QUALITY CONTROL OF WHO PREQUALIFIED VACCINES

F.FUCHS

PAHO Meeting - Rio  28-30 November 2006
NCLs functioning

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
WHO critical functions for vaccine supply

6 Critical Functions

- M. Authorization
- Pharmacovigilance
- Lot Release
- Lab access
- GMPs Inspection
- Clinical evaluation

UN Supply

Purchase by country

Producing country

X X
X X
X X
X X

F.FUCHS - PAHO meeting Rio 28-30 November 2006
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
NCL: access to laboratories

- **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

Applicable to QC testing of PQ vaccines
NCL QA Documentation to run vaccine testing

Level 1
QUALITY MANUAL

Level 2
GENERAL PROCEDURES

Level 3
SPECIFIC PROCEDURES

Level 4
SOPs & OPERATING INSTRUCTIONS

Level 5
QA FORMS
Technical Operating instructions

**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
Calculation softwares

• **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
Method validation

- **Validation protocol (e.g. 30 lots/assays data)**
  - Accuracy, Precision (repeatability & 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**
Analysis report

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
QC of WHO prequalified vaccines: specificities
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: independance
- 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
e.g Afssaps control activity

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 (± 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
Afssaps laboratory experience for PQ vaccines

> 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, nephelemetry, 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
**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 mimic 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
EXAMPLES OF PROBLEMS RAISED BY NCLs

• **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
CONCLUSION

- 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