Quality issues: the good enough vaccine

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Safety

Efficacy

Quality
Ensuring quality

Validation of starting materials

Validation of production process

End product tests

This applies to biologicals and chemicals
HPV vaccines

rDNA L1 protein expressed in yeast or baculovirus:

Validation of starting materials would include viral contamination studies on the insect cells and baculovirus vector, which have not been used for a licensed product before.
End Product tests

Integrity and purity of protein

Integrity of particles
Poliovirus
Type 1
Mahoney

X-ray Structure determination:
J.M. HOGLE, M. CHOW, D.J. FILMAN
(1985)

THREE-DIMENSIONAL STRUCTURE OF
POLIOVIRUS AT 2.9
ANGSTROMS RESOLUTION
Science, 229 1358

(PDB ENTRY: 2PLV)

Radial Depth Cue
Rendering with grasp
(A. NICOLLS) on
Silicon Graphics:
J-Y. SGRO

Image © 1999 Jean-Yves SGRO
In vivo assays: the ability to generate antibodies:

Monkeys (CFR)
Guinea pigs
Chicks
Rats

Expensive, cumbersome, somewhat unpredictable, uses animals.
May reflect human immune response.
Types of antigen that could be measured.

D antigen: expressed mainly on infectious virus
C antigen: expressed mainly on empty capsids, heated virus

Full and empty particles share C and D determinants. Empty capsids can induce neutralising antibody. Measuring D antigen alone is an underestimate of potency.
In vitro assays: the ability to react with antibodies.

Double diffusion
ELISA

Cheaper, more controllable, more precise than in vivo assays.

Not necessarily a reflection of immunogenicity. Not necessarily as controlled as you think (e.g. strain effects, applying a validated test to a different product, detection of degradation of antigen)
Human antibody response after a single dose of IPV (Salk et al)

<table>
<thead>
<tr>
<th>RIVM</th>
<th>Type 1 DU</th>
<th>GMT</th>
<th>Type 2 DU</th>
<th>GMT</th>
<th>Type 3 DU</th>
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<td>4</td>
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<td>35</td>
<td>2</td>
<td>1.5</td>
<td>3</td>
<td>7</td>
<td>3</td>
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<tr>
<td>C</td>
<td>20</td>
<td>&lt;2</td>
<td>2.2</td>
<td>5</td>
<td>4</td>
<td>3</td>
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</table>
Serotype 2

Antibody reaction in ELISA

Ratio inactivated/live

Sabin IPV

Wild IPV

437
1050
437
1050
Relationship between D antigen content and immunogenicity.

Strain effects (affects both immunogenicity and antigenicity)
Batch effects (antigenic quality does not necessarily reflect immunogenic quality)
Matrix (combination) effects
## Rat potency assay-Type 2

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<th>ED50 (in Human doses)</th>
<th>Relative Potency</th>
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<tr>
<td></td>
<td>Sabin 2</td>
<td>MEF1</td>
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<tr>
<td>MEFIPV</td>
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<td>SAB2IPV</td>
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Comparison of D antigen content and Immunogenicity: potency relative to standard. (van Steenis et al 1980)

<table>
<thead>
<tr>
<th>vaccine</th>
<th>D antigen</th>
<th>D antigen</th>
<th>D antigen</th>
<th>Antibody response</th>
<th>Antibody response</th>
<th>Antibody response</th>
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<td>Type 2</td>
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<td>Type 1</td>
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</tr>
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<td>1.0</td>
<td>0.8</td>
<td>&lt;0.2</td>
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<tr>
<td>76-01</td>
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<td>1.4</td>
<td>0.65</td>
<td>&lt;0.02</td>
<td>0.35</td>
<td>&lt;0.03</td>
</tr>
</tbody>
</table>
In vitro assays can be used if they are validated. For IPV this means that they must be validated for a specific product and shown to detect unsatisfactory batches. This may be challenging.

The relationship between antigen content and immunogenicity needs to be demonstrated. Antigen content may be a correlate of immunogenicity for a particular product.
Summary

Biological medicinal products are much more complicated than chemical entities. Consistent quality to show that a batch is the same as batches that have been clinically satisfactory is essential. Markers of quality are not necessarily the same thing as markers of clinical effect.