

VAC2VAC

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VACCINE BATCH TO VACCINE BATCH COMPARISON BY CONSISTENCY TESTING

DCVMN workshop

7-10 May 2018, Hyderabad

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European Vaccine Initiative

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EVI

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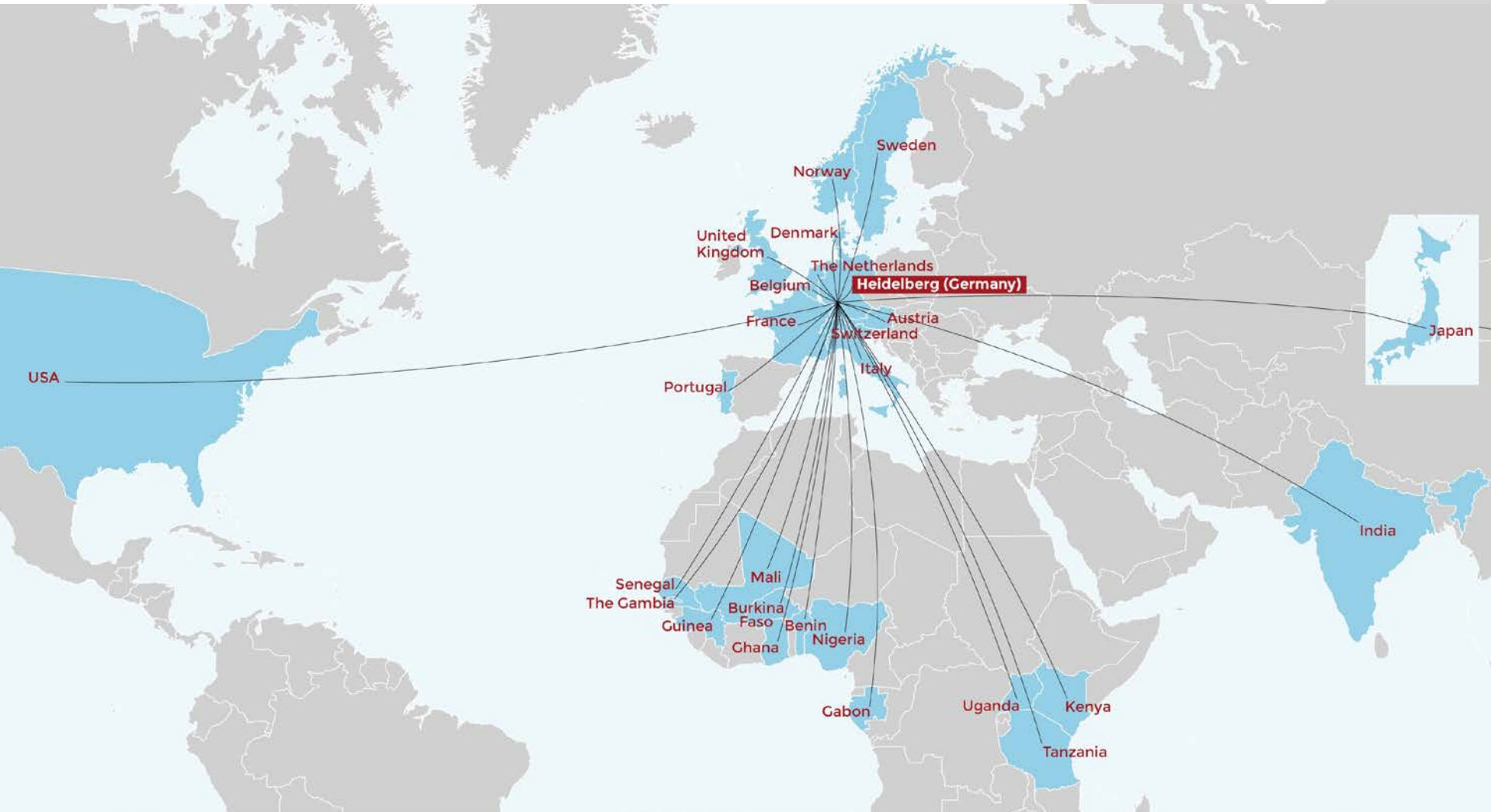


About EVI

- Non-profit Product Development Partnership supporting development of affordable, accessible vaccines for diseases of poverty and emerging infectious diseases
- Current disease portfolio: Malaria, Dengue, Zika, Influenza, Leishmaniasis
- Engaged in other vaccine R&D activities such as vaccine quality testing (VAC2VAC), building sustainable European vaccine infrastructure (TRANSVAC)
- Partnership-based: engaging with academic, public research institutions, private sector, governments, and civil society - including partners from developing countries



EVI's Partner Network





1998 - 2018 About EVI

- Provides operational, managerial and financial support
- Brings together financial, technical and in-kind contributions from public and private sector

Supported by:



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VAC2VAC

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



innovative
medicines
initiative



09/05/2018

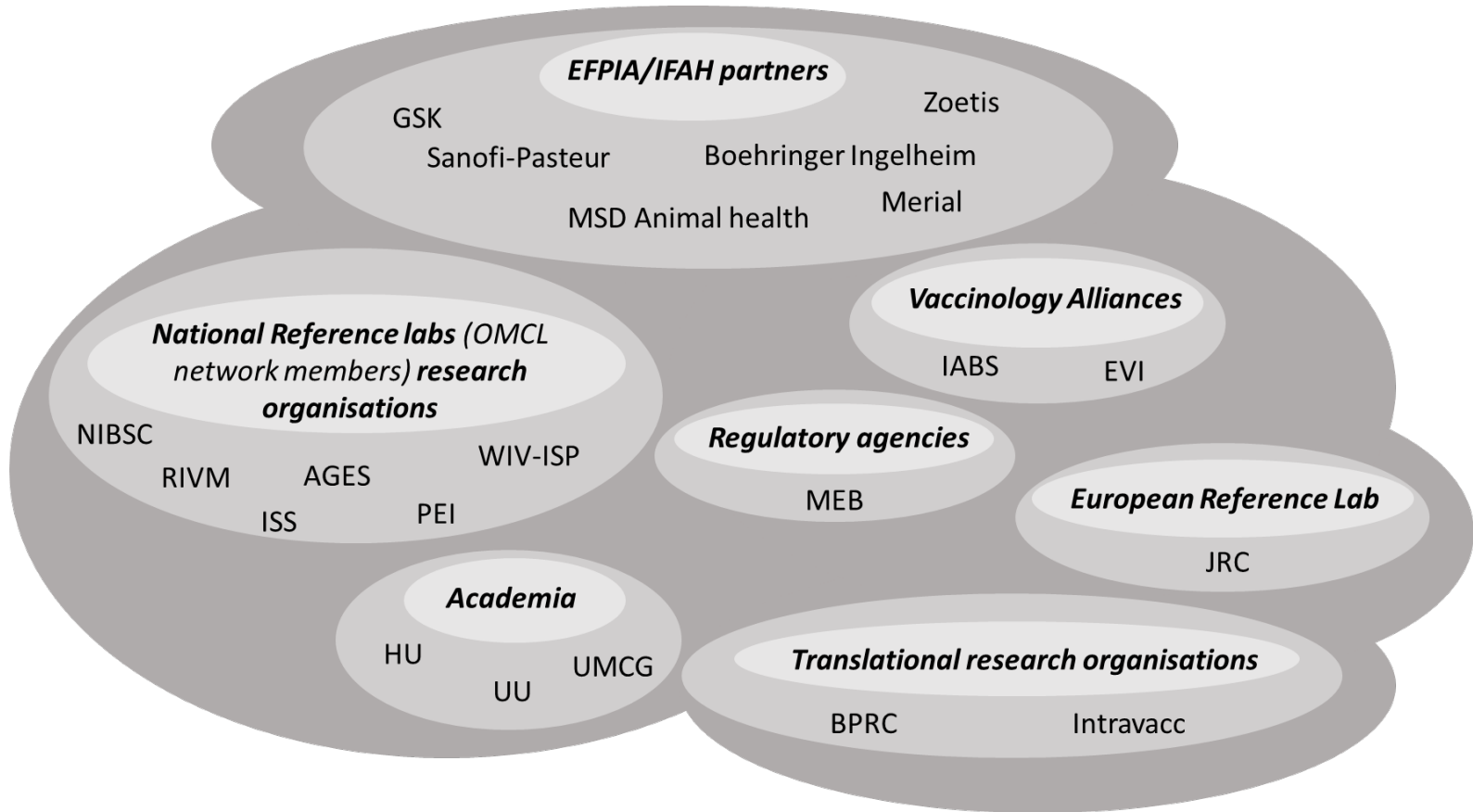
IMI2: OVERVIEW AND OBJECTIVES

- IMI: 2008, IMI2: 2014 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

OVERVIEW

- 21 participants: 15 public partners, 6 EFPIA companies
- Total **budget**:
 - €7.85M EU funding in cash
 - €8.13M from EFPIA partners in kind
- Seven work packages
 - WP 1: **Physicochemical** methods
 - WP 2: **Immunochemical** methods
 - WP 3: **Cell-based** assays
 - WP 4: Multi-parametric assays and **bioinformatics**
 - WP 5: (Pre)**validation**
 - WP 6: Promotion of consistency testing to **regulatory acceptance**
 - WP 7: Consortium **management**

CONSORTIUM PARTNERS



OBJECTIVES AND AMBITION

Proof of concept of consistency approach for batch release testing of established vaccines using sets of *in vitro* and analytical methods

- Develop, optimise & evaluate **non-animal methods** that cover key-parameters for demonstrating batch consistency, safety and efficacy
- (Pre-)**validate** methods and define with **regulators** guidance for regulatory approval and routine use

CONSISTENCY TESTING: INTRO

* leading: safety and potency of a vaccine batch should be ensured

* Consistency testing might be a strategy to move away from animal use

Consistency testing aims to use non-animal assays - instead of animal tests - to ensure that each vaccine batch produced is consistent with a (clinical/historical) batch already proven to be safe and efficacious in registration studies or clinical use



CONSISTENCY APPROACH IN BATCH RELEASE TESTING OF ESTABLISHED* VACCINES

VACCINE BATCH RELEASE TESTING	
<p>Current approach</p> <ul style="list-style-type: none"> • Uniqueness of each batch • Emphasis of Q.C. on final product • Read out is > min. IU/ml (potency) • Use of international reference preparation 	<p>Consistency approach</p> <ul style="list-style-type: none"> • Each batch is one of a series • Emphasis on every step of production process (seed lot, in-process, final product) • Read out is: non deviation from consistency • Benchmarking to clinical/historical batch

* An established vaccine is a vaccine which is being produced by classical procedures: inactivation, detoxification or attenuation

POTENTIAL ADVANTAGES

- Increase in depth knowledge on the product
- Simplification and easier standardisation of methods
- Global streamlining of batch release methods
- Reduction animal use
- Time and cost saving

MODEL VACCINES

Selected human and veterinary model vaccines		
Type	Vaccine	Final batch testing
<u>Human</u>		
Inactivated viral	Tick-borne encephalitis virus (TBEV)	Challenge (mice)
Toxoid, purified protein	Diphtheria (D) , tetanus (T), acellular pertussis(aP); (DTaP)	Challenge, serology (mice, guinea pigs)
<u>Veterinary</u>		
Inactivated viral	Infectious Bronchitis Virus (IBV)	Serology (chickens)
Inactivated viral	Newcastle disease virus (NDV)	Challenge, serology (chickens, target species)
Inactivated viral	Porcine circovirus (PCV)	Serology (pigs)
Inactivated viral	Feline leukaemia virus (FeLV)	Serology (mice)
Inactivated viral	Veterinary rabies	Challenge, serology (cats, dogs, mice)
Inactivated bacterial	Bovine leptospira	Challenge, serology (cattle, guinea pigs)
Inactivated bacterial	Canine leptospira	Challenge, serology (dogs, hamsters)
Inactivated bacterial	Clostridium chauvoei	Challenge (guinea pigs)
Toxoid	Clostridium tetani	Serology (target species, guinea pigs, rabbits)
Toxoid	Clostridium perfringens C	Challenge (mice)

WORK PACKAGE STRUCTURE

WP1 Physicochemical methods

- New biochemical and physicochemical methods to assess the:
- **Proteome** of whole cell and toxoid vaccines
 - **Conformational integrity** of toxoid vaccine (with/without adjuvants,...)

WP2 Immunochemical methods

- New or better methods for **Ag quantity/quality** throughout production
- Assays suitable for **different manufacturers?**
 - *In vitro* methods detect Ag changes relevant to **biological function?**

WORK PACKAGE STRUCTURE

WP3 Cell-based assays

New or better cell-based assays for *in vitro* monitoring of the vaccine:

- **Protective immune response** and/or
- **Safety**

WP4 Multi-parametric assays and bioinformatics

- **Transcriptomics/proteomics** to identify bacterial biomarkers suitable for characterization of *Clostridium tetani* seed strains
- Alternative for the histamine sensitisation test for pertussis vaccine safety based on **kinome analysis**
- Platform technology and identification of **vaccine quality biomarkers** with *in vitro* antigen presenting cells (vaccines/adjuvants)

WORK PACKAGE STRUCTURE

WP5 (Pre)validation

- Criteria for **method** development and validation
- (Pre)**validation** of the selected methods developed in WP1-4
- Guidance document for the design of **multi-centre** validation studies
- Biological Standardisation Programme (**BSP**) of EDQM

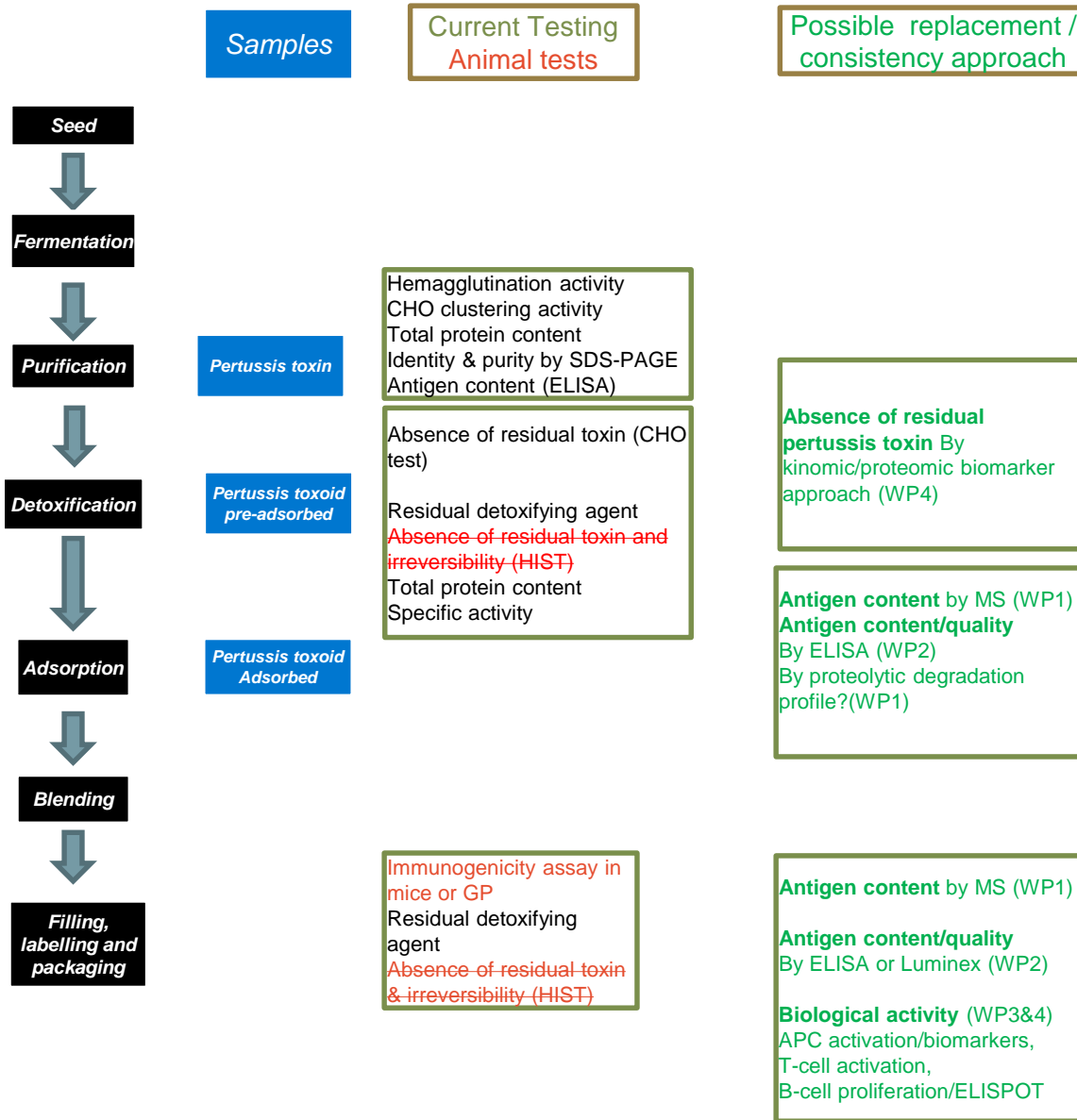
WP6 Regulatory acceptance

- Roadmap for regulatory acceptance of consistency approach as **guidance**
- Facilitate **discussion** between stakeholders on questions and issues linked to consistency approach implementation

ACELLULAR PERTUSSIS

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innovative medicines initiative



Physicochemical methods:

- Mass spectrometry (MS) is being employed to quantify the antigens present in the diphtheria, tetanus, and acellular pertussis (DTaP) vaccines. To do this, signature peptides have been identified and have been successfully analysed through optimization of enzymatic and mass spectrometry methods.
- Enzymatic assays simulating antigen degradation by immune cells have been set up. By coupling these enzyme based experiments with state-of-the-art mass spectrometry, the possible links between immunogenicity (vaccine efficacy) and antigen degradation can be assessed. These assays are intended to provide information about vaccine quality consistency.

Immunochemical methods

- Characterisation of a large number of mAbs for antigens in the DTaP vaccine.
 - antibodies evaluated for binding to native and detoxified (non-adsorbed) antigen
 - determine whether the antibodies are able to detect antigen in adsorbed vaccine samples
 - Affinity measurements ongoing
- Based on the results obtained it is likely that at least one (and in most cases more than one) antibody will be identified as suitable for use in development and validation of immunoassays for DTaP vaccine.

PROGRESS aP

Cell based assays for consistency testing

- *Development of an antigen-specific human B-cell assay for consistency testing of DTaP antigens.* In the second year work has been focused on setting up protocols for detection of antigen-specific B cells and quantification of antigen-specific immunoglobulin production in PBMC in response to bulk antigen.

PROGRESS aP

Multiparametric assays and bioinformatics

- *Alternative pertussis toxin safety test.* The development of an alternative pertussis vaccine safety test has been initiated with the goal of improving the existing CHO cell-based assay. This to allow quantitative molecular marker-based readout to replace current visual readout and to investigate the possibility of using human cells for the same purpose.
 - Several human cell lines were tested and one cell line was selected (A549 cells) on basis of its response to pertussis toxin, to be investigated in parallel with CHO cells.
 - Cells were exposed to pertussis toxin and kinomics analysis was performed that measures the activity of multiple kinases in the cell lysates.
 - The data are currently being analyzed and experiments are being repeated and expanded to obtain additional information.
 - The next steps will be selection of most relevant and useful markers from the analysis and investigation of the potential of these markers in the development of new mechanism-based safety tests.

PROGRESS aP

Multiparametric assays and bioinformatics

- Development of platform technology for studying the interaction of vaccines/adjuvants with antigen presenting cells. This task aims at identifying biomarkers indicative of vaccine potency and at providing knowledge about the mechanism of action of the mentioned vaccines.
 - The major focus of the work has been on identifying suitable cellular platforms, establishing robust protocols for obtaining and differentiating the cells to the desired phenotype, and setting up and validating read-out assays.
 - Cell lines representing antigen-presenting cells (APC) as well as primary peripheral blood monocyctic cell (PBMC)- or bone marrow-derived dendritic cells have been established as suitable cellular platforms for future experiments.
 - Surface marker expression was identified as the most sensitive marker for cell activation. Collection of material (RNA, cell supernatant) for gene expression profiling and proteomics has started.



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Recommendations of the VAC2VAC workshop on the design of multi-centre validation studies

ARTICLE INFO

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Vaccine quality control
Consistency approach
Regulatory acceptance
3R principles
Biological Standardisation Programme

ABSTRACT

Within the Innovative Medicines Initiative 2 (IMI 2) project VAC2VAC (Vaccine batch to vaccine batch comparison by consistency testing), a workshop has been organised to discuss ways of improving the design of multi-centre validation studies and use the data generated for product-specific validation purposes. Moreover, aspects of validation within the consistency approach context were addressed. This report summarises the discussions and outlines the conclusions and recommendations agreed on by the workshop participants.

<https://www.sciencedirect.com/science/article/pii/S1045105618300150?via%3Dihub>

PROGRESS aP

Work on 'Regulatory acceptance of the consistency approach'

- A number of national regulatory authorities (BE, FI, NL, AT) were visited by WP 6 members to introduce the VAC2VAC project as such and to discuss the consistency approach. All representatives of the visited NRAs welcomed the efforts made by the project partners to substitute the old fashioned in vivo tests by non-animal tests and to introduce the consistency concept.

- **Acknowledgement**

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- **Disclaimer**

This communication reflects the author's view, neither IMI nor the European Union, EFPIA, or any Associated Partners are responsible for any use that may be made of the information contained therein

- **Useful links**

- <http://www.imi.europa.eu/>
- <http://www.vac2vac.eu/>
- <http://www.euvaccine.eu/>

THANK YOU VERY MUCH

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