VAC2VAC

Vaccine batch to vaccine batch comparison by consistency testing

Lessons learned from VAC2VAC

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

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vac2vac

FIRST LESSONS: find your partners

- Recognize scientific advances in potency and consistency testing
- Awareness of progress to be made on a scientific and societal level
- Willingness for change based on scientific advances
- Consortium of all stakeholders (private sector, regulatory authorities, OMCL's, scientific world)
- Will to collaborate
- Set clear objectives at the start
- VAC2VAC was fantastic experience of collaboration to increase human and animal health

SECOND LESSON:

- 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

THIRD LESSON: recognize reality

- 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 shits and drifts in results that are 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 have proven consistency, reliability, reduce QC time, suitable for in process (consistency) and batch release control

FOURTH LESSON: compare present with potential of innovation: 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, acellularPertussis)
    - products of different manufacturers.
    - Coefficients of Variance ranging from 16% to 132%
- In vitro critical quality attributes, well characterized much more reliable and 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
  - Rabies high consistency of ELISA glycoprotein detection, little variability compared with high “elasticity” of NIH test
  - Clostridium Chauvoei ELISA

FIFTH LESSON: present/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. /
- One-day symposium by Animal Free Safety Assessment Collaboration (AFSA), 18 international experts (Argentina, Brazil, China, Europe, India, Russia, South Africa, Germany, Belgium, Italy, EU, Japan, South-Korea, Canada, Indonesia and the United States): define the barriers to the complete elimination or waiving of these tests. L Viviani et al,biologicals Volume 63, January 2020, Pages 101-105,
- 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

SIXTH LESSON: important progress made: Eur. Ph. Progress with 5.2.14 implementation

Group 15 advances summarised by Dean Smith, VAC2VAC meeting, November 26, 2021

- Adventitious Agent Testing:
  - Tests for extraneous agents in viral vaccines for human use and for cell substrates for production of vaccines for human use, risk-based and supportive of *in vitro* testing
- GST / Abnormal Toxicity :
  - removed Ph. Eur., WHO discontinuation of test from all future vaccine & biologics documents, all previous recommendations for the use of this test should be disregarded
- Pertussis (P) HIST
  - removed from Ph. Eur
- Tetanus (T) Specific Toxicity
  - removed from Ph. Eur
- PT Irreversibility
  - removed from Ph. Eur
- Diphtheria (D) Specific Toxicity
  - proposed removal from Ph. Eur. with validation of stable toxoid
- Rabbit Pyrogenicity
  - new draft MAT General Chapter for inherently pyrogenic vaccines
- QC for COVID-19 Vaccines
  - currently authorized vaccines in North American and EU use only *in vitro* QC methods (while not linked to Ph. Eur. 5.2.14, consistent with the same principles)
- •DT Potency & Safety Tests
  - *in vitro* assays development through VAC2VAC consortium in consultation with EDQM and EMA in process
- Rabies NIH Test
  - GP ELISA suggested as model assay for substitution in Eur. Ph.5.2.14., consultations with authorities ongoing.

SEVENT LESSON: Barriers, 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

EIGTH LESSON: *in vitro* and consistency approach: way forward

- cGMP production is now globally accepted and basis of consistency
- In process control assures consistency
- Data show that not conforming batches can be detected with in vitro, better than in vivo in a cGMP consistency environment
- Because of elasticity, great variability of in vivo: no sense for in vivo/in vitro comparison, rather look at historical data
- Early dialogue between manufacturers, regulatory authorities and national control laboratories is essential
- 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

Thank you all

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