# VACCINE BATCH TO VACCINE BATCH COMPARISON BY CONSISTENCY TESTING

## Moving away from animal use in vaccine batch testing. The IMI-VAC2VAC project. Opportunities & challenges

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- **Disclaimer**



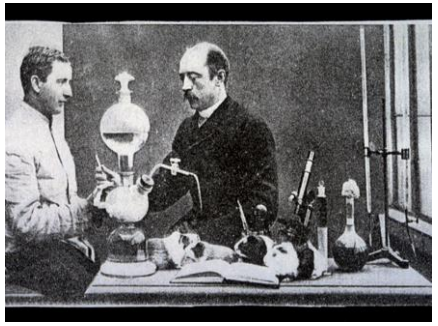
- **Usefull links**
- http://www.imi.europa.eu/
- http://www.vac2vac.eu/

# OUTLINE

- Laboratory animal use in vacine research and testing: the context
- Drivers to move away from animal use in vaccine batch testing
- The 3Rs and the Consistency approach
- The IMI - VAC2VAC project: outline, results, challenges & opportunities
- Conclusions

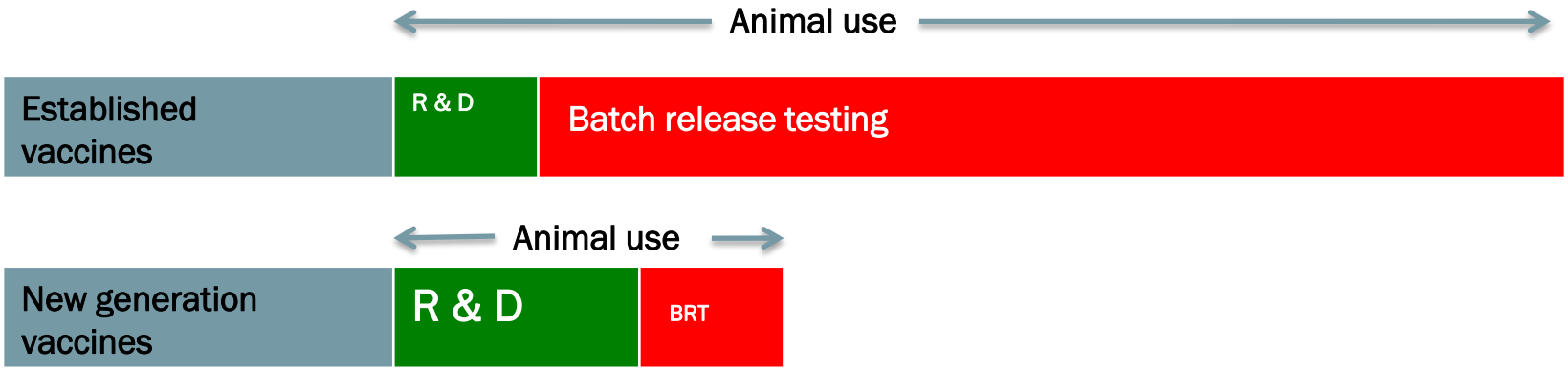
# LABORATORY ANIMAL USE IN VACCINE RESEARCH AND TESTING: THE CONTEXT

- Animal models in 'vaccine' research and testing are rooted in the work of 19th century scientists (e.g. Pasteur/Koch/Behring/Ehrlich)
- Many of the *in vivo* tests for quality control have been developed in the 50s and 60s of the 20th century (e.g. Prigge/Kendrick)
- Current animal use still is significant, estimated to be about 15% of total animal use for biomedical purposes (*De Mattia et al. 2011*)



# LABORATORY ANIMAL USE IN VACCINE RESEARCH AND TESTING : FACTS & FIGURES

- Vaccines are produced in batches. Quality control of **each** batch is required before being released
- Animals are particularly used for batch testing of established vaccines (e.g. Tetanus-, Diphtheria-, Rabies, vet Clostridial)



# DRIVERS TO MOVE AWAY FROM ANIMAL USE FOR VACCINE BATCH TESTING

- Political/societal & Moral drivers
  - Directive 2010/63/EU: Animals are sentient beings and have an intrinsic value
  - Society/politics push for a transition to non-animal research and testing (e.g. Transitie Proefdiervrije Innovatie)

- Scientific drivers
  - relevance and reliability of several models is disputed
  - some models are highly articial

- Economic, pragmatic and safety arguments

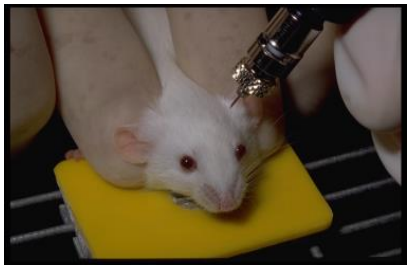
- .....

# Activities at RIVM/NVI/Intravacc to Replace, Reduce or Refine Animal Use (summary)

| Vaccine | Animal test | Three R alternative | Status |
|---|---|---|---|
| Polio vaccine | NHPs | Divers (Cell cultures) | NH |
| D-toxoid | Potency test (challenge) | Serology (reducti refinem | /HO |
| D-toxoid | Spec.tox. | | WHO |
| T-toxoid | | | Ph.Eur./WHO |
| | | ology (reduction + refinement) | Under validation |
| To | cy tests | No.of dilutions (reduction) | Ph.Eur./WHO |
| All vaccines | Potency tests (challenge) | Humane endpoints | Ph.Eur./WHO |

Work has been tedious and time consuming. Particularly in replacing animal use

# TIME FOR A CHANGE!?



1950s


2020

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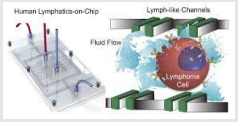
- Product optimization, control and innovative technologies

# VACCINE PRODUCTION AND TESTING: WHY CAN WE DO BETTER NOW?

- Better characterisation of the product at product optimization (consistency of starting material).
- Improved optimization and standardizati
  (consistency of production
- T
  duct monitoring with new and improved
  ncy of testing).

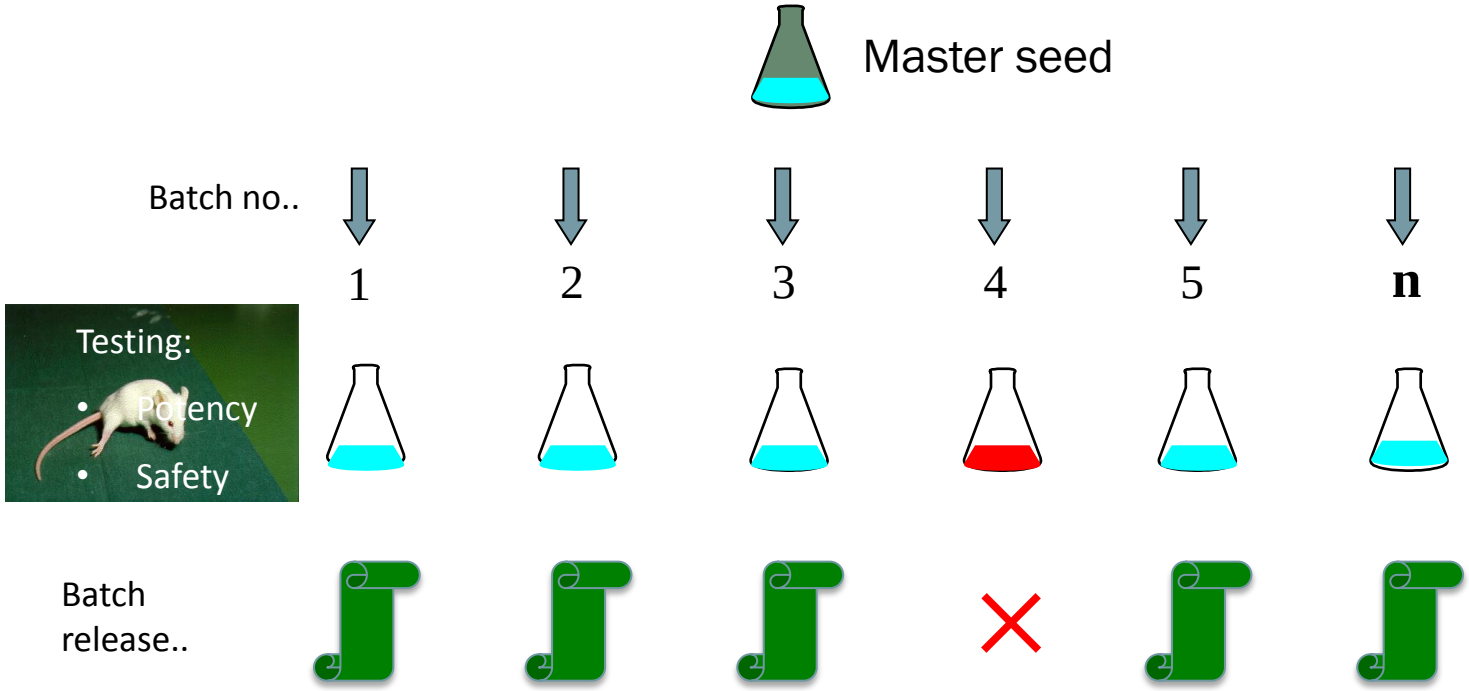



- Use of quality systems to guarantee consistency (GMP, QA, pharmacovigilance) (consistency in oversight).

This might allow for a paradigm shift in vaccine batch testing

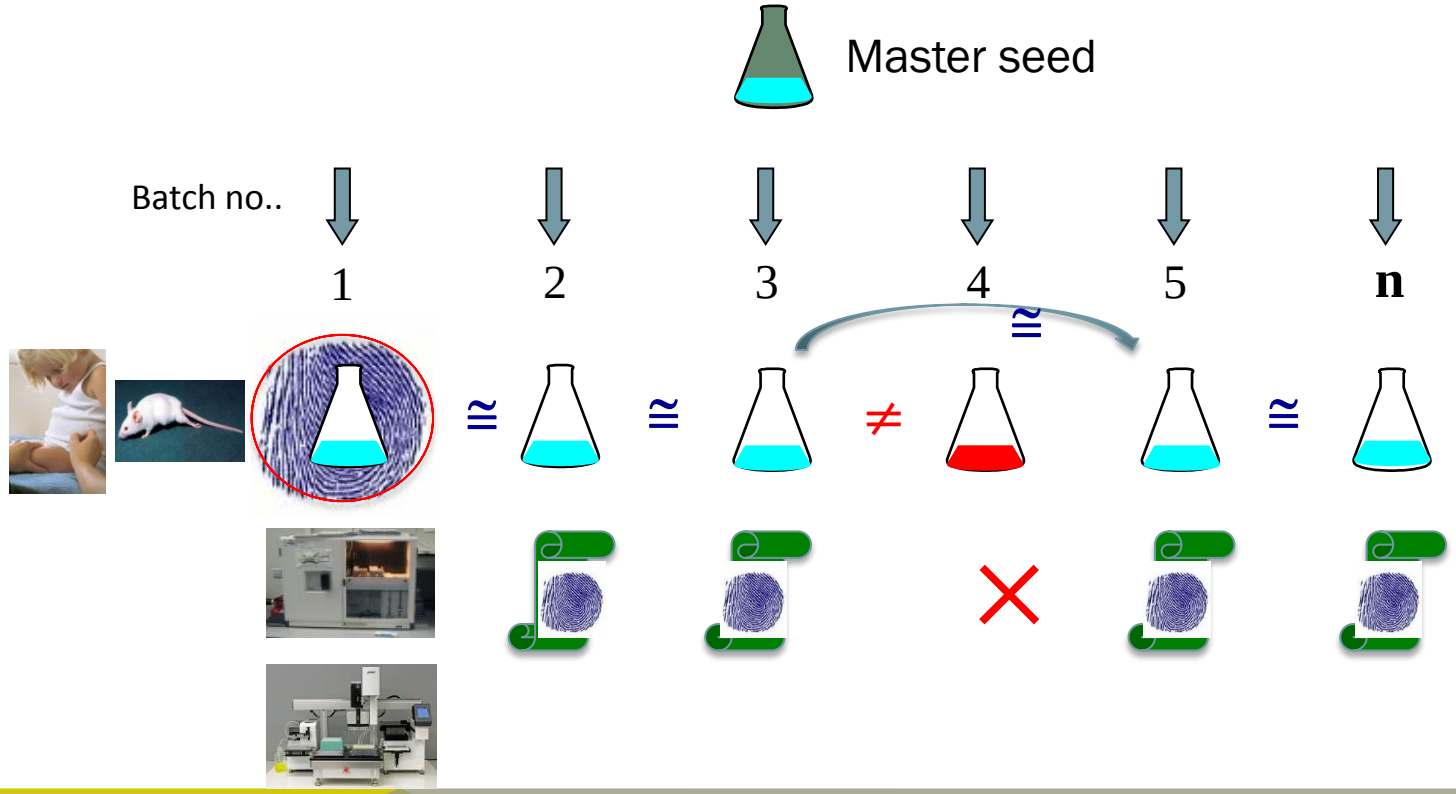
# How can we do better?

**Current paradigm in vaccine batch testing:**
each batch of vaccine of same Master seed is unique and therefore requires extensive testing for potency and safety



# NEW' PARADIGM IN VACCINE BATCH TESTING

**Consistency testing:** each batch of same Master seed is one of a series of batches produced from that master seed



# INTRODUCING
# INNOVATIVE MEDICINES INITIATIVE 2 (IMI2)

# IMI2: Overview and objectives

- IMI1: 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

# INTRODUCING THE IMI2 PROJECT VAC2VAC

# VACCINE BATCH TO VACCINE BATCH COMPARISON BY CONSISTENCY TESTING

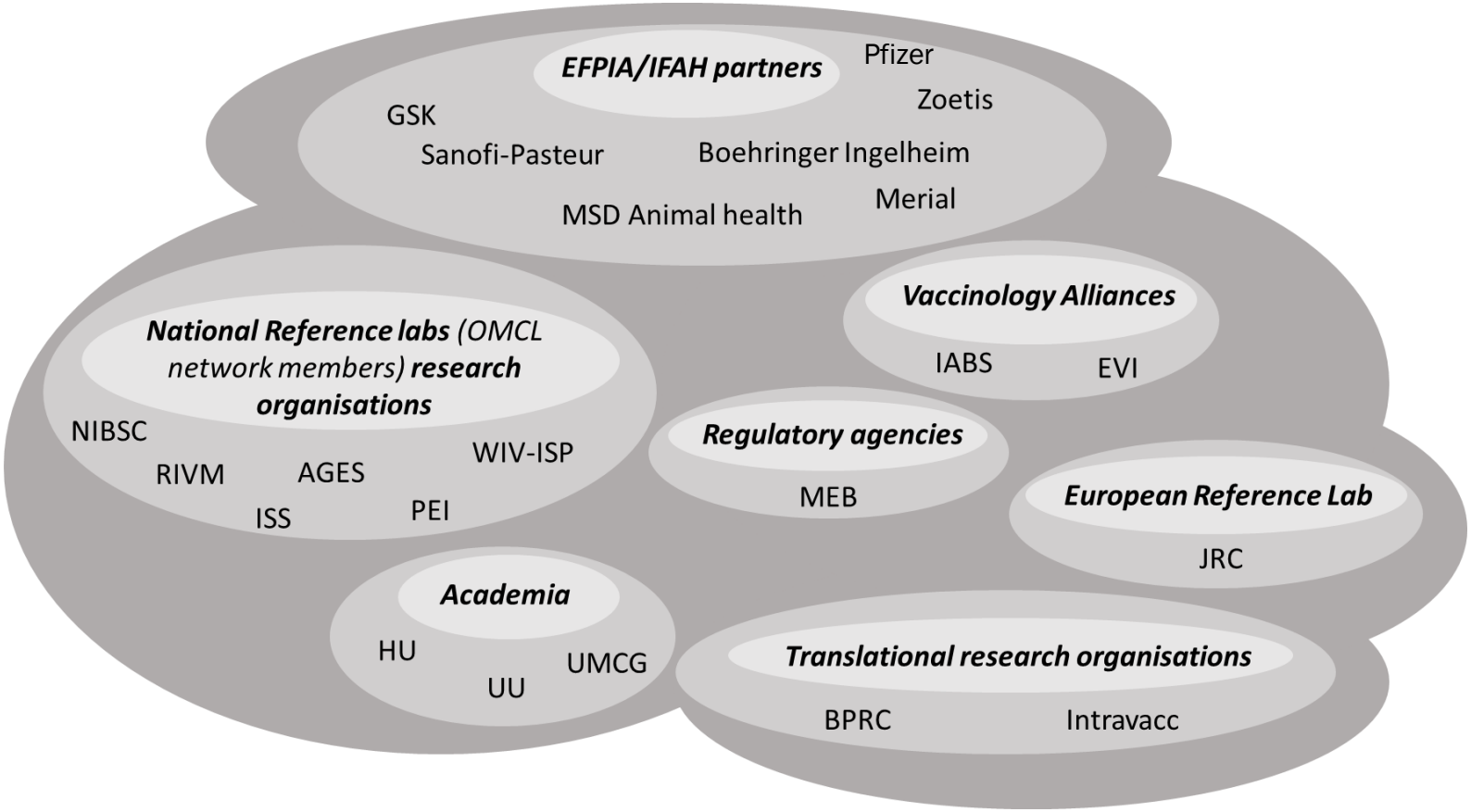
Proof of concept of consistency approach for batch testing of established vaccines using sets of *in vitro* and analytical methods

# OVERVIEW

- 22 participants: 15 public partners, 7 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

  - Oversight : Scientific Management Team (SMT)
    Scientific and Ethics Advisory Committee (SEAC)

# CONSORTIUM PARTNERS



# VACCINES SELECTED FOR PROOF OF CONCEPT

| Selected human and veterinary model vaccines | | |
|---|---|---|
| Type | Vaccine | Final batch testing |
| Human | | |
| 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) |
| Veterinary | | |
| 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) |

# PROGRESS UP-DATE (3.5-YEARS)

| Vaccines | Physicochemical methods (WP1) |
|---|---|
| Leptospira & DTaP | Mass spectrometry promising for demonstrating purity profile |
| Tetanus toxoid | Circular dichroism and fluorescence spectroscopy candidates for assessing structurel conformation |

| Vaccines | Immunochemical methods (WP2) |
|---|---|
| Vet.rabies and Tetanus toxoid | Characterisation and selection of Mabs for antigenicity quantification: Request for validation |
| Tickborne Encephalitis | Immunoassay based on Mabs. Validation request |

# PROGRESS UP-DATE (3-YEARS)

| Vaccines | Cell based (WP3)/Bioinformatics (WP4) |
|---|---|
| Tickborne encephalitis | Monocyte activation test (MAT). Transferred to industry partners |
| Tetanus seed strain | Characterization by -omics technologies |
| DTaP | Human B-cell (isolated) for ELISpot based assays |
| Clostridium perfringens C | Development In vitro safety test |

| Pre-validation & regulatory acceptance | Activity (WP5 and WP6) |
|---|---|
| Project global outreach | Contacts with regulatory authorities and non-regulatory bodies (e.g. BMGF, FDA, Health Canada, OIE, Hsi) |
| Pre-validation | MAT TBEV vaccine; Mab characterization TBEV vaccine |

# CHALLENGES & OPPORTUNITIES (1)

- Catch 21: manufacturers vs. regulatory bodies

  - Manufacturers are reluctant to invest in an alternative test without assurance of regulatory acceptance"
  - " Regulators are reluctant to assure acceptance in the absence of data"

  * *(The way from in vivo to in vitro, 2010 workshop, PEI, GE)*

- Project expectations and output: academia vs. Industry

  - Industry wants as many non animal models as possible being developed and validated by the end of the project period.
  - " Academia wants to invest in scienitific issues to be continued after the project period, to be published in high impact journals

# CHALLENGES & OPPORTUNITIES (2)

- European regulations vs international regulations

  - The gap between European regulations and the regulations in large parts of the world is increasing
  - VAC2VAC has invested in information and collaboration with international regulatory bodies and guideline bodies

- Intelectual Property (IP) and sharing ownership

  - Will be owned jointly by partners involved
  - Secured by signed project agreement

# Moving away from animal use: The way forward: revolution or evolution?

- ✓ Increased awareness & commitment to non-animal testing, (ethics, and particularly science)
- ✓ Progress is being made towards a transition *from in vivo* to non-animal testing, but don't expect the impossible
- ✓ Dutch ambition to phase out animal use for regulatory purposes, including vaccine batch testing by 2025: too optimistic!?
- ✓ Structured approach: in-depth analysis (Streefbeeld) on 3Rs and strategies (e.g. Consistency testing) such as proposed by the NCad

# TRANSITION OF *IN VIVO* TO NON-ANIMAL TESTING


# THANK YOU FOR YOUR ATTENTION