Outline of presentation

- Introduction
- UN tender specifications and WHO recommendations
- Changing landscape
- WHO approaches to address challenges
- Head-ups on Scientific Opinion and Expedited Review Procedures
- Challenges faced with novel vaccines
- Main shortcomings and proposed solutions
- Last comments
Purpose of WHO prequalification

- A service provided to UN purchasing agencies.
- Provide independent opinion/advice on the quality, safety, and efficacy of vaccines for purchase.
- Ensure that candidate vaccines are suitable for the target population and meet the needs of the programme.
- Ensure continuing compliance with specifications and established standards of quality.
Status of WHO prequalified vaccines

12 industrialized country mfrs
- Belgium
- Denmark
- France
- Germany
- The Netherlands
- Hungary
- Italy
- Japan
- Rep. of Korea
- USA
- Switzerland
- Sweden

6 developing country mfrs
- Brazil
- Bulgaria
- Cuba
- India
- Indonesia
- Senegal

82 pre-qualified vaccines used in 112 countries

53% total population
Principles

GMP

Clinical data

Consistency of final product characteristics

Meeting WHO requirements and tender specs

Reliance on NRA
Conditions for PQ evaluation

- NRA of record fully functional
- Vaccine is licensed by the responsible NRA (Scientific opinion by EMEA accepted)
- WHO guidelines/recommendations available
- Listed in the vaccine priority list (low priority vaccines may be postponed)
Conditions for prequalification

Ongoing oversight and commitments by the NRA

- Lot to lot release
- Inspections at regular intervals. Inform WHO of serious GMP deviations
- Post-marketing surveillance for safety and efficacy. Inform WHO in case of reports of serious AEFI
- Inform WHO in case of withdrawals or recalls of lots and license suspensions
Conditions for PQ evaluation

Commitments from the manufacturer

- Report variations to WHO
- Report serious AEFI
- Communicating with WHO
- Provide regular updates of safety profile
- Inform WHO of problems that may impact the quality, safety, efficacy or timely supply of product
Specific aspects considered

- General understanding of production process and quality control methods
- Clinical data relevant for the target population in the recommended schedules
- Production consistency at commercial scale (assessed by testing of samples of final product)
- Compliance with GMP
- Compliance with WHO recommendations and UN tender specifications including labels and inserts
- Programmatically suitable presentation
Technical WHO recommendations

Good Manufacturing Practices


Regulation and licensing

- Regulation and licensing of biological products in countries with newly developing Regulatory Authorities (WHO Technical Report Series No. 858, 1995)

Technical WHO recommendations

- Requirements for the use of animal cells as in vitro substrates for the production of biologicals (WHO Technical Report Series No. 878, 1998)
- Report of a WHO Consultation on Medicinal and other Products in relation to Human and Animal Transmissible Spongiform Encephalopathies. WHO/BLG/97.2
- Guidelines on stability evaluation of vaccines (WHO/BS/06.2049 2006)

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Technical WHO recommendations

Clinical


Non clinical

- WHO guidelines on nonclinical evaluation of vaccines (WHO Technical Report Series No. 927, 2005)
Technical WHO recommendations


- Recommendations for whole cell pertussis vaccine (WHO Technical Report Series No. 941, 2007)

Technical WHO recommendations


- Biological products prepared by recombinant DNA technology (WHO Technical Report Series No. 814, 1991)


- Requirements for Yellow Fever vaccine (WHO Technical Report Series No. 872, 1998)
Technical WHO recommendations


- Recommendations to assure the quality, safety and efficacy of Group A Meningococcal Conjugate vaccines WHO/BS/06.2041-2006)

Technical WHO recommendations

- Guidelines to assure the Quality, safety and efficacy of recombinant Human Papillomavirus virus-like particle vaccines, WHO/BS/06.2050, 2006
- Guidelines to assure the quality, safety and efficacy of live attenuated rotavirus vaccines (oral) (WHO Technical Report Series No. 941, 2007)
Shipping Guidelines

- Guidelines on the international packaging and shipping of vaccines WHO/IVB/05.23
- International shipping guidelines to be revised in 2009 with a target to publish the revised version in Q3.
- WHO-UNICEF policy statement on the use of vaccine vial monitors in immunization services
- VVM PQS performance specification WHO/PQS/E06/IN05.1
Model inserts

Traditional vaccines:
No changes foreseen

Novel vaccines:
Model inserts under preparation
PREQUALIFICATION STEPS

- Scientific review of quality dossier
- Testing of samples
- Consultation with responsible NRA
- Site visit to manufacturing facilities
- Scientific review of clinical data

Changing landscape
(Partners perspective)

GAVI - expanding vaccine portfolio (support for 7 new vaccines)

Efforts made to accelerate introduction of underutilized vaccines

Efforts made to increase coverage to achieve measles elimination/ control goal

Increased demand for concerned vaccines

Expectations of expanding PQ portfolio and of accelerating (fast tracking) prequalification procedure

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Changing landscape
(Manufactures & respective NRAs perspective)

Challenge for producers to ensure adequate/std processes and procedures across sites
Challenging Regulatory Pathways

Demonstration/assessment of quality, safety and efficacy is challenging, in addition assessment of programmatic suitability is a challenge
No "One size fits all" possible

PMS monitoring for safety and efficacy is an issue

May not be licensed in country of origin or licensed for export purposes only

NRA in country of origin may not have required expertise, enough human resources, challenging testing methods
Changing landscape (User countries perspective)

Direct procuring countries purchasing such vaccines may find their regulation quite challenging.

Product profile may not be fully suitable to the conditions of the country and represent a challenge for introduction.

PMS monitoring for safety and efficacy is an issue.

If not licensed in country of origin or licensed only for export, importing country may not be able to license.

Licensing novel vaccines may be challenging, lack of expertise and the required resources.
WHO approach: regulatory oversight

Country of origin
NRA

MAA
Licensure For export
Art. 58

Manufacturer

Lot release certificate
Regulatory inspections

Documentation samples

Receiving country

MAA thru WHO Expedited procedure

WHO Sentinel Network

Lot release certificate

PMS

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What is the CHMP Scientific Opinion procedure (Art. 58)

It is an opinion issued by the CHMP, the scientific committee of the EMEA, in collaboration with the WHO. This opinion is based on the evaluation of an application containing data on the quality, safety and efficacy of the product, and concludes on the benefit-risk of the product.
What is the CHMP Scientific Opinion procedure (Art. 58)

- It is a procedure applicable exclusively to products (vaccines and other medicines) designated as "eligible" by WHO.

- WHO "eligibility" for vaccine products applies to vaccines to be used in the Expanded Programme on Immunization for protection against a WHO public health priority disease.

- Applicants or their contact points must be established in the EEA (Member State of the EU, Norway, Iceland or Liechtenstein).

- Procedure mimics the EMEA centralized procedure for MA.
Two important features

❖ WHO observers and representatives from NRAs from target countries take part in the procedure

❖ The assessment of clinical data takes into consideration the target population and the epidemiology in target countries

Concluding remarks: CHMP has established a procedure that is of the same standard as the centralized procedure for registration of medicines in Europe, which has the additional benefit of taking into consideration suitability of data for target population

Prequalification process can be streamlined
Procedure for expedited review of PQd vaccines

SCOPE AND CONDITIONS

- Intended for countries that source their vaccines through UN agencies, or that use the WHO prequalification as a basis for selection of vaccines for purchase.
- Guidance on how NRAs of such countries can expedite the regulatory review for such products.
- Applies to vaccines used in National Immunization Programmes.
- Not intended to affect post-approval activities in these countries.
- For adoption, national regulations must contain provisions to allow to shorten the normal regulatory approval process.

Details of the "Procedure for expedited review of imported prequalified vaccines for use in national immunization programmes. WHO/IVB/07.08 at

Novel vaccines - Challenges for evaluation by WHO (1)

- Need to ensure that adequate regulatory pathway is in place, that product is licensed or licensable, continuous regulatory oversight in place

- Need to ensure supply through existence of long term agreement

- Need to assess quality
  - Adequacy of production process
  - Adequacy of quality control methods and specifications
  - Stability data
  - Transferability of testing methods to NCL and independent labs
  - Consistency of production
  - GMP compliance, adequate Quality Management System in place
Novel vaccines- Challenges for evaluation by WHO (2)

Need to assess suitability of clinical data

- Adequacy of available clinical trial protocols and data
- Relevance of existing data for target population and immunization schedules
- Co-administration with other EPI vaccines or other interventions
- Immunization schedules, route of administration, etc
- Inter-changeability with other brands of same vaccine
- Safety profile. Phase IV studies may be required, strong pharmaco-vigilance system in place crucial.
- Indications, labelling and inserts
Novel vaccines- Challenges for evaluation by WHO (3)

Need to assess programmatic suitability

- Tender specifications met
- Adequacy of presentation
- Cold chain requirements, stability profile
- Temperature indicators: VVMs, data loggers for shipment, etc
Main shortcomings and solutions

Testing methodologies not always available in independent labs

Need to start transfer of methods at the beginning of evaluation or before this is started

Meetings with manufacturers ahead of submission and during evaluation highly recommended
Main shortcomings and solutions

Available clinical information not always sufficient/adequate

For combination vaccines, all existing clinical info for the same antigens in different products taken as supportive evidence, this is not applicable to novel products

Meetings with manufacturers highly recommended
Main shortcomings and solutions

Some novel products do not fully meet the programmatic needs but are still considered useful for countries in absence of the ideal alternative.

Recommended for use rather than prequalified.

Increased demand for evaluation
Acceleration of introduction
Some products are not "mature" at time of submission. Submission In parallel with licensure has not been successful.

Target timelines for evaluation established
Need for clinical protocols/data at time of submission.
Last comments

Need to revise multidose vial policy.

Need for solution for small multidose vials without preservative

Ongoing, will take time

Interim solution,
  a) Add thiomersal
  b) Addition of text on labels, boxes and inserts (not encouraged) + training + VVM on cap + colour?

Addressing information issue
Web list
Advocacy with partners, NGOs and receiving countries NRAs

New webpage under development

Thanks to all manufacturers for information provided
Publication of basis for PQ (WHO PARs) under consideration