

# **Integration of Influenza Vaccine Evaluations to the Main Stream Prequalification Procedure**

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# Outline of presentation

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- The human influenza landscape from the 1997 Hong Kong outbreak to present and its evolving effects on prequalification: the world outside
- Introduction and subsequent halt of influenza vaccines into PQ activities (2006-2009): expedited procedure for evaluating seasonal influenza vaccines
- The A (H1N1) influenza pandemic (2009-2010): expedited procedure for evaluating pandemic influenza vaccines
- Post-pandemic reintroduction of seasonal vaccines (2010 - ): time to integrate influenza vaccines into the mainstream evaluation procedure – Back to normal?
- Back to the future: complete integration expected in January 2012, tentative starting date of the ECBS endorsed revised procedure for WHO prequalification of vaccines



# The world outside-1

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- After being in steady state for decades, the field of immunization against influenza is undergoing dramatic changes
- Especially since the reappearance of the highly pathogenic H5N1 avian influenza in humans in 2003
- The possibility of an influenza pandemic with a potential case fatality rate over 50 per cent mobilized governments, public health authorities worldwide



# The world outside-2

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- Established vaccine industry responded with intensive production capacity building and additional research and development
- These efforts led to a significantly increased global vaccine production capacity (the yearly influenza vaccine production capacity increased from 350 million to 800 million doses since 2006), and
- the development and licensure of novel type of adjuvanted vaccines which were widely used during the recent H1N1 pandemic in 2009-2010
- With support from WHO and other stakeholders, developing country manufacturers are establishing influenza vaccine production capacities in three continents which led to the licensure of seasonal and pandemic vaccines alike, including prequalification



# Does it sound familiar?

## Humanity under the sword of Damocles?

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- **6 March 2011: Bangladesh** reports 29 outbreaks of H5N1 in Barisal, Chittagong, Dhaka, Khulna, and Rajshahi districts.
- **7 March 2011: India** reports an additional outbreak of H5N1 in poultry in Tripura. **Israel** reports an outbreak of H5N1 in poultry in Jehuda & Samaria (first report of H5N1 in Israeli since May 2010). **Egypt** confirms its 126th human case, in a 32-year old woman from Sharkia governorate (onset date 10 February), and its 127th human case, in a 2 year old boy from Kafr el Sheikh governorate.
- **8 March 2011: Viet Nam** reports H5N1 in poultry in Ha Nam and Quang Ninh provinces.
- **10 March 2011: Egypt** confirms its 128th human case, in a 17-year old woman from Beheira governorate (onset date 27 February), and its 129th human case, in a 17- year-old woman from Dakahlia governorate.

(Source: [http://www.who.int/csr/disease/avian\\_influenza/2011\\_03\\_10\\_h5n1\\_avian\\_influenza\\_timeline\\_updates.pdf](http://www.who.int/csr/disease/avian_influenza/2011_03_10_h5n1_avian_influenza_timeline_updates.pdf) - from the **10 March 2011 update of the web site**)



# Excerpts from a recent report to WHO from the Indonesian Ministry of Health

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- **25 March 2011** - A 2 year old female from Bekasi City, West Java Province developed symptoms on 2 March, was admitted to a health care facility on 3 March and referred to a hospital on 9 March. She has fully recovered from her illness.
- The case's mother (see update, 14 March) died of confirmed avian influenza A(H5N1) virus infection one day prior to onset of illness in the new case.
- The child accompanied her mother to the traditional market where live poultry were sold but investigations into the source of infection are ongoing.
- In both cases laboratory tests have confirmed infection with avian influenza A(H5N1) virus.
- Of the 175 cases confirmed to date in Indonesia, 144 have been fatal.



# Rationale for the introduction of seasonal influenza vaccine PQ option in 2006

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- UN agencies expressed interest for availability of prequalified influenza vaccines
- WHO considered that **prequalification of seasonal vaccine may assist Member States** if pandemic influenza vaccines need to be made available in a short timeframe
- The particular challenges for the regulatory oversight of influenza vaccines necessitated to establish an expedited procedure for evaluation with the aim to properly address the emerging needs developed under the circumstances of the H5N1 threat to humanity



# Expedited procedure for evaluating seasonal influenza vaccines

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- Two annual deadlines were set up for a PQ submission - a reflection on the seasonality of influenza epidemics and the time differences in peak seasons in the North versus the South
- Only licensed influenza vaccines were accepted
- Functionality of the National Regulatory Authority was an absolute criterion for application – all the critical functionality indicators were expected to be fulfilled according to the NRA assessment programme of WHO



# Steps of procedure

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- Review of Product Summary
- File Consultation with the responsible National Regulatory Authority
- Testing of samples for consistency of final product characteristics (last three batches of all dosage forms)
- Site visits to the manufacturing facilities



# Consultation themes with the relevant National Regulatory Authority

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- Conditions of license of the product for North and South
- Consistency of production (testing results)
- Reports of adverse events after immunization
- History of complaints and regulatory actions
- Release of lots for United Nations supply
- Conditions for licensing of vaccine strains for the season
- GMP issues, last three inspections, major violations



# Special considerations

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- The procedures permitted a review of the product summary file in parallel with the testing of samples
- The site visit could be performed during the time of waiting for the test results
- In case of a clinical trial is pending/ongoing for the approaching influenza season the technical review could go ahead with full speed



# Possible waiver of testing: production consistency demonstrable

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- Full details of quality control of the last three consecutively produced batches
- Trend analysis of potency, safety and other assays of all batched produced during the last three years either by manufacturer or responsible authority – manufacturer expected to permit its national authority to share the results of tests with WHO
- Detailed information on batches rejected or recalled during the last three years



# Possible waiver of site visit: pre-conditions

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- Documented evidence that all dosage forms have been found to consistently meet specification - last 3 years
- Relevant plant(s) related to other products were visited by WHO with a satisfactory conclusion - last 2 years
- At least two inspection performed by the domestic functional regulatory authority and both ended with satisfactory conclusions— last 5 years
- Information provided on all batches rejected or recalled as well as on any serious GMP glitches and the corrective actions taken – last 2 years



# Seasonal vaccines prequalified before the 2009-2010 A(H1N1) pandemic

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**NONE**



# Pandemic chronology

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- April 2009: WHO received reports of **sustained human to human transmission** with a novel Influenza A (H1N1) virus in Mexico and USA followed by quick detection of the virus in human cases in three other continents
- 27 May 2009: Vaccine reassortants available
- 11 June 2009: WHO declaration of influenza pandemic caused by Influenza A(H1N1) - at the time of declaration nearly 30,000 confirmed cases have been reported to WHO from 74 countries
- 13 July 2009: WHO recommendation of the use of pandemic vaccines - target groups for vaccination recommended by SAGE
- 10 August 2010: WHO declaration of global shift to the post-pandemic period – the pandemic is officially over



# Expedited procedure for evaluating pandemic influenza vaccines (2009-2010)

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- It was a stratified procedure when **prior seasonal vaccine prequalification** from the same manufacturer had a **definitive accelerating effect** on the approval process versus companies submitting prequalification dossiers without such a seasonal vaccine pedigree
- Only vaccines licensed by functional National Regulatory Authorities (NRAs) were accepted for prequalification evaluation. The actual licensing authority for a particular vaccine is referred as the **responsible NRA of record**
- The expedited procedure was a complementary document to the general WHO guideline on "Regulatory Preparedness for Human Pandemic Influenza Vaccines"



# Vaccine technologies covered by the expedited pandemic influenza evaluating procedure

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## I. Inactivated products produced in either embryonated hen's eggs or in cell cultures

- Whole virion vaccines
- Split vaccines
- Subunit vaccines
- **Adjuvanted** whole virion, split or subunit vaccines

## II. Live attenuated influenza vaccines (LAIV)



# Expedited procedure for evaluating pandemic vaccines. Application classification: Category I

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- Seasonal influenza vaccine is prequalified
- Pandemic influenza A(H1N1) 2009 vaccine is licensed by NRA of record
- Only programmatic aspects were reviewed
- It was expected that the processing time was only 1 day from the time of reception of the dossier



# Expedited procedure for evaluating pandemic vaccines. Application classification: Category II

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- No prequalified seasonal vaccine pedigree
- Seasonal **and** pandemic vaccine licensed by NRA of record
- Other vaccine(s) from the same manufacturer is/are prequalified
- Review of NRA assessment report
- Review of NRA test results or independent testing of samples
- Site visit may be waived on the basis of available GMP inspection reports
- Review of programmatic aspects
- Processing time: 20 days from the time of reception of the dossier
- Processing time: 10 days from the time of reception of dossier (if site visit waived)



# Application classification: Category III/A

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- Seasonal vaccine has not been prequalified but the manufacturer **has experience** in influenza vaccine production
- Seasonal **and** pandemic vaccine licensed by NRA of record
- No other vaccines of the company is prequalified
- The NRA of record is fully functional according to WHO pre-set criteria
- Full assessment process to be conducted on fast track basis in consultation with the NRA of record and complemented with site visit
- Processing time: 20 days from the time of reception of the dossier



# Application classification: Category III/B

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- Seasonal vaccine is not prequalified and the company has **no prior experience** in influenza vaccine production
- Pandemic vaccine licensed by NRA of record
- No other vaccines of the manufacturer is prequalified
- The NRA of record is fully functional according to WHO pre-set criteria
- Full assessment process
- Processing time: 6 months from time of reception of documentation, excluding time taken by manufacturer to respond queries



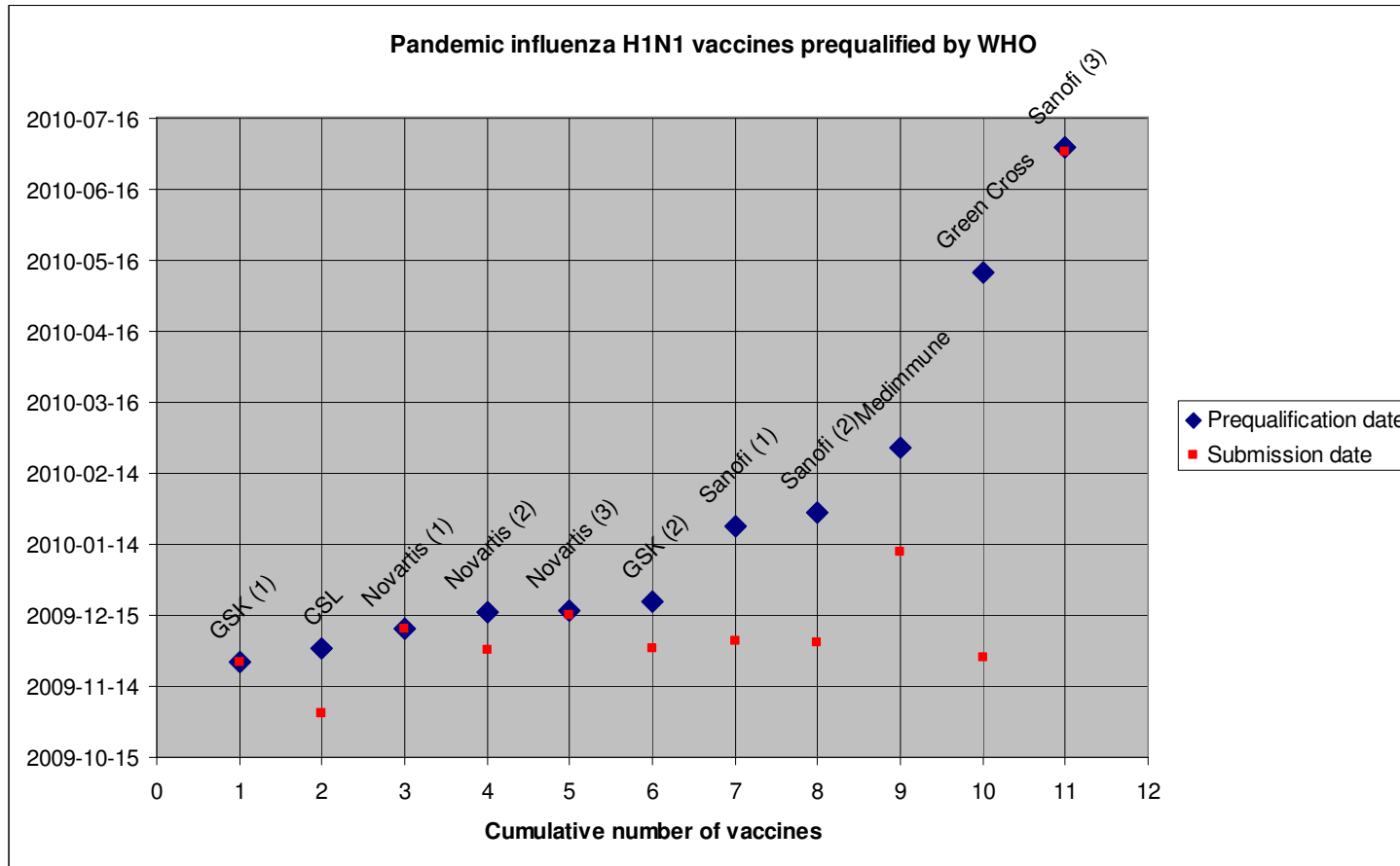
# Seasonal vaccines prequalified during the A(H1N1) pandemic

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- **FluLaval**; split virion, inactivated; GlaxoSmithKline Biologicals North America; produced in Canada  
Date of prequalification: **19 November 2009**
- **Fluvirin**; sub-unit, inactivated; Novartis Vaccines and Diagnostics; produced in the United Kingdom of Great Britain and Northern Ireland  
Date of prequalification: **19 December 2009**
- **Fluzone (2 dosage forms)**; split virion, inactivated; Sanofi Pasteur; produced in the USA  
Date of prequalification: **21 January 2010**



# Cumulative processing time chart of the 11 pandemic vaccines prequalified in 2009-2010



# Original list of WHO prequalified pandemic Influenza A(H1N1) 2009 vaccines-1

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## Egg based inactivated split vaccines

- Panvax (CSL Limited, Australia, 1. XII. 2009, TGA Australia)
- Panenza (Sanofi Pasteur France, 22. I. 2010, AFSSAP France)
- Influenza A (H1N1) 2009 monoval. vaccine (Sanofi Pasteur USA, 27. I. 2010, US FDA/CBER)
- Green Flu-S (Green Cross Corp., Korea, 11. V. 2010, Korean FDA)

## Egg based inactivated subunit vaccines

- Fluvirin-H1N1 (Novartis Vaccines and Diagnostics United Kingdom, 9. XII. 2009, US FDA/CBER)



# Original list of WHO prequalified pandemic Influenza A(H1N1) 2009 vaccines-2

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## Live attenuated vaccines

- Influenza A (H1N1) 2009 monoval. vaccine (MedImmune USA, 25. II. 2010, US FDA/CBER)

## Cell culture based adjuvanted vaccines

- Celtura (Novartis Germany, 17. XII. 2009, Paul Ehrlich Institute Germany)

## Egg based adjuvanted vaccines

- Arepanrix (GlaxoSmithKline Biologicals Canada, 19. XI. 2009, BGTD Canada)
- Focetria (Novartis Italy, 16. XII. 2009, EMA EC)
- Pandemrix (GlaxoSmithKline Biologicals Germany, 21. XII. 2009, EMA EC)
- Humenza (Sanofi Pasteur France, 5. VII. 2010, EMA EC)



# Reintroduction of seasonal vaccines into the prequalification process (2010- )

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- It temporally coincides with the development of the revision of the "Procedure for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies)" document
- The new document was endorsed by the Expert Committee on Biological standardisation (ECBS) in October 2010
- In May 2011 it will be considered by the WHO Executive Board. If accepted it could be implemented on 1 January 2012



# Goals of the revised procedure

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- Vaccines used in immunization programmes are safe and effective.
- Vaccine efficacy data and studies are relevant to the target population.
- Vaccines meet the specific needs of the programme, reflected by the tender specifications: i.e. potency, thermostability, presentation, labeling, shipping conditions, etc.



# Principles of the proposed evaluation procedure

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- Reliance on the National Regulatory Authority responsible for the regulatory oversight of the vaccine.
- Understanding of production process and quality control (QC) methods.
- Production consistency ensured through good manufacturing practices (GMP) compliance.
- Random testing for compliance with specifications.
- Monitoring of complaints from the field.



# Prerequisite for prequalification

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The National Regulatory Authority (NRA) responsible for the product is "functional" as per WHO assessments performed using indicators of the six functions established in the WHO NRA assessment programme



# The prequalification process

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- Review of general production process and quality control procedures
- Testing of consistency of lots
- WHO site audit to manufacturing facilities with observers from the relevant National Regulatory Authority



# Assurance of continued acceptability

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- Reassessments at regular intervals
- Targeted testing programme of lots supplied through UN agencies to monitor continued compliance with specifications
- Follow up of complaints from the field and reports of adverse events following immunization (AEFI)



# In summary

## the proposed revised procedure

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- Introduces increased reliance on collaboration with NRAs during evaluation and also in the post-prequalification period,
- Defines concretely the specifications for critical and desirable characteristics of vaccines from their suitability to developing country immunization programmes, and
- Incorporates numerous elements from the earlier discussed expedited procedures dealing with seasonal and pandemic influenza vaccine prequalification under the heavy challenges of an intense pre-pandemic period followed by an actual pandemic scenario full with surprises



# Conclusion

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- Influenza vaccine prequalification is ongoing as pending submissions are evaluated and new submissions are expected
- Influenza vaccines and the epidemiology of the disease differ significantly from other vaccines or epidemiologies. These differences clearly justified the special treatment of influenza vaccine submissions between 2006 and 2010
- Lessons learnt from the pandemic influenza vaccine prequalification process with its risk-based approach are largely incorporated into the new evaluation procedure proposed. This will make the 2012 integration of influenza vaccines into the main PQ procedure timely and, hopefully, smooth.

