The Consistency approach in lot release testing of established vaccines

Coenraad Hendriksen, DVM, PhD
Netherlands Vaccine Institute (NVI) &
Faculty of Veterinary Medicine, Utrecht University
Established vaccines: produced by the traditional techniques of inactivation or attenuation of the virulent micro-organism or the toxin thereof
- less well characterised
- complex

Newer generation vaccines: subunit vaccines, glyco-conjugate vaccines, rDNA vaccines
- well characterised
Agenda

- Current paradigm in vaccine lot release testing
- Limitations of current paradigm on quality control of established vaccines in the last decades
- Innovation in vaccine quality control in last decades
- The consistency approach: a new paradigm in lot release testing of established vaccines
- Strategy of the consistency approach
- Ongoing activities to support the consistency approach

(DCVMN webinar, January 31, 2013)
Current paradigm in vaccine lot release testing

Production of the established (inactivated) vaccines

Virulent micro-organism/toxin
- Culture
- Concentration
- Detoxification/inactivation
- Purification
- Blending (adjuvant, antigens)

Inactivated vaccine/toxoid final lot
- Safety tests
- Potency tests

Characteristics of current paradigm

- Starting points is uniqueness of every lot produced
- Focus of lot release testing on final product
- Use of an international reference preparation expressed in IU/ml
- Reliance of animal models for safety and potency

(DCVMN webinar, January 31, 2013)
Current paradigm in vaccine lot release testing and limitations

Production of the established (inactivated) vaccines

- Virulent micro-organism/toxin
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  - Concentration
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<table>
<thead>
<tr>
<th>Inactivated vaccine/toxoid final lot</th>
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<tbody>
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<td>❖ Safety tests</td>
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</tbody>
</table>

Ethical aspects: extensive animal use

Validity aspects: reproducibility tests, questionable relevance.

Practical aspects: costs, time required

Use of reference preparation (not like to like)

Science: based on models developed > 50 yrs ago

<table>
<thead>
<tr>
<th>Lab.no.</th>
<th>Assays in mice</th>
<th>Assays in g-ps</th>
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<tbody>
<tr>
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<td>171 (152-193)</td>
<td>357 (289-442)</td>
</tr>
<tr>
<td>2</td>
<td>69 (58-82)</td>
<td>293 (198-429)</td>
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<tr>
<td>3</td>
<td>227 (181-285)</td>
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<td>4</td>
<td>-</td>
<td>378 (278-497)</td>
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<tr>
<td>5</td>
<td>104 (75-145)</td>
<td>241 (180-321)</td>
</tr>
</tbody>
</table>


(DCVMN webinar, January 31, 2013)
Innovation in quality control of established vaccines in the last decades: potency testing

Traditional method

Humane endpoints & no. doses or animals/dose

Serology instead of challenge

www.humane-endpoints.info
Innovation in quality control of established vaccines in the last decades: potency testing

Traditional method

Humane endpoints & no. doses or animals/dose

Serology instead of challenge

Characteristics of innovation

- Focus is on methods, not on process (in line with current paradigm)
- General strategy is to replace, reduce & refine animal use
- Validation and implementation is tedious, time onsuming and expensive
- Does not take into account limitations in animal models and progress in production and control technologies

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Limitations of current strategy

Traditional method
- Vaccine → Immun. → Challenge

Humane endpoints & no. doses or animals/dose
- Vaccine → Immun. → Challenge

Serology instead of challenge
- Vaccine → Immun. → Serology

- Ethical aspects: still extensive animal use, but more humane (not for all vaccines)
- Validity aspects: reproducibility tests, questionable relevance.
- Practical aspects: costs, time required
- Use of reference preparation (not like to like)
- Science: based on models developed > 50 yrs ago

The question is: can we do better?

(DCVMN webinar, January 31, 2013)
Consistency in production of consecutive Diphtheria and Tetanus vaccine lots produced

(DCVMN webinar, January 31, 2013)
Current vaccine production: progress being made

- Better characterisation of the product at product optimisation and production (consistency of starting material).

- Improved optimisation and standardisation of production process (consistency of production process and product).

- Tight in-process control and product monitoring with new and improved testing tools (consistency of tests performed).

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

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Production of the established (inactivated) vaccines

Virulent micro-organism/toxin

Culture

Concentration

Detoxification/inactivation

Purification

Blending (adjuvant, antigens)

Inactivated vaccine/toxoid final lot

Safety tests

Potency tests

New techniques

Quality by design

In-Process testing

GMP

QA

DCVMN webinar, January 31, 2013
Consistency testing : definition

‘…… a concept which includes GMP, process validation and in process and final product tests and is aimed at verifying if a manufacturing process produces final lots which are consistent with one that fulfils all the criteria of Quality, Safety and Efficacy as defined in the marketing authorization, with the ultimate goal of replacing animal tests’

(De Mattia et al. 2011)
Consistency testing in vaccine quality control: procedure

Consistency approach in vaccine batch release testing

1. Test first few lots thoroughly; in non-animal models but also in laboratory animals and in target species (clinical/historical batch).

2. Based on this information, specify the profile of the vaccine (fingerprint) based on clinical, manufacturing and testing criteria. Set alert and acceptance criteria and criteria for deviations from consistency.

3. Subsequent vaccine lots produced should have the same profile as the clinical lot. The consistency in profile is monitored by non-animal techniques.

4. If so, the vaccine lot can be released for use.

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Consistency testing: how does it differ?

Consistency aims to change paradigm (established) vaccine lot release testing

Traditional concept of vaccine lot release testing

- Each lot produced by a manufacturer is considered to be a unique product
- Use of Reference preparation
- Emphasis in quality control of each vaccine lot is on final product
- Quality control includes several animal models and is animal demanding

New paradigm: Consistency testing

- Each lot produced by a manufacturer is one of a series and is NOT unique
- Use of clinical lot
- Makes use of:
  - strict application of quality systems (GMP, QA)
  - quality by design
  - extensive in-process testing
  - new innovative analytical tools

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Set of parameters developed for consistency testing of toxoid (D and T) vaccines as being under study at NVI

**Production parameters**
- Optical density
- pH
- Flocculation titre
- Endotoxin
- Protein Nitrogen
- Protein
- Residual formalin
- *In vitro* safety test (Vero)
- Reversion (Vero)
- Osmolarity
- etc.

**Product quality parameters**
- Kf (flocculation time)
- purity
- various physico-chemical tests
- Moab binding (biacore)
- DAFIA (Direct Alhydrogel Formulation Immunoassay)
- etc.

Parameters can be used to set alert criteria and acceptance criteria

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Consistency approach: types of techniques for in-process and final lot control

**Physico-chemical**
- circular dichroism
- fluorescence spectrometry
- colourimetric assays
- etc.

**Application**
- secondary & tertiary structure proteins
- protein conformation, protein modifications
- free amino groups in proteins

**Immuno-chemical**
- biosensor analysis
- ELISA (with Mabs)
- electrophoresis
- etc.

**Application**
- epitope quality, antigen-antibody kinetics
- peptide mapping, ag quantification
- purity, protein modification, stability

**In vitro functional**
- binding assays
- Immune cells
- etc.

**Application**
- antigen binding
- antigen processing, B/T cell responses, cytokine

*(DCVMN webinar, January 31, 2013)*
Structural characterisation of adsorbed toxoid by physico-chemical methods (Metz et al.)

Four physicochemical techniques:

- Bis-ANS fluorescence
- Circular dichroism
- ATR-FTIR
- Differential scanning calorimetry (DSC)

Fluorescent probe (Bis-ANS)

Strong fluorescence increase after adsorption of DTd to Al(OH)₃

Differential scanning calorimetry

Shift of IR spectrum upon adsorption of DTd to Al(OH)₃

Circular dichroism

Secondary structure changes upon adsorption

(DCVMN webinar, January 31, 2013)
Antigenic fingerprints of diphtheria toxoid: adsorbed and desorbed

Dim25 = 100
Consistency approach: what makes it attractive?

Implementation of the approach in lot release testing will result in:

- more meaningful batch release as quality is linked to a clinical lot and better understanding of your product (**scientific benefits**)

- quality control will be less time consuming (a few days instead of 2 months) (**economic benefit**)

- apart from clinical lot (first few lots) NO animal use is required for lot release testing (**animal welfare benefit**)

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Consistency testing: the challenges

- **Tests**: what set of tests is needed and will this be the same for every vaccine. Product specific.

- **'Risk assessment'**: what products are ready for implementing the consistency principle. **Consistency is NOT a one-for-all strategy!**

- **Vaccine blending**: adjuvant and antigen – antigen interaction.

- **Validation**: how to compare fundamentally different approaches.
EPAA and the Consistency approach: the way forward

ECVAM workshops in Ispra: 2005 and 2006


EPAA Vaccine Project kick-off meeting “Application of the 3Rs and the Consistency Approach for Improved Vaccine Quality Control”, Brussels, 7 April 2011
EPAA and vaccine consistency

Partnership between industry and Commission services committed to the 3Rs, joining forces for the promotion of alternatives in regulatory testing (launched in 2005):

- European Commission
  DGs: Enterprise and Industry, Research and Innovation, Environment, Health and Consumer Protection, Joint Research Centre

- Individual companies (35)

- 7 European trade federations, such as
  - chemicals (CEFIC)
  - cosmetics (Cosmetics Europe)
  - pharmaceuticals (EFPIA)

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Main goal: proof-of-concept of the consistency approach for established products in pilot studies for a number of selected vaccines

Activities: mixture of quick wins (achieve 3Rs benefits with existing techniques and within existing regulatory framework) and hard wins (additional research/different regulatory framework)

Aims:
- Identify priority projects (vet and human vaccines)
- Set alert and acceptance criteria for in-house monitoring and batch release
- Bring to stage of validation by Ph.Eur.
- Conduct supporting activities: funding for further research and dissemination of info and organizing conferences
Responsibilities Committees

- **The EPAA Vaccine Project Committee** (9 members from industry, Ph.Eur, and academia)
  - Monitors progress of the project and coordinates
  - Reports to the EPAA
  - Involved in seeking funding for projects
  - Responsible for internal and external communication and dissemination

- **The EPAA Vaccine Technical Committee** (19 members from industry, regulatory bodies, Ph.Eur., EMA & academia)
  - Identifies and proposes vaccines, methods and consistency parameters for pilot cases and creates expert working groups
  - Provides technical guidance and advice
  - Reports to the Vaccine Project Committee on progress
  - Participates in twice yearly Technical Committee meetings

*(DCVMN webinar, January 31, 2013)*
Progress EPAA Vaccine Project

- Kick-off workshop 7th April 2011
  - 50 attendees plus 11 by teleconference

- Conferences & Publications, etc..

- Inventory of existing initiatives completed

- Two Technical Committee meetings held: prioritisation of projects (DTaP vaccines, rabies vaccine, clostridial vaccine)


(DCVMN webinar, January 31, 2013)
FP7 call EU

• Proposal currently under construction

• Involvement of 13 partners (4 from industry, 2 SMEs, 2 OMCLs, 2 governmental institutes, EDQM, EURL-ECVAM, CF-consultancy

• EMA is advisor to project

• 4 major research topics: physico-chemical techniques, immuno-chemical techniques, in vitro functional methods, bioinformatics

• 3 supporting workpackages: Pre-validation criteria for consistency tests, promotion to regulatory acceptance, dissemination & exploitation

• Budget : 3 M€

(DCVMN webinar, January 31, 2013)
Conclusions

- Current paradigm of vaccine quality control should be reconsidered

- The consistency approach is considered to be an alternative to the current paradigm, at the moment at least for some products

- The consistency approach links lot to a lot that has shown to be potent/effective and safe

- The consistency approach reduces animal use, improves insight into quality and safes time

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Conclusion:

EPAA project is an interesting challenge for vaccine manufacturers, regulatory bodies and academia to work together with the ultimate goal to improve vaccine quality and to replace animal testing

- Manufacturers are reluctant to invest in alternatives without assurance of regulatory acceptance”
- Regulators are reluctant to assure acceptance in the absence of data”

(Potency test of veterinary vaccines: The way from in vivo to in vitro, 2010 workshop, PEI, GE)
Consistency testing: literature


*(DCVMN webinar, January 31, 2013)*
Thanks for your attention!

Coenraad.Hendriksen@nvi-vaccin.nl