex4 Validation: Validation is an essential part of good manufacturing practices (GMP). It is, therefore, an element of the quality assurance programme associated with a particular product or process. The basic principles of quality assurance have as their goal the production of products that are fi t for their intended use.

Validation of 3Rs opportunities

ICH Guideline Definition: Objective of validation is to demonstrate that the procedure is suitable for its intended purpose (ICH Q2 R1)

EU Official Medicine Control Laboratories (PA/PH/OMCL (13) 82 2R):Data should demonstrate that the proposed testing and acceptance criteria are sufficiently under control to guarantee reproducible quality of the products at release and adequate control during shelf-life.

Resources:
https://www.ich.org/page/quality-guideline
https://www.edqm.eu/medias/fichiers/validation_of_analytical_procedures_paphomcl_13_82_2r.pdf
https://www.dcvmn.org/Chemistry-Manufacturing-and-Controls-fostering-implementation-of-vaccine

Validation of 3Rs opportunities

Types of validation studies

Single-lab validation study, e.g. according ICH Validation guidelines (ICH Q2 R1), for a given product.

Multi-lab validation study, e.g. ring trial or collaborative study to establish a new method to be used for a class of products.

- *Recommendations of the VAC2VAC workshop on the design of multi-centre validation studies. Biologicals 52 (2018) 78–82*
- *The majority of 3Rs methods' validation has been carried out through the EDQM Biological Standardization Programme, or via EURL-ECVAMN (and ICCVAM) in collaboration with WHO.*

Validation of 3Rs opportunities

Product specific validation:

Data from an international collaborative study cannot be used to set product specifications with the new method.

Importance of setting (new) specifications for existing products properly to avoid undue batch rejection when using the new method.

Importance of providing with more guidelines from regulators on how to set specifications/validity/acceptability criteria for new methods.

Resources:
https://www.edqm.eu/en/alternatives-animal-testing#Achievements%20of%20the%20Biological%20Standardisation%20Programme%20for%203Rs
https://ec.europa.eu/jrc/en/eurl/ecvam/alternative-methods-toxicity-testing/validated-test-methods/biologicals

Validation of 3Rs opportunities

- When replacing in vivo methods with non-animal based methods, it is necessary to demonstrate that the non-animal based methods are valid.

- Due to the inherent variability of animal tests, the typical one-to-one comparison may not be suitable.

- The European Pharmacopoeia addresses these issues in a new chapter (*5.2.14 Substitution of in vivo methods by in vitro methods for the quality control of vaccines*).

Validation of 3Rs opportunities

Examples of barriers to 3Rs methods' validation

- Risk averse Regulators
- Investment (costs/time /internal resources)
- Lack of interest from Regulators
- Complex relationship between Industry & Regulators
- Design of Validation studies
- Complexity of legacy products
- Reagents/Materials availability
- Lack of Regulatory Alignment

Acceptance of 3Rs opportunities

The term "acceptance" implies that regulator(s) considers a method appropriate to be used in a regulatory context (e.g. batch release testing).

EU. PH. 5.2.14 Substitution of in vivo methods by in vitro methods for the quality control of vaccines.

- Discussion on this piece of legislation has started in 2012 and implemented in 2018.
- International group of experts from EU, US and Canada.
- Most advance and clear statement from a regulatory agency on the acceptance and implementation of 3Rs.

Acceptance of 3Rs opportunities

Products/Tests demanding animal testing	3Rs acceptance/Implementation
Rabies NIH test	35 years of in vitro assays development (SRID, in vitro neutralization & stability indicating GP ELISA) yet no implementation.
GST for vaccines	20 years of effort resulted the GST deletion in US in 2015; in EU in 2019; ECBS recommendation in 2018.
Pertussis vaccine HIST	20 years of efforts had little impact for the HIST, WHO or national guidance. Replaced in EU in 2020.
Toxoid irreversibility testing	Decades of toxoid stability data supporting licensed vaccine toxoid stability, in vivo irreversibility testing still generally required.
Rabbit pyrogenicity	Preferred by most authorities over a Monocyte Activation Test (MAT).
DPT potency & safety tests	Lack of progress via conventional pathways-> VAC2VAC

Acceptance of 3Rs opportunities

Many non-live vaccines are controlled through production, lot release & stability testing without the use of in vivo assays e.g.,

- Human Papilloma Virus (HPV) Vaccines; recombinant viral-like particles (VLP) plus adjuvant(s), controlled with physical, chemical methods and ELISA
- Meningococcal and Pneumococcal Bacterial Conjugate Vaccines; defined polysaccharides conjugated to carrier proteins, controlled with physical and chemical methods

Modern QC control strategies for those vaccines is based on a combination in vitro methods to monitor the key quality attributes necessary to maintain the efficacy and safety profile of the product established at licensure, which are also monitored over product's shelf-life.

Acceptance of 3Rs opportunities

Eu. Ph. 5.2.14 on In Vivo and In Vitro Assays for Vaccine QC:

- All QC methods "*should ensure comparability of the quality attributes between commercial batches and those batches originally found to be safe and efficacious in clinical studies* or, for veterinary vaccines, in the target species."

- However, "the inherent variability of in vivo assays can make them *less suitable than appropriately designed in vitro assays* for monitoring consistency of production and for assessing the potential impact of manufacturing changes. As a result, it is essential to continually to challenge the scientific value and relevance of these in vivo test methods."

Acceptance of 3Rs opportunities

Cont.

- “The use of appropriate in vitro methods … enhances the predictability of the release of safe and effective vaccine lots for use.”

- In some cases, an existing in vivo method may need to be substituted by more than 1 in vitro method to characterize the key qualitative and quantitative attributes measured by the existing test.

Acceptance of 3Rs opportunities

Examples of barriers to 3Rs methods' acceptance

- Communication issues between Industry and Regulators
- Insufficient Data/Documentation provided by manufacturers to regulators
- Lack of appropriate guidance from regulators to manufacturers on their validation's expectations
- New Methods are not compendial methods (or not yet)
- Lack of awareness of new methods

Implementation of 3Rs Opportunities

- A new method is implemented when it is used by a manufacturer (or a control authority) for the quality control of a given product.
- Prerequisite is that the regulator accepted the new method for the quality control based on the information provided by the manufacturer.

Implementation of 3Rs Opportunities

Why 3Rs methods are not implemented?

- Lack of global harmonization of testing requirements
- Technical difficulties for the product specific validation
- Cost of product specific validation
- Lack of successful scientific and business case studies
- Reagents availability

Implementation of 3Rs Opportunities

Global deletion of General Safety Tests
ATT / GST / Innocuity test.

- ATT/GST deleted form EU. PH. Monographs, FDA requirements, and several national requirements (Brazil, Argentina, South Africa, India and several will follow soon, hopefully)
- WHO ECBS recommends that innocuity test should no longer be included into WHO recommendations

Implementation of 3Rs Opportunities

Current manufacturing processes, which include the implementation of Good Manufacturing Practices (GMP) and comprehensive quality control measures (including in-process controls), were considered to be more appropriate than the innocuity test in assuring the quality and safety of vaccines and other biological products.

The Committee reviewed the historical inclusion of the innocuity test in the documents published in the WHO Technical Report Series and concluded that its complete omission would not compromise the quality and safety of vaccines and other biological products.

Implementation of 3Rs Opportunities

Therefore, the Committee recommends the discontinuation of the inclusion of the innocuity test in all future WHO Recommendations, Guidelines and manuals for biological products published in the Technical Report Series, and that a clear indication be made in its report that the inclusion of this test in previously published WHO Technical Report Series documents be disregarded.

WHO collaborates with other international stakeholders in the implementation of 3Rs. A project to review all TRS and consider the inclusion of 3Rs is foreseen in the next future – pending funds.

Implementation of 3Rs Opportunities

Ongoing Collaborative study to validate new method for Human Rabies Vaccines.

BSP148 – ELISA for potency testing of human rabies vaccines

- Impressive number of participating laboratories (11 manufacturers, 20 National Control Laboratories)
- Vaccines from many manufacturers covering most important strains (11 vaccines)

Implementation of 3Rs Opportunities

Key Resources:

EDQM BSP Programme -

https://www.edqm.eu/en/alternatives-animal-testing

EURL-ECVAM –

https://ec.europa.eu/jrc/en/eurl/ecvam

IABS –

https://www.iabs.org/

European Vaccine Initiative –

http://www.euvaccine.eu/

Implementation of 3Rs Opportunities

Cont.

ICCVAM –

https://ntp.niehs.nih.gov/whatwestudy/niceatm/accept-methods/index.html?utm_source=direct&utm_medium=prod&utm_campaign=ntpgolinks&utm_term=regaccept

VAC2VAC –

http://www.vac2vac.eu/

DCVMN 3Rs Working Group -

https://www.dcvmn.org/-expert-working-groups-

Humane Society International (recent MoU signed by DCVMN) –

https://www.afsacollaboration.org/non-animal-vaccine-testing/

Special 3Rs consideration for COVID19 vaccines

What are the key contributes of applying 3Rs in an emergency situation.

Research

- InSphero creates several human tissue models including 3D human liver spheroids that can be used to assess how drugs or chemicals might be metabolized—broken down or activated—by our livers. These models can mimic liver function for up to four weeks in the lab and can quickly provide results. Remarkably, in response to the coronavirus outbreak, they are making their 3D InSight™ Human Liver Models available for free for exploratory COVID-19 treatment testing.
- Epithelix is a leader in 3D human lung tissues for safety testing and cancer research, including their MucilAir model of the human airway, which mimics the human airway in several important ways. The platform could also be used to assess the efficacy of new potential treatments.

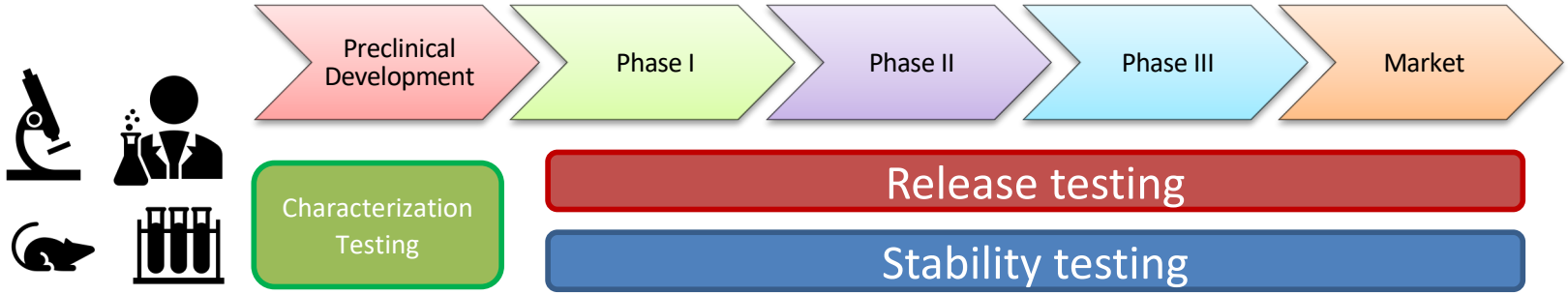
Special 3Rs consideration for COVID19 vaccines

- YuMab researchers have an animal-free antibody against SARS-CoV-2 by using an advanced selection process that is faster and more accurate than traditional animal-based methods. The antibodies bind to a surface protein of SARS-Co-V2, thereby potentially blocking the virus from infection.
- MatTek's 3D tissue models of the human airway and deep lung are being used for a number of coronavirus-related research projects.

Special 3Rs consideration for COVID19 vaccines

Development and Clinical Phases

- Replacement principle is integrated from beginning of development
- Well characterized product
- Best use of clinical phases



Special 3Rs consideration for COVID19 vaccines

What to consider:

- In vivo potency not considered as the primary test for evaluating potency
  - used to confirm the identification of CQA(s) supporting potency
- Knowledge-based definition of control strategy (QbD)
  - CPP and CQA supporting potency are identified in product design (QbD approach)
  - Highly characterized product allowing to accumulate knowledge on product
- Performant / Relevant in vitro assay
  - Using mAb targeting active epitope (& clinical relevance of the epitope)
  - Solid performances demonstrated in assay validation and in routine use
  - Superiority of in vitro assay(s) to detect product evolution / alteration was demonstrated
- Link to clinical studies
  - Fully supported by in vitro testing

Special 3Rs consideration for COVID19 vaccines

International Coalition of Medicines Regulatory Authorities (ICMRA)
http://www.icmra.info/drupal/en

Global regulators map out data requirements for phase 1 COVID-19 vaccine trials

- Opportunities to leverage knowledge accumulated with platform technology should be considered to accelerate the development of a SARS-CoV-2 vaccine manufactured using the same platform.
- If a platform technology utilized to manufacture a licensed vaccine or other investigational vaccines is well characterized, it is possible to use toxicology data (e.g., data from repeat dose toxicity studies, biodistribution studies) and clinical data accrued with other products using the same platform to support FIH clinical trials for a SARS-CoV-2 vaccine candidate.
- For all SARS-CoV-2 vaccine candidates it is necessary to obtain data in animals and to characterize the immune response induced by a SARS-CoV-2 vaccine candidate.
- It is not required to demonstrate the efficacy of the SARS-CoV-2 vaccine candidate in animal challenge models prior to proceeding to FIH clinical trials.

THANK
YOU

THANK YOU