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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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.
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

• 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

IN VITRO and consistency approach: way forward

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