Human H5N1 and Pandemic Vaccines
Practicalities of Production:
A perspective from Industry

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Pandemic Influenza Working Group
European Vaccine Manufacturers

4th Joint EC/ECDC/WHO Workshop on pandemic influenza preparedness

Luxemburg, 25-27 September 2007
Presentation outline

• Challenge and commitment of the vaccine industry in flu pandemic preparedness
• Practicalities of Influenza vaccine production (seasonal and pandemic)
• How to secure pandemic vaccine production
• Impact of R&D efforts and increase in production capacity on (pre-) pandemic vaccine supply
• Key priorities for industry and the international community
The challenge of pandemic preparedness

Deliver as much pandemic vaccine as quickly as possible after the pandemic has been declared

Timely

R & D
Regulatory

Develop prototype vaccines

Sufficient

Production

Adapt Flu vaccine production

A shared responsibility between industry, national and international health authorities, academia...

and a real political willingness
The vaccine industry is committed to pandemic preparedness

- Collaborate with governments and intergovernmental bodies to address preparedness issues (inc. allocation of pandemic vaccines and liability)
- Propose/support measures to increase global access to vaccines for humans
- Adapting and expanding manufacturing capacity in line with demand
- Ensure maximum production of pandemic vaccine in shortest timeframe
- Evaluating alternative/complementary vaccination strategies
- Develop and license safe and immunogenic pre-pandemic vaccines
Flu Pandemic Preparedness: Two Options

Two major challenges for effective vaccine
• How to get enough vaccine doses?
• How to induce protection as early as possible?

World-wide H5N1 Pandemic

Manufacturing before pandemic and stockpile

Pre-Pandemic Vaccine

Pandemic Vaccine

Vaccine Manufacturing during pandemic
Practicalities of seasonal influenza vaccine production

Each year: 2 new vaccines within a 6-month timeframe
Global seasonal Influenza Vaccine Production timelines

- **Egg supply organisation**

  - **Egg supply for production**
    - Seed lots
    - Monovalent batches

  - Filling
  - Blending

  - Pharmaceutical File

  - Clinical Trial

  - WHO meeting
    - D0 = mid Feb

  - Reagent availability
    - Mid May

  - July/August

- **Ref Member State Release**

- **Vaccine Delivery**

C. Gerdil: Bergen meeting 2-3 May, 2002
Egg-based Influenza Vaccine Production*

Embryonated eggs are stored for 10 to 12 days, constantly turned to ensure the healthy development of the embryos.

Courtesy: Solvay

* www.ifpma.org/influenza
Egg-based Influenza Vaccine Production

Left: After 2 to 3 day incubation, the allantoic fluid is harvested with an automated vacuum system.
Right: Zonal centrifuge for purification of influenza virus.
Courtesy: CSL Limited

* [www.ifpma.org/influenza](http://www.ifpma.org/influenza)
Cell-based Influenza Vaccine Production

Electron micrograph of influenza virus particles

Whole virus
Split virus
Subunit (surface antigen)
Live attenuated

Cell Culture Production Plant
Courtesy: Novartis Vaccines and Diagnostics

Fermenter 1
Cell Propagation
Fermenter 2
Cell Propagation
Fermenter 3
Cell propagation, High Cell Density
Fermenter 4
Virus Production

MDCK cell line grown in suspension culture
Copyright Novartis Behring GmbH & Co KG

* www.ifpma.org/influenza
Pandemic vaccine development

Use as much as possible current know-how to switch in a timely manner facilities to pandemic vaccine production.

Vaccines

- Inactivated vaccine
  - WVV
  - Split vaccine
  - Subunit vaccine

- Live attenuated vaccine

Production substrates

- Conventional eggs
  - SPF eggs

- Cells
  - MDCK
  - VERO
  - PerC6
  - EBx

Formulation

- Adjuvant
  - Extemporaneous
  - Ready to use formulations

Presentation

- Multidose presentation
- Vials
- Simplified packaging documentation
- Counterfeiting issues

Adapted from European Vaccine Manufacturers
<table>
<thead>
<tr>
<th>Company</th>
<th>Strains</th>
<th>Regulatory status</th>
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<tr>
<td><strong>GSK</strong></td>
<td>H9N2 &amp; H2N2</td>
<td>Submitted EMEA Dec. 05</td>
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<td>H5N1 (whole + alum)</td>
<td>EU Marketing Authorisation (March 07)</td>
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<td>Accepted by EMEA for review (Jan. 07)</td>
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<td><strong>Novartis</strong></td>
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<td>Submitted EMEA Jan 06</td>
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<td>Submitted EMEA (Nov. 06) Review ongoing. Assessments reports finalised</td>
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<td><strong>Pre-Pandemrix</strong></td>
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**MOCK-UP/PANDEMIC**

**PRE-PANDEMIC**
## Timelines for pandemic vaccine production*

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<th>Week</th>
<th>-12</th>
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<td>Reference centers</td>
<td>Declaration of pandemic by WHO</td>
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<td>Choice of the candidate strain for the production of the vaccine</td>
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- 6 months overall timeline from pandemic declaration to first supplies of pandemic vaccine
- 12 weeks between the arrival of the strain and the availability of the first doses, if reagents are available
- Reagents need to be available 7 weeks after arrival of the strain

* Timelines for pre-pandemic vaccine development are the same than those of seasonal flu vaccines
Factors influencing timelines and capability for pandemic vaccine production

- Availability timing of vaccine candidate strains & specific reagents +++
- RG strain manipulation permit* (GMO and biosafety, regulation, MTA ,…)
- Ability to convert easily production facility to pandemic vaccine production (validation by local authorities)
- Simplified data packaging documentation (flexible & universal availability of the vaccine)
- Streamline dose release process (collaboration with ONCLs)

* More critical for pre-pandemic vaccines
How to to secure pandemic vaccine production (1)

• Procedures for avian RG vaccine candidate production (WHO biosafety group lead )

• Adaptation of facilities and practices to produce avian strains in total compliance with appropriate bio-safety standards

• Produce different candidate strains at industrial scale to :
  – Understand the impact of such strains on current production processes and flows
  – Anticipate pandemic vaccine availability (simulation plans)

• Validate large scale production step (including F&P) to ensure delivery of a safe and consistent product
How to secure pandemic vaccine production (2)

- Anticipate any potential disruption in the pandemic production due to crisis situation: Business continuity planning*
- Secure production capability
  - Year-round egg supply with geographic diversity and security stocks
  - Critical raw materials (vials, stoppers and packaging documentation)
  - Human resource plans in crisis situation
  - Protection of sites, workers and products
- Production simulations to assess capability for pandemic vaccine (and other priority vaccines) production and supply

Seasonal influenza vaccine production and estimated capacity*

- Data from MIV Study Group: Vaccine 23: 5133-5144, 2005
- 2006/2007 production by IVS members (n=11)
- Potential 12 months full production by IVS members (n=10)**
- Estimated 2010 production capacity by IVS members

* IFPMA / IVS internal survey, April 2007
** 12 months continuous production, 7 days a week, 24 hours a day
The impact of dose-sparing strategies and extrapolated capacity of Flu Seasonal on global pandemic needs

Extrapolation of Flu Seasonal & Pandemic doses capacity*

<table>
<thead>
<tr>
<th>Year</th>
<th>SV (300)</th>
<th>FPC (SV)</th>
<th>PV</th>
<th>SV</th>
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<td>2007</td>
<td>565</td>
<td>6,780</td>
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<td>1,000</td>
<td>12,000**</td>
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<td>2010</td>
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</table>

- **SV**: Seasonal Vaccine
- **PV**: Pandemic Vaccine
- **FPC**: Full Production Capacity

- 3,75 µg/dose
- 15 µg/dose x 3

- Dose-sparing achievement
- Production capacity increase / pending vaccination coverage increase
- Distribution issues to be solved for pandemic

- * IVS survey April 2007
- ** Assuming same growth properties as seasonal vaccines
The potential impact of dose-sparing strategies and capacity of Flu Seasonal on global Flu pandemic needs

- Successful antigen-sparing strategies and adjuvant technology achieved by major manufacturers could potentially solve the pandemic supply issue and make pre-pandemic strategies a reality.

- Production capacity might no longer be an issue – but the 6 month production lead time is (and needs to be covered by pre-pandemic vaccines)

- **Three priorities**
  1. Stockpiling of pre-pandemic vaccine
  2. Procurement and distribution of pandemic vaccines
  3. Implementation of seasonal flu vaccination policies
Implementation of seasonal flu vaccination policies: Flu vaccination uptake in 11 EU countries*

1. Vaccination rates in the elderly (65 years+) do not meet WHO objectives in some countries

* Source: TNS survey 2006/7
Data in file
Implementation of seasonal flu vaccination policies: Flu vaccination uptake in 11 EU countries*

2. Vaccination of at risk <65 years is considerably lower than the elderly

- Vaccination Coverage Rate (%)

- ≥65 years
- < 65 years at risk

* Source: TNS survey 2006/7; Data in file
3. Coverage of healthcare workers is lower than other target groups

- ≥65 years
- < 65 years at risk
- Healthcare Workers

* Source: TNS survey 2006/7
Data in file
Implementation of seasonal flu vaccination policies: Three key drivers would improve vaccination uptake*

1. Pro-active behaviour of HCW

2. More education / communication on the disease and vaccine

3. Adequate funding of vaccine / vaccine administration

Sample size all countries: 3825
Sample size all countries: 2349
Source: TNS survey 2006/7. Data in file
Key priorities and challenges for the industry

• Complete development and licensing process
  – Define optimal formulations
  – Develop appropriate and standardised immunological tools and animal challenge models

• Address technical issues of the supply and logistics
  – filling and packaging (multidose vials)
  – Stability, storage, supply chain …

• Establish new vaccination strategies (pre-pandemic)
  – Vaccination schedules
  – Duration of the protection
  – Cross-reactivity/protection with new mutated strains
  – Booster with homologous and heterologous strains
Key priorities and challenges for Member States and International organisations

- Define allocation and procurement processes for all countries
- Consider a policy for use of H5N1 stockpile and pandemic vaccines
- Develop and/or strengthen critical health systems and infrastructure for vaccine delivery (inc. injection material)
- Ensure implementation of seasonal influenza vaccination policies (inc. forecast and evaluation)
- Support industry efforts
The way forward: Working in partnership
The potential impact of dose-sparing strategies and capacity of Flu Seasonal on global Flu pandemic needs

• Optimistic view
  – Successful antigen-sparing strategies achieved by major manufacturers could potentially solve the pandemic supply issue
    Antigen production capacity might no more be an issue

• Realistic view
  – Simple mathematical model to be consolidated (many remaining technical issues)
  – This will only be achieved if seasonal flu vaccine demand fits projected increase in seasonal flu production capacities

Two priorities
1. Implementation of seasonal flu vaccination policies
2. Procurement and distribution of vaccines