

# QUALITY CONTROL OF WHO PREQUALIFIED VACCINES

*Agence française  
de sécurité sanitaire  
des produits de santé*



**F.FUCHS**

**PAHO Meeting - Rio 28-30 November 2006**

## 1- Example of a NCL in a producing country (France)

- Routine Functioning of the NCL lab
- Lot release activity for vaccines

## 2- QC of WHO prequalified vaccines (PQ)

- The upstream QC testing before PQ of vaccines
- The monitoring of PQ vaccines
  - Testing constraints
  - QA issues



Scientific &  
technical  
Experience

# WHO critical functions for vaccine supply



6 Critical Functions	UN Supply	Purchase by country	Producing country	
M. Authorization	X X	X X X X	X X X X X X	
Pharmacovigilance				
<b>Lot Release</b>	[Hatched]			[Hatched]
<b>Lab access</b>				
GMPs Inspection				
Clinical evaluation				

# QC testing by NCL: needs & requirements



- Absolute need for the NCL to access the product specific MA file (should be involved in the licensing phase)+ any MA variation
- Need for adequate lab facilities + trained staff + Quality manager
- Need for QC testing plan (nature & frequency of tests) + written SOP's + written criteria for decision making: QC checklist, sampling, methods, specifications
- Absolute need to access inspection reports, complaints (e.g stability)
- Traceability of NCL results: raw data analysis, control charts and tools to monitor consistency
- In addition: review of LSP, checking of labelling and packaging

- **Whatever the NCL status is: need for quality assurance system**
- Standardised & validated assays => to allow relevant interpretation of QC test results
- Equipments: documentation in place, maintenance, calibration
- Qualification & expertise of staff, auditing systems
- **Validation of methods, use of standards and reference reagents; trend analysis of results**
- Participation in collaborative studies, performance studies

A large green arrow with a black outline, pointing to the right. It has a small black shadow underneath it.

**Applicable to QC testing of PQ vaccines**

# NCL QA Documentation to run vaccine testing



## e.g titration of MMR vaccines

- Domain
- Responsibilities
- Facilities
- Materials (e.g plates)
- Equipments
- Reagents (commercial & in house)
- Titration procedure description
- Reading
- Calculation & interpretation
- Saving and archiving
- Qualification of autoclaves
- Temperature monitoring (e.g incubators, refrigerators)
- Pipettes checking gravimetric method
- Checking of scales
- Checking of ODs readers
- Checking of laminar flow equipments
- Checking of pH meter

- **Commercial softwares = considered as validated**
- QA forms (life cycle monitoring)
- Password to data access
  
- **In house softwares**
- To select a secured language (beware Excel), secured access (password)
- Full development & validation procedures
- Periodic checking with a set of raw data

- **Validation protocol (e.g 30 lots/assays data)**
  - Accuracy, Precision (repeteability & intermediate precision), Linearity
  - Specificity, Sensibility, Detection level & Limit of quantification
- **Statistical process control (SPC):**
  - Control charts
  - Trend analysis
  - Comparison manufacturer & NCL data; *in vitro/in vivo* correlation

# Results

## Validity and conformity criteria



- Need to explain choice criteria (e.g CPE positive/negative).
- **To describe statistical calculation method**
  - Quantitative methods: Parallel line model, slope-ratio model
  - Qualitative methods: Probits, angular
- **Biological & statistical validity criteria**
  - Monitoring of a reference material by control charts
  - Use of primary (IS) or secondary standards (BRPs)
  - Action when invalid assays, investigation
  - Retesting procedures
- **Conformity criteria & rules for combinations**

## Should mention:

- Request (who, what, deadlines, etc..)
- Product Characteristics
- Date(s) of assay(s)
- Method
- Result (& precision)
- Total number of assays to issue a result
- Conformity / specifications.
- Signature by the QC lab responsible person

A purple callout box with a white border and a shadow, containing the text "Analysis report".

Analysis report

# QC of WHO prequalified vaccines: specificities

*Agence française  
de sécurité sanitaire  
des produits de santé*



# QC of Prequalified vaccines: a formal WHO/NCL agreement



- Need for a WHO/NCL agreement (yearly) : absolute confidentiality
- No disclosure of test results, of manufacturer concerned
- Impossible to ask a NCL to test PQ vaccines of a manufacturer already tested/ released by the NCL: independence
- List of generic vaccines known in advance (e.g DTwP, Hib, OPV etc..) to allow NCL to manage and organise
- Easy to run usual QC test methods for classical vaccines (DTwP, OPV, MMR): potency, virus titration, specific toxicity, pyrogens, LAL etc..)
  - No specific reagents/ Only skilled staff needed
- **Need for detailed manufacturer test method & specific reagents if needed**

20 valencies, >50 different vaccines, >200 trade names released

PQ vaccines selected amongst these vaccines

- **Viral vaccines live & inactivated**
  - OPV m & t, IPV, Influenza, Hep A, HepB, MMR, Yellow fever, Varicella
- **Bacterial vaccines live, inactivated, polysaccharide ( $\pm$  conjugated)**
  - BCG, BCG for immunotherapy
  - Diphtheria, Tetanus, aPertussis, wPertussis, Cholera
  - Hib, Pneumococcal, Meningococcal, Typhoid, Leptospirosis
- **Combined vaccines**
  - Tri, tetra, penta, hexavalent vaccines

# Afssaps laboratory experience for WHO expertise



- **All vaccines**

- In vitro potency tests e.g ELISAs for viral and bacterial antigens
- Pyrogens
- Sterility
- Endotoxins
- Degree of adsorption, pH, aluminium, phenol, thiomersal, adjuvant
- Appearance, residual moisture, volume
- Stability testing

## > 150 DIFFERENT ASSAYS ROUTINELY PERFORMED

### • Viral vaccines

- Cell culture titrations (microplates, PFU, pock forming unit assay)
- SRD assay
- [Neurovirulence (OPV)]

### • Bacterial vaccines

- Culture (viable count), mycobacteria
- In vivo potency tests (D, T, wP, aP, hep B, hep A, IPV, rabies, tuberculins)
- In vivo safety tests (WHO), toxicity tests (D, T, wP, aP, HST)
- In vitro toxicity tests (CHO cells)
- Excessive dermal reactivity
- Physico chemical methods: polysaccharide testing, HPLC, DIONEX, anthrone, nephelometry, molecular sizing

# QC testing of PQ vaccines do we have limitations?



- More complex for new sophisticated vaccine combinations (DTaP/Hib/IPV/HepB or polysaccharide vaccines)
  - Need for « product specific » reagents and methods=> ownership of manufacturers (patented: e.g Hep B in vitro potency)
  - Important to know technical details: e.g specific diluent for adjuvanted vaccines
  - Need for appropriate validation: strict application of NCL in house SOP's for related products not possible (e.g free PS, molecular size)
  - According to QA systems impossible to use reagents from other manufacturers/sources= difficulty
  - **Comparability with manufacturers results could be questionable**
  - **Could raise concerns on opposability of results in case of discrepancy (lack of validation)**



# Potency test of Hepatitis B vaccines & Standard for the immunogenicity and in vitro test.



- Abbott to discontinue Auszyme kit (IVRP & in vivo)
- Have accepted to extend deadlines for supplying NCLs
- European bodies & WHO to look for possible alternatives
- Ultimate goal is to establish a common assay used for all rDNA HBV vaccines
- Various attempts to develop methods: manufacturers have worked on their own, EDQM + F + UK + B together
- For the time being no consensus on the strategy & technical approach

# Potency test of Hepatitis B vaccines & Standard for the immunogenicity and in vitro test.



## Manufacturers approach

- **MSD**

- Have bought (patented) the Abbott monoclonal antibody used & developed their in house IVRP assay
- Legal impossibility for Pharmacopoeias to recommend this method

- **GSK**

- Have developed an in house assay potential candidate as common assay using in house reagents (inhibition test)
- Recently have changed their strategy and have patented their method
- NCLs would be free to use it without financial obligations (fees & licensing agreement for manufacturers)

# Potency test of Hepatitis B vaccines :

## Where we are



- Negotiations ongoing with GSK
  - GSK patent would not impair lot release on the European market but however would impair lot release of European NCLS for exports markets & WHO PQ testing
  - It is likely that non EU manufacturers will not license the GSK method and will try to establish their own method
- => **major difficulty for NCLs to have to run various product specific Hep B methods**
- => **European bodies and NCLs to look for a non patented method (Cuban?)**

# Technical challenges for testing some PQ combined vaccines

- Manufacturers should have identified potential interactions leading either to diminish or increase response to individual components compared to individual components alone
    - in the appropriate animal model supposed to mimik response in human
- ⇒ Need for appropriate design of QC strategy
- ⇒ Need for appropriate QC tests *in vivo* and *in vitro* (potency): relevant studies in animal
- ⇒ **Could be difficult to an NCL without the background to test and interpret**
- ⇒ Need for Pharmacopoeia requirements and reference preparations



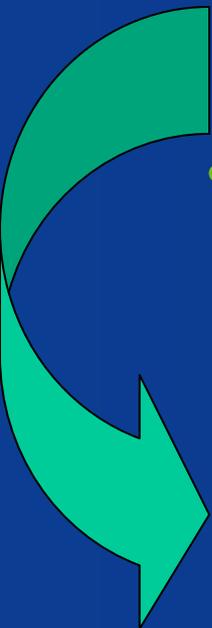
- It is difficult to transpose *in vivo* potency assays for single component to the combos: response to each antigen should be assessed: quantitative & qualitative (antibody class, avidity, affinity, half-life, neutralising capacity etc..)
- Case by case:
  - Appropriate animal species
  - Dose-range
  - Route & location of injection
  - Volumes of injection
  - Dilutions (buffers, procedure)
  - Test preparation and a standard should be compared

- **DTaP+ Hib**

- Do not behave in QC tests as expected from D, T, wP, Hib separately
- D, T, wP enhances antibody response to Hib
- Probably due to adjuvant effect of wP + a mimicking effect

- **Case of PRP tetanus toxoid conjugate in combos**

- Enhancement of tetanus antitoxin response
- Tetanus toxoid content of conjugate is comparable with the quantity present in D, T, wP
- Question of possible excessive dose of tetanus toxoid if several conjugate vaccines are used

- 
- A large, thick green arrow on the left side of the slide, pointing from the top towards the bottom, indicating a flow or continuation of the information.
- NCL testing of prequalified vaccines requires:
    - Skilled staff & appropriate facilities
    - QA system in place for vaccine testing (lot release)
  - Increasing the number of WHO PQ vaccines = New challenges for testing NCLs
    - Rigorous scientific & technical expertise
    - Experience in R&D for vaccines QC
    - Minimum background knowledge on combos
    - To give more guidance to WHO on the scientific & technical issues related to the new PQ vaccines compared to the past