VAC2VAC

Vaccine batch to vaccine batch comparison by consistency testing

3Rs implementation vaccine batch-release testing: Current state-of-the-art and future opportunities

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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.

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VAC2VAC: Overview

- 21 participants, 15 public partners, 3 EFPIA companies, 3 HealthforAnimal companies

- Total budget:
  - ➢€7.85M EU funding in cash
  - ➢€8.13M from EFPIA partners in kind

VAC2VAC PARTNERS:

- **EFPIA/HEALTHFORANIMALS** partners: GSK, Sanofi, Pfizer, BI, MSD Animal Health, Zoetis
- **NATIONAL REF LABS/ OMCL/RESEARCH ORGANISATIONS:** NIBSC, RVIM, AGES, ISS, PEI, SCIENSANO
- **VACCINOLOGY ALLIANCES:** IABS-EU, EVI
- **REGULATORY AGENCY:** MEB
- **EUROPEAN REFERENC LAB:** JRC
- **ACADEMIA:** HU, UU, UMCG
- **TRANSNATIONAL RESEARCH ORGANISATIONS:** BPRC, Intravacc
- **Countries:** Austria, Belgium, France, Germany, Italy, The Netherlands, UK, EU.

ONE HEALTH APPROACH

- Vaccines for humans and animals face the same challenges, when changes from *in vivo* to *in vitro* methods or even to consistency are intended
- Cross-collaboration of the two areas of medicines is extremely beneficial
- The one health approach is strengthened

RECOGNIZE REALITY IN VIVO TESTING

- NUMBERS: global estimate > 10 million animals/year E. Lilley et al., Biologicals https://doi.org/10.1016/j.biologicals.2021.10.002
- Very high variability of animal potency test
- Difficult to control in vivo assays against shifts and drifts in results dependent of animal supply
- No predictability for potency / efficacy in target species
- Time consuming process (at least 1 to 2 months)
- Costly
- Hampers vaccine availability
- In vitro alternatives: consistent, reliable, reduce QC time, suitable for in process (consistency) and batch release control

IN VITRO FOR POTENCY:

- IN VIVO: extremely high variability and lack of consistency:
  - Stalpers et al., Vaccine 39 (2021) 2506–2516: variability of in vivo potency release assays for four DTaP (Diphtheria, Tetanus, acellular Pertussis)
    - products of different manufacturers.
    - Coefficients of Variance ranging from 16% to 132%
- In vitro critical quality attributes, well characterized much more reliable
- VAC2VAC achievements:
  - DTaP (P. Stickings November Stakeholders meeting): in vitro (ELISA and LUMINEX) variability different labs and products less than 10%
  - TBEV: ELISA superior to quantify antigen compared with mouse, excellent potency indicator
  - Veterinary Rabies high consistency of ELISA glycoprotein detection, little variability
  - Clostridium Chauvoei ELISA: highly specific to differentiate degraded from non-degraded

IN VITRO SAFETY

- ATT(ABNORMAL TOXICITY TESTING) not corresponding with its initial objective set early 20th century: ensure safe and consistent antiserum production. Lacks scientific rationale: **historical results do NOT allow to take reliable conclusions.** J Pharm Sci. 2014 Nov;103(11):3349-3355. doi: 10.1002/jps.24125 jho grabe et al. /

- VAC2VAC Achievement:
  - Clostridium Perfringens residual toxin detection on THP1 cells
  - Clostridium Tetani: human and veterinary
  - MAT to replace rabbit pyrogen test TBEV
  - THP 1 cells for feline leukaemia vaccine

BARRIERS AND FEAR FACTOR

- Tests done for decades lead to « why change? »

  political pressure to test batches first *in vivo* regularly

- Fear for novelty is normal
- Therefore:
  - Stepwise approach to understand barriers which may differ
  - Listen, listen, listen and…… listen again
  - Answer with science based data as generated in VAC2VAC
  - Show merit of extensive testing during production process
  - Use examples: COVID vaccines animal use only for pre-clinical development, HPV vaccines, conjugated meningococcal and pneumococcal vaccines

IN VITRO and consistency approach: way forward

- cGMP production now globally accepted and basis of consistency
- In process control assures consistency
- Not conforming batches better detected in a cGMP consistency environment
- Elasticity, great variability of in vivo: no sense for in vivo/in vitro comparison
- Rather look at historical data
- Think globally about consistency and substitution, envisage substitution as adaptation of global control strategy vs 1 to 1 replacement.
- Consistency to deliver faster and more reliable products to patients
- Must include regulators, OMCL's, science and manufacturers
- References: The consistency approach for the substitution of in vivo testing for the quality control of established vaccines: practical considerations and progressive vision Jean-Francois Dierick et al. Open Research Europe 2022, 2:116 Last updated: 05 JAN 2023. Rational arguments for regulatory acceptance of consistency testing: benefits of non-animal testing over in vivo release testing of vaccines,Marcel H.N. Hoefnagel et al. SSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ierv20