The European Partnership for Alternative Approaches to Animal Testing

European Commission

EPAA
a PARTNERSHIP
to FACILITATE
REGULATORY
ACCEPTANCE
of ALTERNATIVE
METHODS

EPAA progress and successes in 3Rs for biologicals

Dr Catrina Stirling
On behalf of EPAA

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1 What is EPAA

I EPAA at a glance

STATUS
Partnership between European Commission & Industry stakeholders.

PURPOSE
To facilitate development, acceptance and validation of alternative approaches**.**

MILESTONES
Created in 2005. Renewed for the 2nd time in 2015.

SCOPE
Operates **across 7 industry sectors.** Covers Regulatory testing.

I EPAA Vision & Mission

Vision

The vision of EPAA is the replacement, reduction and refinement (3Rs) of animal use for meeting regulatory requirements through better and more predictive science.

Mission

- Promote **development and acceptance** of alternative methods
- Enhance **international collaboration** & mutual recognition of alternatives
- Foster **knowledge sharing** on 3Rs among the partners
- **Facilitate dialogue** between stakeholders contributing to **animal welfare**

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I EPAA Membership

- 5 Commission DGs
- 7 European trade federations for 7 industry sectors
- 35 Companies

Companies & SMEs

European Industry Federations

European Commission

- DG GROW
- DG ENV
- DG JRC
- DG RTD
- DG SANTE

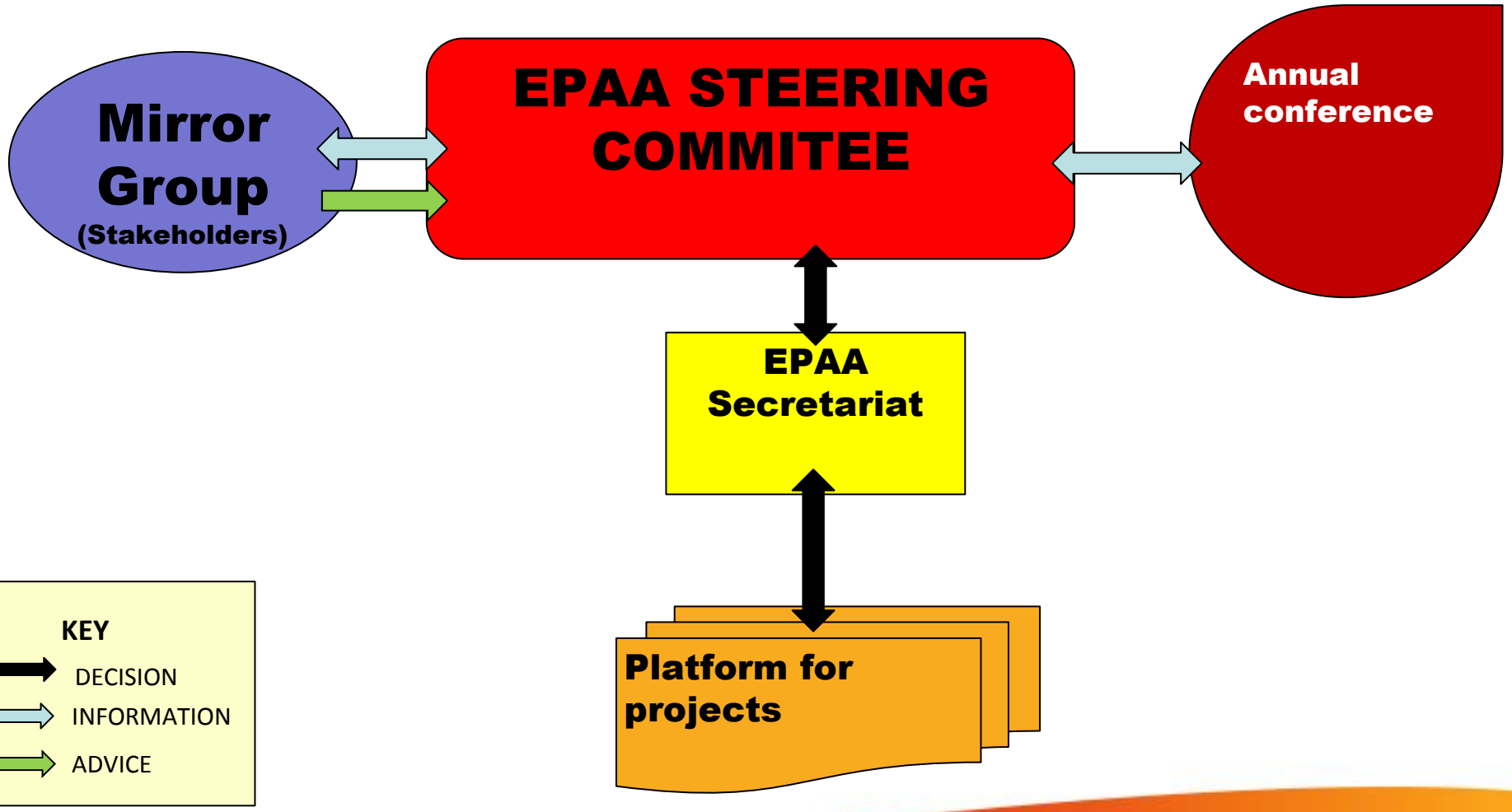
I EPAA Remit

7 industry sectors committed to support alternative methods for regulatory safety testing and/or quality & potency testing:

- **Animal Health**
- **Chemicals**
- **Cosmetics**
- **Crop Protection**
- **Fragrances**
- **Pharmaceuticals (incl. vaccines)**
- **Soaps & Detergents**

I EPAA Structure

A Public-Private Partnership



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EPAA Ongoing Projects list

- Harmonization of 3Rs in Biologicals
- Exposure prediction (ADME)
- Human Rabies vaccines
- Clostridial vaccines
- Advancing 3Rs in Regulatory Toxicology: Carcinogenicity
- Acute toxicity testing
- Skin sensitisation optimised strategies
- Skin sensitisation – Difficult substances

2 VCA Projects

The Vaccine Consistency approach Project

The **vaccines consistency approach (VCA)** for batch release is based upon thorough characterisation of the vaccine during manufacture, including formulation, using non-animal testing. The quality of subsequent batches is guaranteed by the strict application of quality systems and of a consistent production of batches that are comparable to reference lots of known potency and safety.

The VCA is already used for recently registered vaccines, whereas many vaccines developed several decades ago, continue to rely on animal tests for confirming the quality of each batch.

Due to the potential of the VCA to significantly reduce the number of animal tests used in vaccines quality control, the EPAA initiated this project with the aim to provide a framework for resolving remaining scientific and technical issues and for fostering the regulatory adoption of VCA as a **non-animal approach** for quality control of established (conventional) vaccines.

The Vaccine Consistency approach Project

A- Overall History

January 2010: Workshop jointly organised by EPAA and EURL ECVAM in Brussels discussed the VCA and its potential to reduce the number of animal tests used in **quality control** of human and veterinary vaccines (De Mattia et al 2011, The consistency approach for quality control of vaccines: A strategy to improve quality control and implement 3Rs, Biologicals 39, p 59-65). As a follow up, the EPAA agreed in late 2010 to initiate a VCA project, the kick-off meeting of which was organised in **April 2011**.

Stakeholders

European Commission, industry (European vaccines manufacturers), European Medicines Agency (EMA), national regulators, OMCLs (Official Medicines Control Laboratory), EDQM (European Directorate for the Quality of Medicines and HealthCare), international regulators (observers from US, Canada and India) and academia.

The Vaccine Consistency approach Project

Milestones

- **7 April 2011:** Kick-off meeting - Application of the Three Rs and the Consistency Approach for Improved Vaccine Quality Control (Flash Report)

Milestones of the specific working groups:

1. DTaP

- Workshop on **30-31 August 2012** (Flash Report)
- No activities started under EPAA umbrella since a lot of activities were ongoing elsewhere (avoid duplication)
- In 2016: activities supported by IMI 2 funding programme (VAC2VAC – IMI 2 Call 3).

The Vaccine Consistency approach Project

Project achievements

- One peer reviewed publication:
  - De Mattia et al 2015, The Vaccines Consistency Approach Project: an EPAA initiative, Pharmeuropa Bio& SN, May 2015, p 30-56.

The Technical Committee, where the Commission provided visibility and all parties committed to alternatives shared scientific know-how,

- raised awareness of all stakeholders (industry, regulators, civil society) on the Vaccines Consistency Approach;
- facilitated cross sharing between human and veterinary vaccines helping to promote new testing paradigms;
- offered coordination, identified scientific gaps and enabled early collaboration helping to address them;
- prepared the ground for the IMI-2 Vaccines consistency project to work towards ultimately replacing animal testing in batch release of vaccines. This project has been accepted and will start in March 2016. With a funding of approx. 8m Euros, this project will help develop new methods, work towards their validation and ensure regulatory engagement with an ultimate aim to lead to acceptance by regulators, implementation and use by industry.

The Vaccine Consistency approach Project

B- Clostridial vaccines

This work stream aims at replacing in-process controls which use testing on animals, with cell culture based assays that have been developed by MSD Animal Health with support by the NC3Rs. The application of the consistency approach is feasible for clostridial vaccines but *in vitro* tests remain to be developed for some important strains.

Three workshops were co-organised with EDQM, Council of Europe, on:

- **19 March 2013** (Flash Report)
- **11 September 2013** (Flash Report)
  helped prepare the Clostridium septicum vaccine collaborative study (BSP130)
- EDQM BSP130 study successfully completed in 2015; demonstrated concordance of *in vivo* and *in vitro* methods.
- **15-16 September 2015:** Egmond aan Zee, the Netherlands (link to *report to be added*) discussed the results of the BSP130 study as a proof of concept and start of validation for Clostridium septicum vaccine in process control methods.
- Next: in 2016 a Phase III study (formal in vitro test full validation) will be progressed as part of BSP130 and with the support of EPAA.
- Final aim is to introduce the alternative methods into the Ph. Eur. relevant monograph(s).

Status report

BSP130

Testing of clostridial vaccines

Current Testing for Clostridial Antigens

In process – *in vivo* tests:

– Toxicity of toxin (Minimum lethal dose, MLD)

– Toxicity of toxoid (MLD)

– Antigenicity of toxoid (Total Combining Power, TCP)

slide provided by Keith Redhead

Joint EPAA / EDQM Project

Approach:

Selection of Clostridium septicum vaccine

Selection of cell line assay to be validated against the use of the mouse as toxicity indicator in TCP/MLD

Recruitment of group of participants from manufacturing and OMCL backgrounds in different countries able to test this type of toxin and/or toxoid in the *in vivo* and/or *in vitro* assays

Performance of an international collaborative study, with toxins and toxoids from various sources and of different strengths, to validate the *in vitro* assays and to correlate them against the *in vivo* tests

BSP130

Cell line assay for in-process toxicity and Ag testing of *Cl. septicum* vaccine Ag

Summary of results

Conclusions and recommendations

- Good concordance between *in vivo* and *in vitro* methods was shown for MLD and TCP assays…
- … but only at the level of the grand mean. For individual assays the reproducibility (*in vivo* and *in vitro*) is not sufficient to show satisfactory concordance.
- Statistical analysis was difficult because of too many uncontrolled parameters. A better plate design is needed to allow for reliable estimates of the toxin equivalence (instead of the MLD) and the TCP, from individual assays.
- Several proposals for improved plate design are included in the study report. Computer simulations show that a much better reproducibility might be achieved.

Joint EPAA / EDQM (BSP) Project Status

- Participants Workshop Sponsored by EPAA
- 15-16 September 2015 satellite meeting to IABS meeting in Egmond Aan Zee *The Consistency Approach and Alternative Methods: Towards Non-Animal-based Testing in Vaccine Development and QC*

  - **Report of workshop online publicati**

    February 2016

Joint EPAA / EDQM (BSP) Project Status

The workshop participants agreed on the design of a potential follow-up study where an optimised protocol for the cell based-assay developed in BSP130 would be validated in order to be proposed as a compendial test for residual toxicity testing (alternative to the current *in vivo* test used for assessing toxicity in residual toxicity and immunogenicity testing).

EPAA and ECVAM-JRC agreed to co-sponsor the project extension and Dr. Marlies Halder (ECVAM-JRC) was nominated as the contact person between EDQM and the EPAA Vaccines Consistency Approach project.

Joint EPAA / EDQM (BSP) Project follow up study

–The final report was adopted and it was agreed to run a collaborative study Phase III along the following lines:

- Project leaders: In addition to Dr. Redhead and Dr. Bruckner, Dr. Botond Siklodi (CEVA Phyllaxia) was nominated as co-project leader. Dr. Siklodi is in charge of the pretesting of study materials and methods
- Methods: *in vitro* only (TCP and MLD) using an optimised design

The Vaccine Consistency approach Project

C - Human rabies

This work stream aims at replacing the current in vivo immunization challenge test for batch release (the NIH test) by *in vitro* tests based on antigen quantification (ELISA).

Workshops were organised on:

- **8-9 October 2012** (Flash Report)
- **9-11 May 2015** Joint Veterinary & Human Rabies Vaccines workshop; (*report in preparation, to be published soon)*
  Agreed that *in vitro* ELISA is acceptable to replace current challenge/serology tests
- Collaborative study to identify most suitable ELISA was finalised in 2015
- Global agreement reached regarding the way forward
- Next: in 2016, in cooperation with EDQM (Council of Europe) preparation of a formal validation study supported by EPAA.

3. Veterinary rabies

- **5-6 November 2012** Workshop (Flash Report)
- Activities ongoing at manufacturer level
- Cross-fertilization from the learnings of the Human rabies project
- In 2016: supported by the IMI-2 funding programme (VAC2VAC – IMI 2 Call 3)

Human Rabies
potency test replacement

Project Responsible: JM CHAPSAL

Objective: Replacement of in Vivo Rabies potency test

by in vitro method

Status: Questionnaire/information letter sent to manufacturers in December, Vaccines strains identified and 4 Chineses manufacturers involved, publication of workshop 2015 in Vaccine still pending approval **BSP 148 study proposal approved by EDQM end June (no sub-potents lots will be tested)**

Next Milestones: End 2016 - protocol of BSP collaborative study plan to be prepared, EDQM letter to participants OMCLs & manufacturers from Europe and other regions (North & Latin America, India, China, Africa...)

- Regulatory requirements for Human rabies vaccines (Ph Eur 0216, WHO TRS 941) :
  - product potency is to be estimated by the in vivo challenge (NIH) test
  - the test must be performed on each final lot

- Issues with the in vivo challenge (NIH) test :
  - painful in vivo challenge assay, contrary to the Ph. Eur. 3Rs strategy
  - very high variability : 25-400%
  - need for BSL3 containment due to the use of live rabies virus

- The in vitro ELISA, as an alternative to the NIH test, is :
  - in accordance with the Ph. Eur. 3Rs strategy: replacement
  - already used by some manufacturers/OMCLs
    for blending and monitoring of the consistency of production

N.B.: the NIH test is not used to set the vaccine dose

- The global replacement of the NIH test by an *in vitro* method is hindered by the absence of a common standardised method

- International initiatives for the development of an alternative *in vitro* method conclude on the feasibility of an ELISA approach for the batch release of non-adjuvanted vaccines

→ 2012 Workshop (Arcachon-1 meeting)

Based on the availability of ELISAs using well-characterized monoclonal antibodies recognising only the protective trimeric form the glycoprotein,

an international collaborative study was set up to select an appropriate ELISA method

2015 Workshop (Arcachon-2 meeting)

The working group determined that
the "Sanofi Pasteur ELISA" method is an appropriate assay
for further development in a BSP study :

- the ELISA uses 2 mAbs that bind conformational epitopes
  - on well-defined antigenic sites
  - inducing protection
- the ELISA does not recognise the non-immunogenic soluble glycoprotein
- the ELISA clearly discriminates potent from heat-degraded subpotent vaccines

→ manuscript of the study report will be submitted for publication in Vaccine

The proposed ELISA method

- uses mAbs that are highly characterised
- uses mAbs that are specific to the conformational trimeric form of the glycoprotein - which is responsible for the protection conferred by the vaccines
- does not recognise the inactive soluble glycoprotein
- recognises most vaccine strains used worldwide for human rabies vaccines
- discriminates sub-potent vaccines altered by various methods: alkylation/reduction, thermal degradation, BPL inactivation
- is not based on a commercial kit
- the mAbs are accessible to all laboratories
- preliminary study supports good transferability of the method

BSP Phases

- Phase 1
  - Preparatory phase 2017
    - procurement & pre-testing of samples
    - preparation of the study protocol and reporting sheets
    - logistical arrangements (invitations, shipments,...)
- Phase 2
  - Collaborative study
    - transferability & robustness of the method
    - use of the 7th WHO IS
- Phase 3
  - Reporting phase
    - laboratories to test routine batches
    - determination of the potency specifications of the vaccines in view of the revision of the Ph. Eur. monograph 0216

BSP Study

- **Participants**
  - OMCLs & manufacturers
  - Europe and other regions (North & South America, India, China,...)
- **Test samples**
  - WHO IS for Rabies vaccines (inactivated, non-absorbed – 7th IS)
  - Panel of marketed vaccines covering various strains (PV, PM, Flury LEP, CTN, aGV,...)
- **Study design**
  - 3 independent assays, duplicate testing of each sample
  - Common ELISA SOP
  - optional, as available : in-house ELISA method
  - Standard reporting sheets
  - Central statistical analysis

3 Biologicals

EPAA – vision & mission

EPAA is committed to:

accelerate the development, validation and acceptance of alternative approaches to further the three Rs of animal use in regulatory testing.

Global harmonization of 3Rs in biologicals is an EPAA priority within its focus on international acceptance/international convergence of testing requirements.

The European Partnership for Alternative Approaches to Animal Testing

BIOLOGICALS PROJECT BACKGROUND

- Biologicals (vaccines, hormones, immunoglobulins, blood products) are manufactured by biological processes of inherent variability, and require a strict quality control strategy to secure consistent quality from batch to batch.

- Required safety and potency control tests (in vivo or in vitro) are incorporated in monographs of relevant pharmacopoeias.

- Differences in test requirements and protocols between countries still give rise to unnecessary repetition of testing.

- Art. 13 of DIR 2010/63 asks that a procedure using animals is not carried out if another method for obtaining the same result is recognized under EU legislation.

BIOLOGICALS PROJECT APPROACH

Differences in testing requirements seemed to have **more of a historical than scientific basis** and merited **evaluation to see where scientific evidence allows moving towards acceptance of a 3Rs-approach**.

After an **initial mapping of international requirements and key players**,
EPAA hosted an **international workshop mid September 2015** to discuss four case studies (human and veterinary vaccines) and to define the most effective **pathways for international convergence**.

INTERNATIONAL WORKSHOP ON BIOLOGICALS

15-16 Sept 2015, Egmond aan Zee (NL)

<u>45 Participants from:</u>

Brazil

Canada

China

India

Japan

Mexico

US

EU countries & Switzerland

OIE (World Organisation for Animal Health)

WHO (World Health Organisation)

EMA (EU Medicines Agency)

EDQM (EU Directorate for Quality of Medicines and Health Care)

Expected deliverables – how to move towards better regulatory science?

- Understand **reasons for differences** in regulatory acceptance of 3Rs methods across regions

- Understand **barriers to harmonized implementation of 3Rs** in regulatory practice and on data requirements that would facilitate implementation

- How **could alternative methods improve the efficacy and scientific reliability** of safety or potency testing?

- Define **steps towards harmonized translation/uptake of 3Rs** into regulatory practice

  - which concrete area(s) / case study(ies) could become a subject of a specific coordinated action at a global level?

Case studies discussed at the workshop

1. Deletion/waiving of **general safety tests** (ATT, GST) at WHO level and from national regulatory requirements

2. Deletion/waiving of **general safety tests** (ATT/GST; TABST) at VICH level and from national regulatory requirements

3. Towards replacement of in **vivo potency assays** for for Diphtheria and Tetanus vaccines

4. Swine Erysipelas vaccine: *in vitro* ELISA assay to replace *in vivo* immunization-challenge test

Workshop recommendations

SAFETY TESTS

- Encourage deletion of ATT / GSTs / TABST from all national / jurisdictional legal requirements & international guidance

  - Ph. Eur. Monographs
  - WHO recommendations
  - OIE guidelines

- Explore means to contact key countries at legislator level

Workshop recommendations

POTENCY TESTS

- Achieve convergence on the scientific principles of the use of appropriately validated *in vitro* replacement methods
- Include key regulators and manufacturers from the start in discussions
- Collaborative studies could result
- New assays as means to unify different regulatory approaches in different jurisdictions
- Harmonised assays desirable, but product-specific assays may also be acceptable

Achievements: Eur Pharmacopeia

Currently the ATT is still mentioned in the production section of 51 monographs for a diverse range of products in the Ph. Eur. including vaccines for human use, antibiotics and other pharmaceuticals.

Abnormal Toxicity in Ph.-Eur.

The test still applies to 51 monographs:

- 4 monogr. on antibiotics
- 2 monogr. on antifungal drugs
- 4 monogr. on (anti-)coagulants
- ✓ 2 monogr. on botulinum toxins
- ✓ 1 monogr. on containers for blood products
- ✓ 1 monogr. allergens
- 29 monogr. vaccines (ref. to 2.6.9)
- 2 monogr. vaccines (ref. to 2.6.9 but modified)
- 4 monogr. vaccines (Request for deletion, outdated)
- ✓ 1 monogr. anthrax vaccine (no ref. to 2.6.9)
- ✓ 1 Immunosera for human use (animal)

Requests for revision to delete the ATT are submitted for most monographs and passed on to relevant Expert Groups 15, 7 and 6. Decisions on the deletion are expected for the Commission Meetings in **November 2016 and March 2017**.

Achievements: WHO & OIE

Revision of WHO guidelines

Formal letter to encourage deletion of GST/ATT/test for innocuity from WHO recommendations submitted. To be addressed by ECBS at the next meeting in **October 2016**.

Revision of OIE guidelines

Formal letter requesting the deletion of TABST from OIE recommendations sent. To be discussed at next meeting of the OIE Biological Standards Commission in **September 2016**.

Next steps: Outreach in prioritized non-EU countries still requiring ATT/GST and TABST in national legislation

- **Japan**

Aim to discuss the way forward towards implementation of the workshop recommendations at 2016 Asian Congress on Alternatives and Animal Use in Life Sciences (15-18 November in Japan)

- **Brazil**

EPAA to interact with BRACVAM which is already collecting data to propose to Brazilian Pharmacopoeia the deletion of ATT from the monographs.

4 IMI Vac2Vac

innovative medicines initiative

Vac2Vac

IMI2: OVERVIEW AND OBJECTIVES

- Launched in 2008 as Public-Private Partnership (PPP) between European Union and European Federation of Pharmaceutical Industries and Associations (EFPIA)
- World's largest PPP in health research:
  - total budget 2014-24: €3.28 billion
  - 50% in cash from EC, 50% in kind from EFPIA and other organisations
- Brings together companies, universities, public laboratories, small and medium-sized enterprises (SMEs), patient groups and regulators in collaborative projects
- Aims to speed up development of next generation of drugs, vaccines and treatments

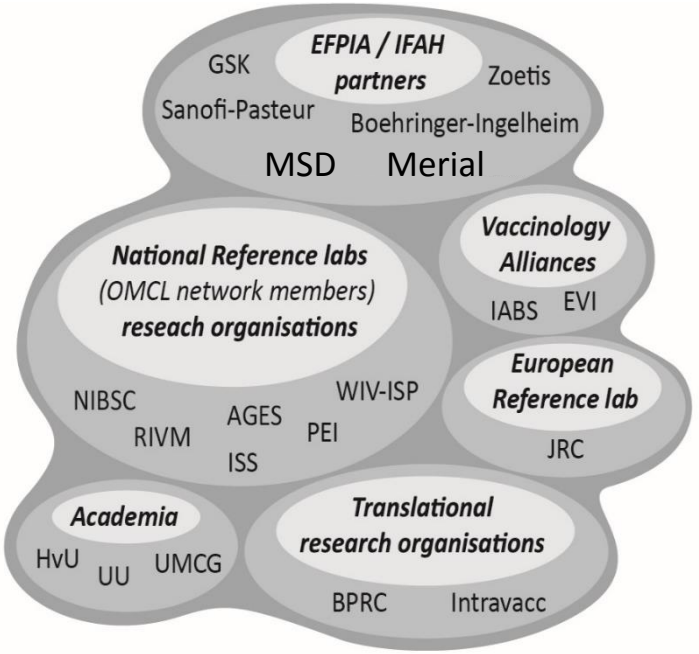
VACCINE BATCH TO VACCINE BATCH COMPARISON BY CONSISTENCY TESTING (VAC2VAC)

OBJECTIVES AND AMBITION

- Provide proof of concept of consistency approach for batch release testing of established vaccines using sets (toolbox) of in vitro and analytical methods
  - ➢ Develop, optimise & evaluate non-animal methods that cover key-parameters for demonstrating batch consistency, safety and efficacy
  - ➢ Have (pre-)validated methods & together with regulators define procedural guidance for regulatory approval and routine use

CONSORTIUM PARTICIPANTS

	Participant organisation name
1	European Vaccine Initiative (EVI) (Coordinator
2	National Institute for Public Health and the Environment (RIVM)
3	National Institute for Biological Standards and Control (DH-NIBSC)
4	Paul-Ehrlich Institute (PEI)
5	European Commission, Joint Research Centre (JRC)
6	University of Utrecht (UU)
7	University Medical Center Groningen (UMCG)
8	Institute for Translational Vaccinology (Intravacc)
9	University of Applied Sciences Utrecht (HU)
10	Istituto Superiore di Sanità (ISS)
11	Austrian Agency for Health and Food Safety (AGES)
12	International Alliance for Biological Standardization for Europe (IABS-EU)
13	Scientific Institute of Public Health (WIV-ISP)
14	Biomedical Primate Research Centre (BPRC)
15	Sanofi Pasteur (SP)
16	Zoetis Belgium SA (Zoetis)
17	Merial (Merial)
18	Boehringer Ingelheim (BI)
19	Merck Sharp & Dohme (MSD)
20	GSK Biologicals (GSKBio)



EXPECTED RESULTS AND IMPACT

- Enhance replacement, reduction or refinement of animal use (3Rs)
- Development, optimization and evaluation of analytical methods to be used in the consistency approach for vaccine quality control
- Demonstrate proof of concept of consistency approach for several types of established veterinary and human model vaccines
- Secure European leadership in vaccine quality control testing
- Develop roadmap for regulatroy acceptance within Europe and beyond
- Global dissemination of knowledge

WORK PACKAGE STRUCTURE

WP1 Physicochemical methods	• Develop and optimise biochemical and physicochemical methods to assess proteome of complex whole cell vaccines and toxoid vaccines and to assess the conformational integrity of toxoid vaccine components in the presence and absence of other active components (e.g. adjuvants).
WP2 Immunochemical methods	• Develop and optimise immunochemical methods for monitoring consistency of antigen quantity and/or quality of antigen throughout production process • Investigate whether the assay is suitable for testing vaccine from multiple different manufacturers • Investigate the extent to which in vitro methods are able to detect antigenic changes relevant to biological function of vaccine
WP3 Cell-based assays	• Development, optimization and application of cell-based assays that allow in vitro monitoring of parameters, linked to the biological function of vaccines (i.e. capability to induce a protective immune response) or their safety (i.e. absence of toxicity).

WORK PACKAGE STRUCTURE

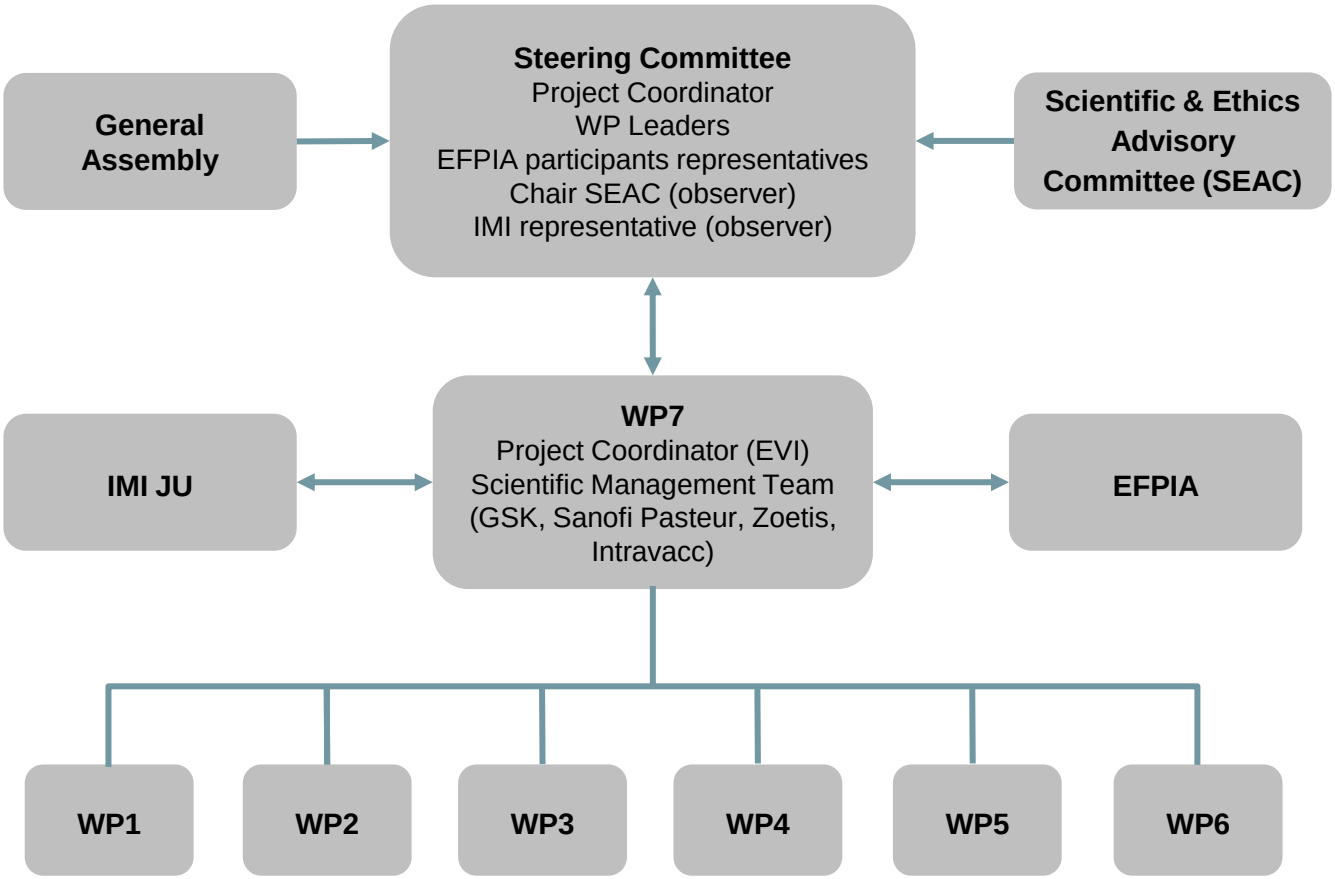
WP4 Multi-parametric assays and bioinformatics	• To develop transcriptomics/proteomics technology and identify bacterial biomarkers suitable for characterization of Clostridium tetani seed strains • To develop an alternative for the histamine sensitisation test for Pertussis vaccine safety based on kinome analysis • To develop platform technology and identify biomarkers for the assessment of vaccine quality based on responses of antigen presenting cells to exposure to vaccines/adjuvants in vitro in support to WP3
WP5 (Pre)validation	• Develop criteria for method development and validation; • Design and coordinate (pre)validation studies of the methods developed in WP1-4 and selected by the steering committee; • Develop a guidance document for the design of multi-centre validation studies • Prepare proposals for multi-centre validation studies under the Biological Standardisation Programme of EDQM
WP6 Regulatory acceptance	• Define a roadmap for regulatory acceptance of consistency approach with the goal to provide a basis for guidance on regulatory implementation of new tests developed • Facilitate discussion between different stakeholders on specific questions and issues that introduction of consistency approach might raise

WORK PACKAGE STRUCTURE

WP7
Consortium management

- Scientific and administrative-financial coordination of the project
- Establish effective communication among the consortium partners
- Monitor the impact achieved
- Establish a dissemination plan and implement the activities foreseen
- Ethical oversight of project
- Identify and appropriately protect intellectual property generated by project

GOVERNANCE


General Assembly
Steering Committee
Project Coordinator
WP Leaders
EFPIA participants representatives
Chair SEAC (observer)
IMI representative (observer)
Scientific & Ethics Advisory Committee (SEAC)
IMI JU
WP7
Project Coordinator (EVI)
Scientific Management Team
(GSK, Sanofi Pasteur, Zoetis, Intravacc)
EFPIA
WP1
WP2
WP3
WP4
WP5
WP6

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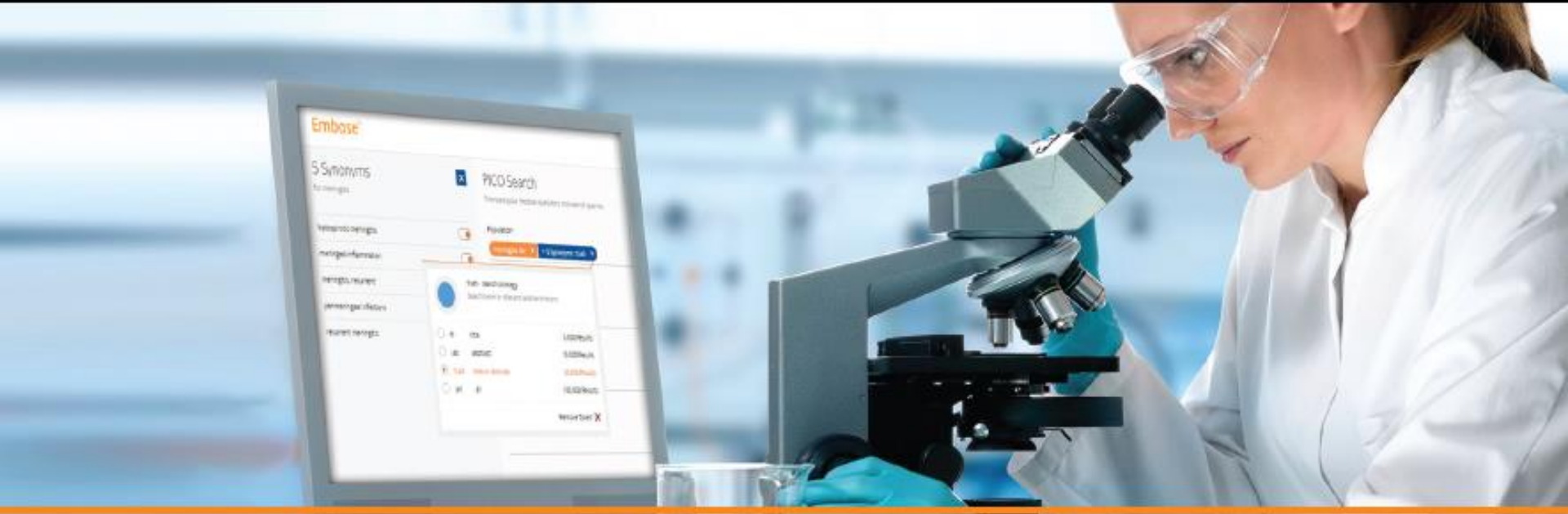
- The VAC2VAC project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement N°115924. This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA.
- **Usefull links**
- http://www.imi.europa.eu/
- http://www.vac2vac.eu/



3Rs SCIENCE PRIZE 2016

Call for submissions

The European Partnership for Alternative Approaches to Animal Testing

European Commission

10.000€ Prize grant

23rd September 2016 deadline

For outstanding 3Rs contribution

Open to European scientists working on Alternatives

Granted by a jury from EC, industry & civil society

EPAA annual conference: Save the date!

Science based regulation

5th December 2016
Brussels, Belgium

Free Registration via
https://ec.europa.eu/growth/sectors/chemicals/epaa/index_en.htm

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QUESTIONS?