# VAC2VAC: Progress summary of first year

## Background

The overall objective of the "Vaccine batch to vaccine batch comparison by consistency testing" project (acronym: VAC2VAC) is to demonstrate proof of concept of the consistency approach for batch release testing of established vaccines. This means that animal-free assays - instead of animal tests - shall be used to ensure that each vaccine batch produced nowadays is consistent with a batch already proven to be safe and efficacious in registration studies. Hence the name "consistency approach". It covers vaccine potency, safety and animal welfare. Due to the nature of the animal-free assays, the consistency approach also clearly will speed up the release time so that vaccine batches will be available for vaccination much quicker.

**The project's first objective** is to develop, optimise and evaluate non-animal methods to demonstrate that the critical quality attributes of each vaccine batch remains consistent. Methods will be developed that can be used to test several types of human and/or veterinary vaccines currently on the market as well as for different adjuvants that are included in some vaccine formulations to enhance the immune response.

**The project's second objective** is to work with regulatory authorities to develop guidance for regulatory approval and implementation of the newly developed methods.

The three main steps to reach these objectives are:

***1) Development of new or optimisation of existing non-animal methods for consistency testing***
This is the core activity of the project, with a focus on development and optimisation of physicochemical methods, immunochemical methods, cell-based assays, and multi-parametric assays & bioinformatics. All these activities will focus on non-animal methods that can be applied at different stages throughout the production process, including the formulated drug product where possible. The human and veterinary vaccines included in VAC2VAC were selected based on the number of the animals currently used for vaccine quality and safety testing, the severity of the currently used animal test or, in some cases, as models for complex adjuvants that are difficult to characterise with existing methods.

***2) Pre-validation of selected methods***
For selected methods developed in VAC2VAC, small-scale multi-centre studies will be set up to assess the transferability and inter-laboratory reproducibility of the methods. Methods that are successful in these pre-validation studies and that are proposed for inclusion in regulatory monographs, will be submitted to the EDQM Biological Standardisation Programme to be considered for further validation studies.

***3) Regulatory acceptance of the consistency approach***
To maximise the chances of regulatory acceptance and implementation of the consistency approach for batch release, the development of methods in VAC2VAC will be involve close cooperation between public partners and industry partners in consultation with the regulatory bodies and VAV2VAC Scientific and Ethics Advisory Committee (SEAC).

## Progress during the first year of the project

***Work on 'Development of new or optimisation of existing non-animal methods for consistency testing'***
During the first year of the VAC2VAC project, a system for the management of samples and reagents was developed (including a database of all sample requests/status and a log of all shipments) and multiple Material Transfer Agreements between VAC2VAC partners were agreed. This allowed for delivery of vaccine samples from Industry partners to Public partners and initiation of the laboratory work summarised below.

Physicochemical methods
The development of mass spectrometry assays for Leptospira and DTaP (Diphtheria, Tetanus, Pertussis) vaccines has started. The objective is to be able to quantify antigens in the complex vaccine which may contain multiple different components and sometimes adjuvant.

Conformational fingerprinting (a technique that can be used to monitor vaccine quality based on the structure of the antigen) of the tetanus vaccines has also been initiated.

Immunochemical methods
Preliminary work has been started on the development and characterisation of monoclonal antibodies that will be used in the development of antigen content and quality assays for human and veterinary vaccines.

Cell based assays for consistency testing
The development of assays based on vaccine mediated activation of special reporter cell lines has started for the different antigens/vaccines.
Development of an antigen-specific antibody producing B-cell assay is ongoing for DTaP vaccines.
Work on the development of a safety test for tetanus vaccines has started by determining the sensitivity of the reporter cell line to tetanus toxin. In addition, preparatory work has started on the development of a cell-based assay for toxicity testing of veterinary *C. perfringens* C antigen.

Multiparametric assays and bioinformatics
The characterization of *Clostridium tetani* seed strains has started. DNA sequencing, RNA sequencing and targeted proteomics have been used to characterise a seed strain for stable and reproducible production of toxin for human vaccines.
The development of an alternative pertussis vaccine safety test has been initiated with the goal of improving an existing cell-based assay to allow a fully quantitative readout.
Development of platform technology for studying the interaction of vaccines/adjuvants with antigen presenting cells is ongoing for different antigens. The aim is to develop functional tests to evaluate adjuvant stability and/or to develop an *in vitro* potency test.

***Work on 'Pre-validation of selected methods'***
A template describing requirements for method development and validation has been developed and is now being revised based on comments received from the consortium partners. Once implemented and completed by the testing laboratories, the template will help the consortium decide which methods should be prioritised for pre-validation and validation.

A workshop focussing on the development of guidance for the design of multi-centre validation studies was held. Representatives of each project partner were in attendance, together with selected project scientific advisory committee members and representatives from European regulatory bodies. Key outputs from the workshop will be published on the VAC2VAC website in the coming months.

***Work on 'Regulatory acceptance of the consistency approach'***
Two meetings were organised during the first year in which key action points were defined resulting in the main accomplishments summarized below:

- Contact with regulators established:
  Outreach to JEG3R's, now Joint Working Group on the Application of the 3Rs in Regulatory Testing of Medicinal Products (J3RsWG).
- Training session on Consistency Approach, November 2016:
  All partners of the VAC2VAC project underwent general training to align their vision and approach.
- A Template "Study outline for Regulatory Input form WP6" has been developed and is now implemented in the VAC2VAC consortium.
  This provides the aims and development strategies of the different tests in progress. It will enable to determine any regulatory gaps in the development strategy and to engage in early interactions with regulatory agencies so as to maximise the chances of the new animal-free methods being accepted.
- The focus in year 2 will be outreach to international regulatory agencies.