Waiving in Vaccines for human use

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JM Chapsal, PhD, Analytical Process & Technology
Waiving in Vaccines for human use

Outline

- Introduction
- Waiving
  - By deletion
  - By replacement
  - By the consistency approach
- Regulatory environment
- Impact
- Conclusion
Introduction

Animal use: All stages of vaccine life cycle

- Basic research on disease mechanisms
- Use of models of diseases to test candidate vaccine
- Preclinical: safety, immunogenicity, efficacy
- Production
- Control development (process and testing validation, detoxification, inactivation, ...)

Quality control for batch release
Comparison of relative percentages of animal used for regulatory purposes and release activities

**Scope:** Routine batch release

Two families of *in vivo* tests for release activities

**Safety tests:**
- Low number of animals
- 20% for regulatory activities

**Potency tests:**
- High number of animals
- 80% for regulatory activities
### Comparison of the 20th Century Annual Morbidity and Current Morbidity in the USA:

#### Vaccine Preventable Diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>20th Century annual morbidity</th>
<th>2009 reported cases</th>
<th>Percentage decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smallpox</td>
<td>29005</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Diphtheria</td>
<td>21053</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Measles</td>
<td>530217</td>
<td>71</td>
<td>100</td>
</tr>
<tr>
<td>Mumps</td>
<td>162344</td>
<td>1991</td>
<td>99</td>
</tr>
<tr>
<td>Pertussis</td>
<td>200752</td>
<td>16858</td>
<td>92</td>
</tr>
<tr>
<td>Polio</td>
<td>16316</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Rubella</td>
<td>47745</td>
<td>4</td>
<td>100</td>
</tr>
<tr>
<td>Tetanus</td>
<td>580</td>
<td>14</td>
<td>98</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>20000</td>
<td>243</td>
<td>99</td>
</tr>
</tbody>
</table>

The 3Rs and vaccine control: Introduction

• 80’s-90’s marked by EU harmonization
  • Legal and ethical background to 3R’s
  • Community Code making Ph Eur monographs official standards
  • Mutual recognition of results throughout the EDQM
  • Biological Standardization Program and achievements

• 90’s up to now marked by 3R’s implementation in Ph Eur

• Waiving
  Waiving of ATT and specific toxicity DT, single dilution assay for DTPa, MAPREC, Move tests from Final Container to Final Bulk
  In vitro assay for HAV, HBV, IPV, HiB, Residual D toxin

Waiving in Vaccine batch control testing: Waiving by deletion (Ph. Eur.)

- **General tests**
  - Abnormal Toxicity Test *(GST)*
  - Move tests from Final Container to Final Bulk

- **Bacterial vaccines**
  - specific toxicity DT
  - single dilution assay for DTPa
  - Immunogenicity conjugate Vaccines

- But after proof of manufacturing consistency/historical review

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*Image credit to Sanofi Pasteur*
Waiving by Replacement: Safety tests

**Short term target** as most of these tests are direct with known mechanisms-manufacturing consistency

- **General test**
  - Pyrogens by Endotoxins-Monocyte activation tests

- **Viral vaccines**
  - *Inactivation*: Primary Monkey cells for effective inactivation of Polio Vaccine (IPV) with bioengineered continuous cells lines (L20B), Immunofluorescence on cells lines for Rabies
  - Viral Adventices agents
  - MAPREC* for OPV

- **Bacterial vaccines**
  - Residual/irreversibility of toxoid: *in vivo* test for residual/irreversibility of Tetanus toxoid by *in vitro enzymatic and/or binding* tests, *Inactivation in vivo* test for residual/irreversibility of Diphtheria toxoid by *in vitro* VERO cell tests
  - Histamine assay for residual Pertussis toxin assay by qPCR or *in vitro* PT sensitive cells test

*Mutant Analysis by Polymerase Chain Reaction and Restriction Enzyme Cleavage*
Potency testing seen as a tool for demonstrating the ability of a vaccine batch to induce protective immunity after administration into humans.

For well established vaccines: Animal-based models extensively used for measuring the biological activity of vaccines batches compared to a reference of known biological activity.

Huge retrospective history

Are *in vivo* assay relevant tools?
In vivo potency tests used and relied upon for decades but

First bottleneck in release lead-time

- High variability (C.V: ~15-50% versus 2-10%)
- Invalidity requiring investigations & re-tests
- Animal strain selection - Genetic backgrounds
- Animals availability and health status
- Animal house capacity
- Retesting by National Control Authorities...

~ 50 to 70% of the total production cycle
~ 10% of control activities but 50% of control costs
~ 80% of control animal use
Waiving by Replacement: Potency

Long term target:

Vaccine

- Antigen quantification (well known correlation with clinical data): Rat-Chick potency (IPV) by D antigen content by ELISA, Mice immunogenicity test by ELISA (Hepatitis A) by antigen quantification by ELISA.... but Bacterial toxoids and Rabies vaccines

- Antigen characterization: Biochemical-Biophysical assays
Artificial immune systems: *in vitro* biomimetic of the human immune response

- Application of the VaxDesign artificial immune system to the projects.
  
  The MIMIC® (Modular IMMune In vitro Construct) System is an in vitro surrogate of human immune system that enables researchers to evaluate the immune response to a vaccine, or other biologic, directly in a human immune system. [www.vaxdesign.com](http://www.vaxdesign.com)
**Waiving by the Consistency Approach**

3Rs principles application is allowed through diverse compendial initiatives for Potency and Safety testing.

**Potency**
- *In vivo* Evaluation of protective immune response

**Immunogenicity**
- *In vivo* Evaluation of specific Responses

**Antigenicity**
- *In vitro* Evaluation of antigenicity: Waiving

Consistency tools for release

Knowledge and Control of vaccine manufacturing process

- Clinical
- Commercial

Correlation with human response?

**Notes**
- EP, WHO...

**Sanofi Pasteur**

- The vaccine division of sanofi-aventis Group
**Waiving by Consistency : An Holistic Approach**

- **Shift in paradigm**

- **From** the classical QC approach: Demonstrate the potency/safety of each batch by testing a few samples using a variable *in vivo* assay

- **To** the confirmation of product consistency by monitoring critical steps during production *rather than* relying on control of some samples as the sole indicator of safety and efficacy

- The application of the consistency principle (Holistic approach) is to demonstrate that each batch complies with the defined Quality profile of the clinical lots shown to be safe and efficacious

<table>
<thead>
<tr>
<th>GMP rules &amp; guidelines</th>
<th>QA system</th>
</tr>
</thead>
<tbody>
<tr>
<td>✓ Development</td>
<td>Process validation (Design space)</td>
</tr>
<tr>
<td>✓ Production</td>
<td>Process capability &amp; monitoring (PQR)</td>
</tr>
<tr>
<td>✓ Control strategy</td>
<td>Identification of relevant suitable testing</td>
</tr>
<tr>
<td>✓ Testing history</td>
<td>Huge positive retrospective</td>
</tr>
<tr>
<td>✓ Field history</td>
<td>Post-marketing surveillance/Ph4 CT</td>
</tr>
</tbody>
</table>
Is the consistency approach a reasonable approach for release?

- Yes! **Pre-requisite**: Accept that *in vitro* tests do not provide and do not have to provide the same information as *in vivo* tests

- But *in vivo* to be maintained as **characterization tool**
  - For long-term stability studies
  - If changes in production process
  - For investigations purposes
  - If breach in the consistency...
Regulatory environment

Regulations should support the application of Waiving initiatives on a broad basis

- e.g. development of the new methods through collaborative studies implying all parties
- e.g. application of the mechanism for reducing in vivo testing by OMCLs during Official Batch Release
- e.g. supporting waiving of tests with no added value like some general safety tests

Application of the consistency principle would strengthen confidence in new approaches

- e.g. one in vivo test principle (by manufacturer or NCL)
- e.g. acceptance of the principle of partial reduced testing for QC release (one lot every X lots is tested in vivo)
Waiving and vaccine production: Reality

“It is not sufficient to have validated alternative methods if these are not accepted by authorities in charge of implementation and enforcement. Ways should be sought to increase involvement of authorities at all stages in order to ensure that alternative methods are effectively being used in regulatory compliance testing.”*

Isolated initiative: Limited chance of success

Regional initiative: Limited impact if not accepted worldwide

* The European Partnership for Alternative Approaches to Animal Testing
One world or many worlds?

- EU
- USA
- China
- Japan

Mfcr test for release
Mfcr test at importation
National Control Laboratory

WHO

Local requirements/Local Pharmacopoeia
Lack of harmonisation

80% vaccine world production in Europe
One world or many worlds: Abnormal toxicity test (ATT – GST)

- **Different methods approved by the NRA**
  Ph. Eur, US, JP; ChPh

- **Several approaches required by Authorities**
  
  - Each commercial lots
    WHO, JP; ChPh
  
  - Significant number of commercial lots and waiving request
    USA
  
  - Until proof of manufacturing consistency/historical review
    Ph. Eur.
  
  (re-assessment in case of significant process change)

- In 1999, the WHO expert Committee on Biological Standardization stated that the collection of global data on the value of the ATT would be initiated. Ten years later:
  
  - 25 out of 29 TRS still refers to ATT
  
  - 9 out of 25 refers to ATT omission once consistency of production established to the satisfaction of the NRA

- In some countries, ATT is still considered as a key safety test
3Rs and vaccine production: Reality

EPAA initiative for 3R’s alternative program development and execution for vaccines:

Development  Validation  Coll studies  Approval  Implementation

Academia  Manufacturers  EDQM  European Ph  Manufacturers

Manufacturers  ECVAM

OMCs  OMCLs  WHO  Int’l Authorities  Local Contr Lab

Technical committee

Integration and synchronisation of initiatives, prioritisation transversal collaboration, strong alignment on 3Rs alternative programme and execution, Consistency approach as a strategy to implement 3R’s
Waiving impact on animal use in a global vaccine company
Waiving impact on animal use in a global vaccine company

- Continuous reduction

- 35% of reduction of animal use in the last 10 years.
  - not a decrease of activities.
  - 2 animal facilities have been closed despite the increase of production level.

- This achievement has been obtained with several approaches

1. **Optimization** of tests
2. **Waiving** approaches
3. **Refinement** leading to reduction
4. **Favouring of** *in vitro* methods for vaccine development
The successful implementation of waiving for regulatory testing of vaccine depends on:

- High quality science
- Understanding, recognition and implementation of the change by all stakeholders
- Authorities should agree on
  - Waiving
  - In vivo is not a gold standard
  - In vitro is not in vivo mimic
Waiving of animal testing in Human Vaccine

Waiving means short term efforts for long term benefits

Thank you

In 1738, French engineer Jacques de Vaucanson made the first biomimetic animal.