IMI2 Call 3 topic
‘The consistency approach to quality control in vaccine manufacture’

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Background

- The testing of many established vaccines for market release uses decades-old methods as required by the Regulatory Authorities.
  - Current tests are slow, expensive, imprecise, painful and distressing to the large numbers of animals used.
- The Consistency Approach is a new paradigm for improved quality control of established vaccines which moves away from the current focus on testing the final product and high reliance on *in vivo* models, to an integrated in-process and final product quality monitoring programme during vaccine lot production using non-animal methods (in line with 3Rs principle and European Directive 2010/63).
- In the last decades significant progress has been made that might justify a change in the lot release paradigm.

Need for public-private collaboration

- Identified large gaps in the armamentarium and regulatory acceptance of in vitro tests for vaccine release testing
- Vaccine manufacturers currently use a mixture of in-vitro and in-vivo methods in their in-process and final lot testing.
  - Historical information on performance of production methods
  - Information on past QC is vital for defining alert and acceptance criteria for current and future test.
- Technological gaps hitherto identified vary from vaccine to vaccine, and tests and knowledge need to be developed in such a way as to complement existing processes..
- The regulator’s role in this partnership is key to assure that all approaches are harmonized and globally acceptable.

Objectives of the full project

- To demonstrate proof-of-concept of the consistency approach to the human and veterinary vaccine manufacturing process.
- To facilitate the regulatory acceptance of the consistency approach
- How we want to achieve our objective:
  - by predictive technology and methodology innovation in the areas of analytical methods, in vitro models, and bioinformatics
  - translate these new technologies to a set of consistency tests that will allow improved monitoring of vaccine quality during production and final formulation.
  - agreed road map for implementing new consistency approach advanced methodologies into the regulatory pathway involving relevant international bodies.

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Pre-competitive nature

- All vaccine manufacturers are facing same issues as they are using same methods based on pharmacopeial requirements
- Common interest to adress those issues
- Unique opportunity to overcome regulatory roadblocks moving away from mostly single acting stakeholders and a difficult-to-manage complex framework towards a coordinated, cross-sector, interdisciplinary, long-term, large-scale, trans-national effort

Expected impact on the R&D process

- Leverage novel technologies to build proof of concept for changing vaccine lot release paradigm
- Reduce the use of animals in R&D
- Contribute to the access to medicines reducing the lead time and costs, including development costs
- Improve the R&D process beyond vaccine manufacturing potentially support any cross-fertilization opportunity within biologics for convergence of regulations.

Suggested architecture of the project – 1/2

- Model antigens chosen to demonstrate POC
  - diphtheria, clostridials, rabies, pertussis and erysipelas
- 7 work packages
- WP 1: Physicochemical methods for consistency testing
  - Development of physicochemical methods for conformational fingerprinting.
  - Development of non-animal proteolytic assays to mimic antigen processing.
- WP 2: Immunochemical methods for consistency testing
  - Development and optimisation of immunochemical assays, development of methods for determining antigen content of adjuvanted vaccines.
- WP 3: In vitro functional models for consistency testing
  - Development and optimisation of *in vitro* models to monitor parameters that are closely linked to the functionality of vaccines (i.e. capability to induce a protective immune response)

Suggested architecture of the project – 2/2

- WP 4: Bioinformatics
  - Development of genomics and bioinformatics techniques to evaluate the safety of toxoid vaccines.
- WP 5: Validation criteria, transferability and inter-laboratory reproducibility of consistency approach methods
  - Definition of validation criteria for consistency approach methods, design and coordination of small-scale collaborative studies evaluating the transferability and inter-laboratory reproducibility of the methods identified;
- WP6: Promotion of consistency testing to regulatory acceptance
  - Definition of a roadmap for regulatory acceptance of the consistency approach with the goal of providing a basis for guidance on regulatory implementation of new tests developed for the consistency approach
- WP 7: Consortium management
  - Project management, facilitation and streamlining of cooperation
  - Communication and dissemination activities

Expected contributions of the applicants

Provide both pre-clinical (safety, CMC, assay development) and clinical expertise and ability for interdisciplinary and inter-sectorial work and to cover the following critical fields:

- 1) Physicochemical techniques for conformational fingerprinting of antigens
- 2) Proteolytic susceptibility of antigens to mimic APC action
- 3) Immunochemical assay development
- 4) Manufacturing processes and production consistency
- 5) Antigen-adjuvant interactions
- 6) *In vitro* cell models of immune responses
- 7) Genomic and proteomic profiling
- 8) Regulatory expertise
- 9) Understanding of GLP, QA
- 10) Animal models and laboratory animal science

Expected (in kind) contributions of EFPIA members

- Supply of materials e.g. adjuvanted and non-adjuvanted toxoid
- Technology transfer & inter-laboratory evaluation
- Comparison of in vitro and in vivo tests, if relevant
- Participation in meetings and workshops
- Participation in transferability and inter-laboratory reproducibility studies.

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What's in it for you?

- For academic researchers :
  - Funding for basic research that contributes to 3Rs
- For SMEs
  - Access and understanding of new consistency test methods and support for developing these
  - Opportunity to collaborate with Pharmaceutical companies
- For patients' organisations
  - Limited to knowledge that vaccine manufacturers are working towards reducing animal usage for routine vaccine testing and thus securing vaccine supply
- For Regulatory agencies
  - Early engagement on novel methods and approaches to facilitate regulatory acceptance

Key deliverables of the full project – 1/3

1) Demonstration of **proof-of-concept** for use of non-animal assays and techniques/key process parameters leading to an integrated end to end quality and safety monitoring programme during vaccine lot production for a number of model vaccines.

- Proof of concept for in vitro tests for a range of human and veterinary vaccines, for instance: safety tests for toxoid products (diphtheria and clostridials), potency tests for viral vaccines (rabies) and bacterial vaccines (pertussis and erysipelas), etc.
- A set of non-animal methods for which proof-of-concept has been demonstrated for model vaccines and that could also be used for other vaccines after optimisation and evaluation. This could include key process parameters to be monitored, antigen assays, adjuvant assays and other consistency measures.

Key deliverables of the full project – 2/3

2) **Development, optimisation and evaluation** of techniques to be used in the CA for vaccine lot release testing.

- **Physicochemical techniques** to ensure the consistent conformation of the antigen
- **Immunochemical methods** to analyse epitopes important for the induction of functional/protective cellular or humoral responses as well as to assess antigenicity and adsorption in adjuvanted formulations
- ***In vitro* functional methods** to demonstrate functional immunological responses
- **Genomics and proteomics** assays to monitor genetic profiles of specific toxicity.

Key deliverables of the full project – 3/3

3) Global dissemination of knowledge and training for stakeholders on those new methodologies and approaches.

4) Input into improvements of existing or development of new regulatory guidance to facilitate consistency approach to vaccine release testing

Questions?

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