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

• 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


• 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
EIGHTH 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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