Influenza at the interface between humans and animals

Influenza A (H1N1)v: EMEA Status Report

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30 October 2009

Overview of presentation

- **Preparedness activities (2003-2009)**
- **Current activities (April to October 2009)**
- **Current situation - Vaccines**

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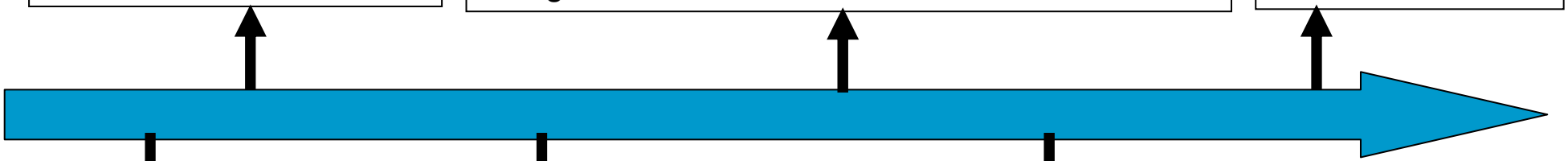
Highlights of pandemic preparedness activities since 2003

2004
- 2 CHMP Guidelines adopted introducing concept of a core pandemic dossier (mock up vaccine)

2006/7
- Assessor training on EMEA pandemic procedures & assessment issues
- CHMP recommendations on PV plan as part of the RMP of pandemic vaccines MAAs
- Registration of Focetria H5N1 MAA

2009
- Registration of Celvapan H5N1 MAA



2003
- Extensive pandemic preparatory work at EMEA, with industry, since 2003

2005/6
- EMEA publishes EMEA pandemic plan

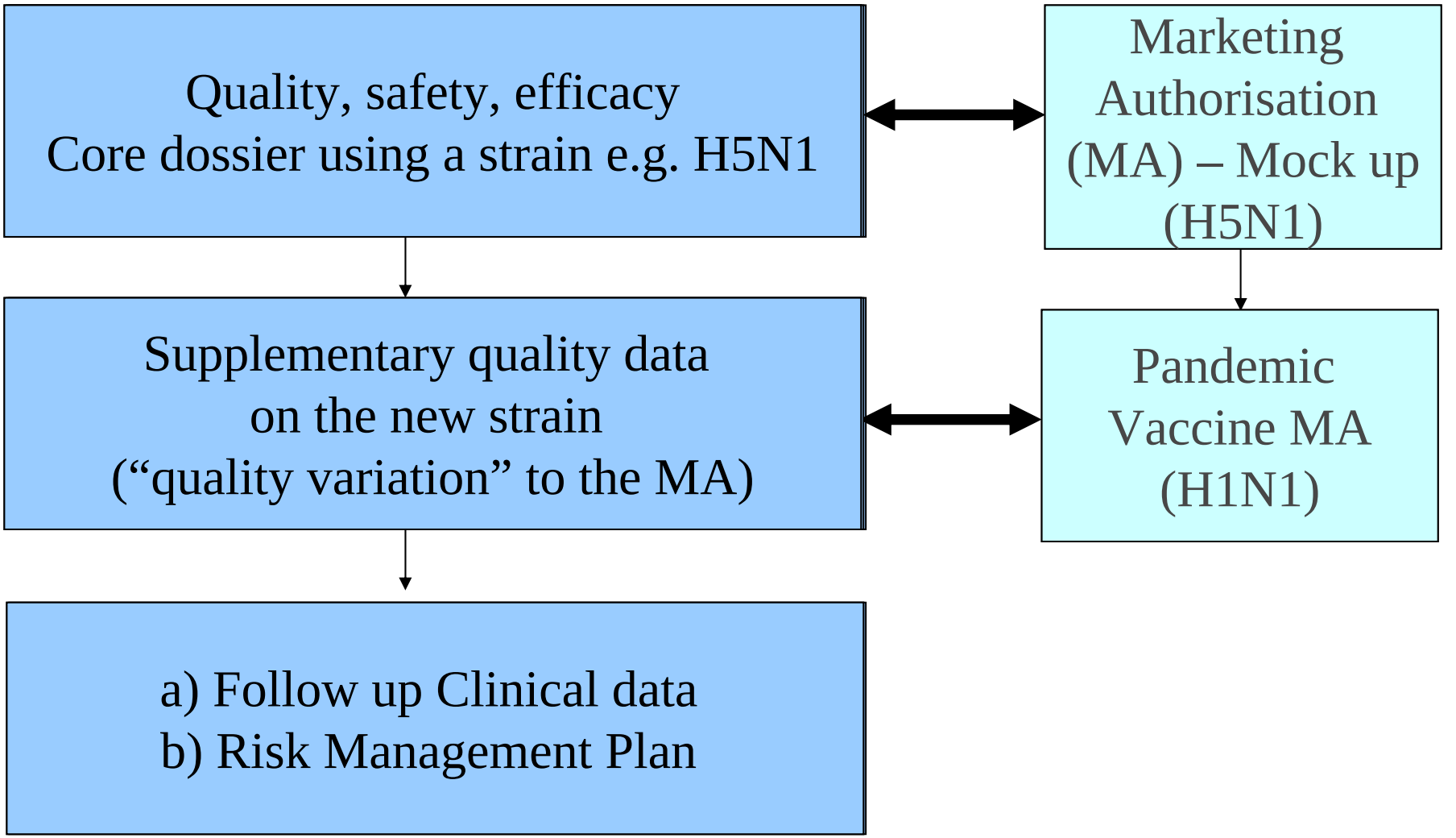
2007/8
- Update of antiviral review by CHMP
- EMEA Pandemic communications plan & presentation to SANCO & ECDC
- EMEA Pandemic business continuity planning and exercise
-Joint EMEA–NCA BCP pandemic workshop
- Registration of Pandemrix H5N1 MAA

What is a Mock-Up Pandemic Vaccines?

- **Mock-up vaccine is a vaccine containing viral antigen(s) to which humans are immunologically naïve, e.g. H9N2 / H5N1.**

- **Scientific data with a mock-up vaccine are relevant for the pandemic vaccine:**
  - » Manufacturing and quality data
  - » Clinical experience in naïve population
  - » Evaluation of novel concepts prior to a pandemic e.g. use of adjuvants with the objective of increasing available doses, establishment of dosing schedule

Mock up strategy



Mock-Up Pandemic Vaccines

Product name	Adjuvanted/ non-adjuvanted	MAH
FOCETRIA	**Adjuvanted with MF59**	**Novartis Vaccines and Diagnostics S.r.l** **MAA approved on 2nd May 2007**
PANDEMRIX	**Adjuvanted with AS03**	**GlaxoSmithKline Biologicals SA** **MAA approved on 20th May 2008**
CELVAPAN	**Not Adjuvanted**	**Baxter AG** **MAA approved on 4th March 2009**

What has been done by the EMEA?

- **In order to get approval of pandemic vaccines as soon as possible after an outbreak of pandemic:**
  - » Strategy was to update the 3 mock-up MAs (based on H5N1 data), which had already been approved with data on new virus strain A (H1N1)v
  - » 3 vaccines: Focetria (Novartis), Pandemrix (GSK Biologicals) and Celvapan (Baxter)

- **Follow-up of pandemic vaccines / antivirals once approved**

- **Clear Communications on issues within remit of EMEA**

Overview of presentation

- Preparedness activities (2003-2009)
- **Current activities (April to October 2009)**
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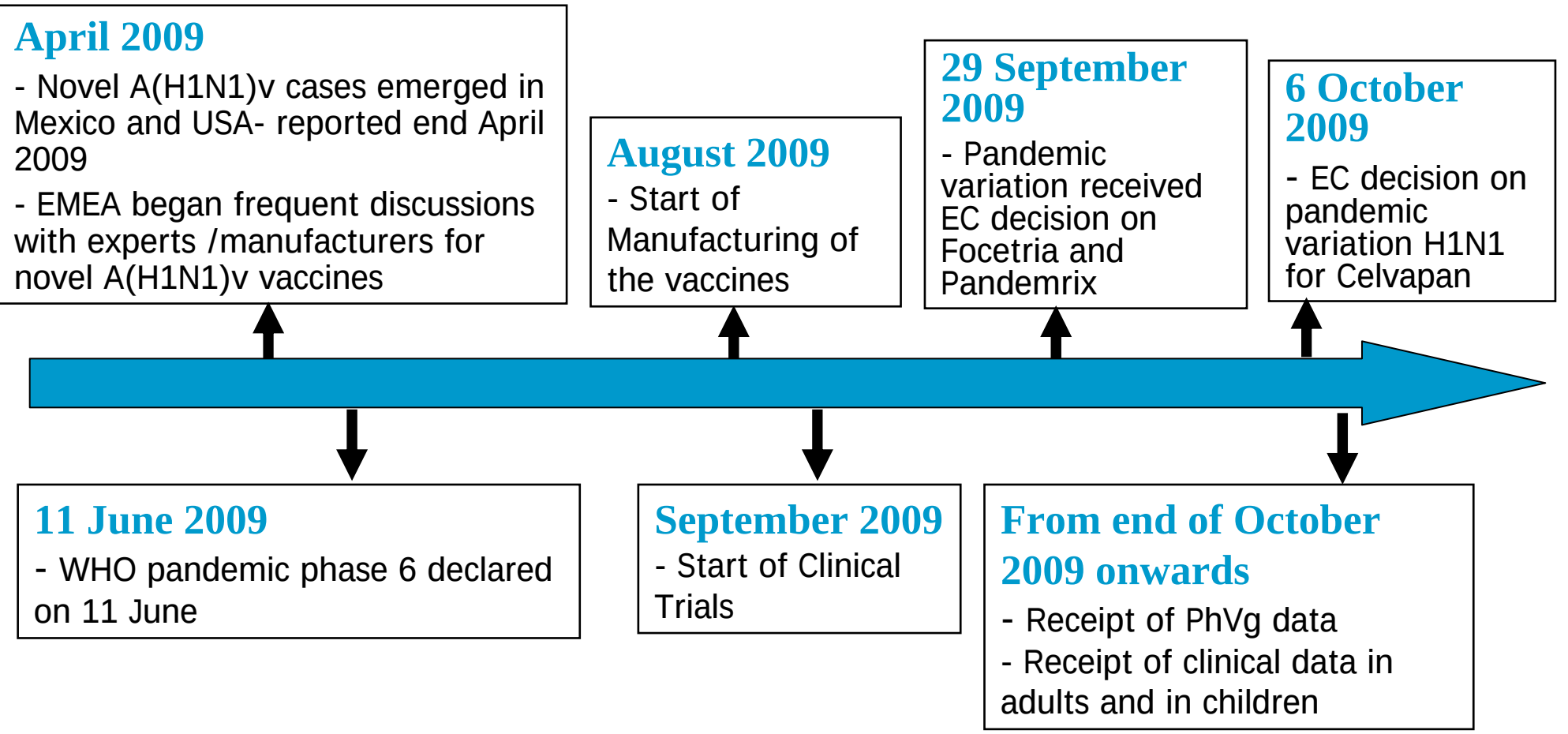
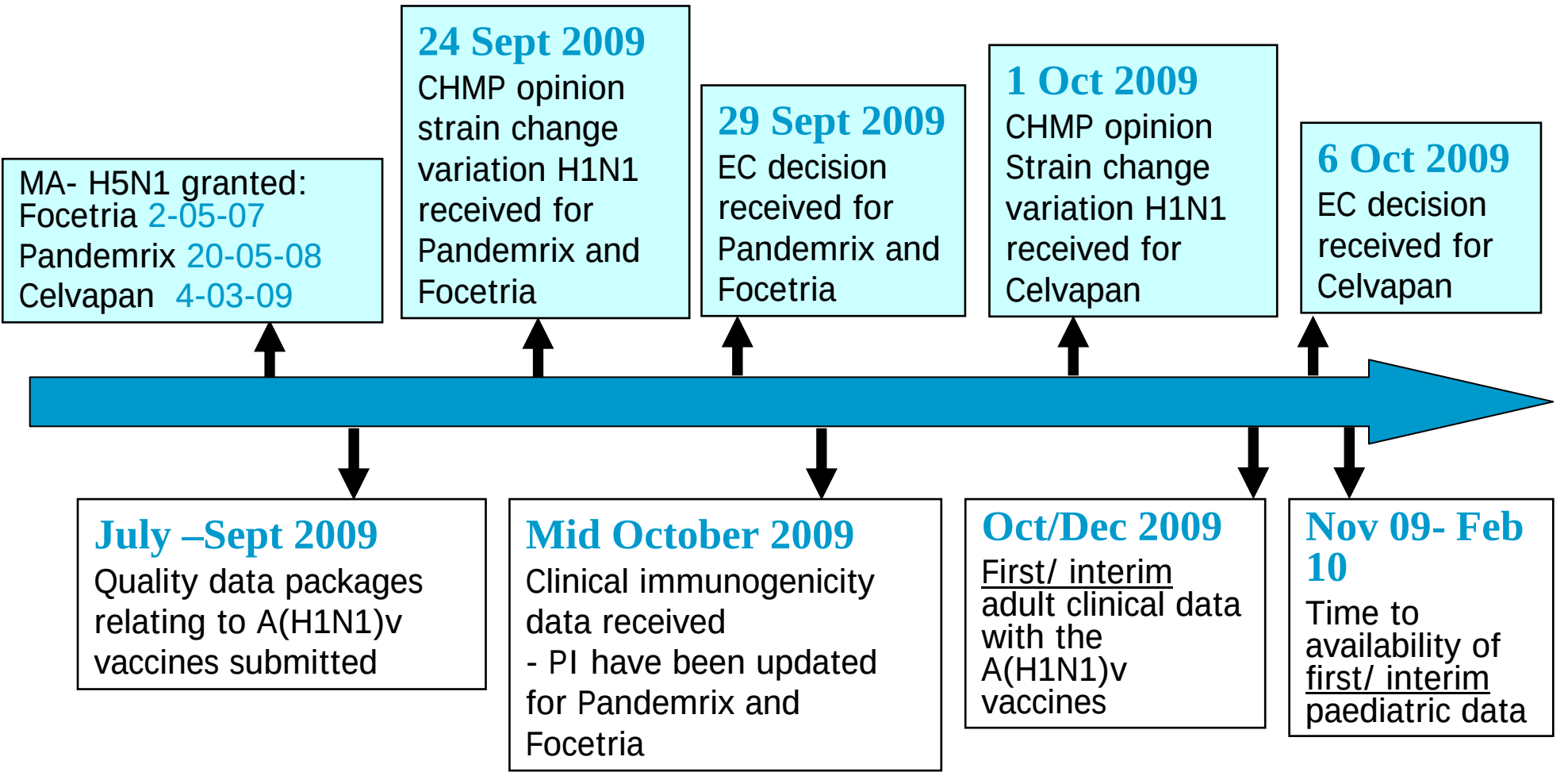
Highlights of pandemic activities since April 2009



What has been done by the EMEA to achieve approval of pandemic vaccines?

- Regular strategy meetings
- EMEA meetings with companies
- Participation in Health Security Committee meetings (DG SANCO)
- Participation in ongoing Ad hoc task-force meetings on vaccine development and vaccination strategy (SANCO-ENTR-EMEA-ECDC)
- International discussions – teleconferences with WHO and interactions with FDA/Health Canada/Japan /TGA

Timelines to availability of data for mock-up vaccines



Product Information - Vaccines

- **Clinical Indication: Prophylaxis of influenza in an officially declared pandemic situation.**
- **Data for mock up MAs are available in adults (18-60 years) and the elderly (>60), and, in some cases, also in children.**
- **The Product Information does not preclude the use of these vaccines in any age group or special population group. There is a clear statement that these vaccines should be used in accordance with official guidance. Benefit-risk were evaluated by CHMP for each age group.**
- **Thus, they allow national authorities to use these vaccines in population groups for which there are no data, if they perceive that there is a need to do so. For example:**
  - Young children
  - Very elderly (> 80 years)
  - Pregnant Women

Post Authorisation - Product Risk Management Plan

- **Stringent post-marketing surveillance commitments are in place for all mock ups in their Risk Management Plan as follows:**
  - For each vaccine, the company will perform a post-marketing study on 9,000 patients across all age groups, recruited at the start of the vaccination campaign.
  - Each company will provide every month a report (simplified Periodic Safety Update Report [PSUR]) on all adverse reports notified by patients and HCPs.
  - Adverse events as well as adverse events of special interest (e.g. neurological disorders) that have been identified based on experience with similar vaccines will be specifically monitored for the pandemic vaccines together with other adverse events.
  - Special population groups, such as pregnant women, children and immuno-compromised subjects will be specifically monitored in the post-marketing study, using existing or newly established registries and networks of healthcare professionals.

Post Authorisation -Product Risk Management Plan

- **Extensive amounts of safety and efficacy data are / will be received in a very short space of time after the initial authorisation of the pandemic strain change variation.**
  - » Therefore, patients will need to have access to the very latest information updates and HCPs will receive information to reinforce traceability of the products and stimulate adverse event reporting.

- **The use in larger vaccination campaigns will facilitate detection of rare vaccine associated adverse events**

- **The effectiveness of use in the field is monitored in accordance with protocols developed by the ECDC**

Clinical data review

- Clinical immunogenicity data for Celvapan, Focetria and Pandemrix was received in October
- Following review of the data, the CHMP maintained its recommendations adopted in September: the 3 vaccines should preferably be used as 2 doses, at least 3 weeks apart
- However, for Pandemrix and Focetria, the limited data currently available indicate that 1 dose may be sufficient in adults.
- A 1 dose schedule may be used in healthy adults and consideration can be given to using the same schedule in children and adolescents (> 10 years old)
- This recommendation, which already applied to Pandemrix, can now also be applied to Focetria. The data for Celvapan are still insufficient for the CHMP to modify its previous position.

Clinical data review

- **For Pandemrix:**
  - The additional data with the H1N1 vaccine confirmed the recommendation made in September.
  - The vaccine should preferably be used as a 2-dose schedule, but 1 dose may be sufficient in adults 18- 60 and consideration can be given to using the same 1 dose schedule in children and adolescents (> 10 years old).
  - The immunogenicity results show that 1 dose of Pandemrix brought about an appropriate level of protection

- **For Focetria:**
  - The data are sufficient to conclude that the vaccine should preferably be used as a 2-dose schedule, but 1 dose may be sufficient in adults 18-60. This is based on immunogenicity results in healthy adults 3 weeks after vaccination that satisfied all of the CHMP's criteria
  - Consideration can be given to using the same 1 dose schedule in children and adolescents (> 9 years old).

- **For Celvapan:**
  - While the CHMP awaits further data, the dosage schedule remains as 2 doses, with a 3 week interval, in all populations.

Overview of presentation

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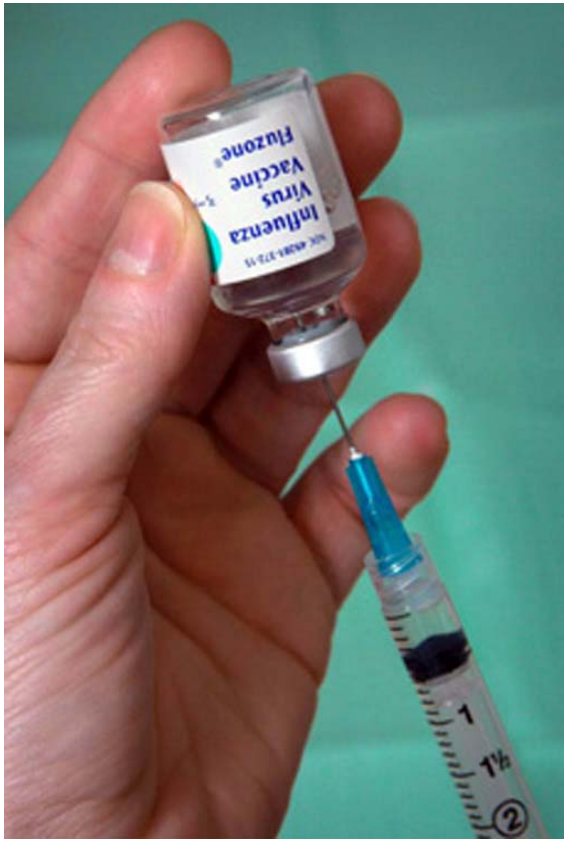
Concluding Remarks - 1

- **3 vaccines for H1N1 pandemic influenza have received an EC Decision:**
  - » Focetria (Novartis) on 29-10-09
  - » Pandemrix (GSK Biologicals) on 29-10-09
  - » Celvapan (Baxter) on 06-10-09

- **EMEA has worked closely with companies and other stakeholders (e.g. DG Sanco, DG Enterprise, WHO, etc…) to achieve the expedited and in-depth assessment of the vaccines**

- **EMEA has put in place post-marketing commitments to monitor the use of the vaccines**

- **EMEA has ensured full transparency of the regulatory review process and outcomes to facilitate Member States' decision making.**



Concluding Remarks – 2 – Pandemic vaccines activities are not over!

- **Further Clinical and PhVg data are, and will, be received for the mock up vaccines**

- **Two emergency procedures are on going:**
  - » Arepanrix (split virion, inactivated, adjuvanted with AS03- 3.75 μg per dose)

  - » Humenza (split inactivated H1N1 with oil-in water adjuvant (AF03): 6ml multidose 0.5ml dose contains 11.3 mcg thiomersal excipient)

Concluding Remarks – 3 – Emergency Procedure MAAs

- **Manufacturers who do not have a mock up MA, are still able to use an alternative regulatory route for authorisation of their pandemic vaccine, i.e. emergency procedure.**
- **These vaccines are still eligible for the EMEA rolling review process in order to obtain rapid feedback to the respective companies on the data as it becomes available.**
- **Quality, safety and efficacy data packages will be required for these products.**
- **Procedures from two companies are currently on going**
- **Submission of applications for non-adjuvanted vaccines are currently being investigated (discussions are on going with the company),**
- **CHMP opinions for Arepanrix and Humenza are expected by the end of the year provided data are satisfactory**

Thank you for your attention

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More info

http://www.emea.europa.eu

Pandemic website

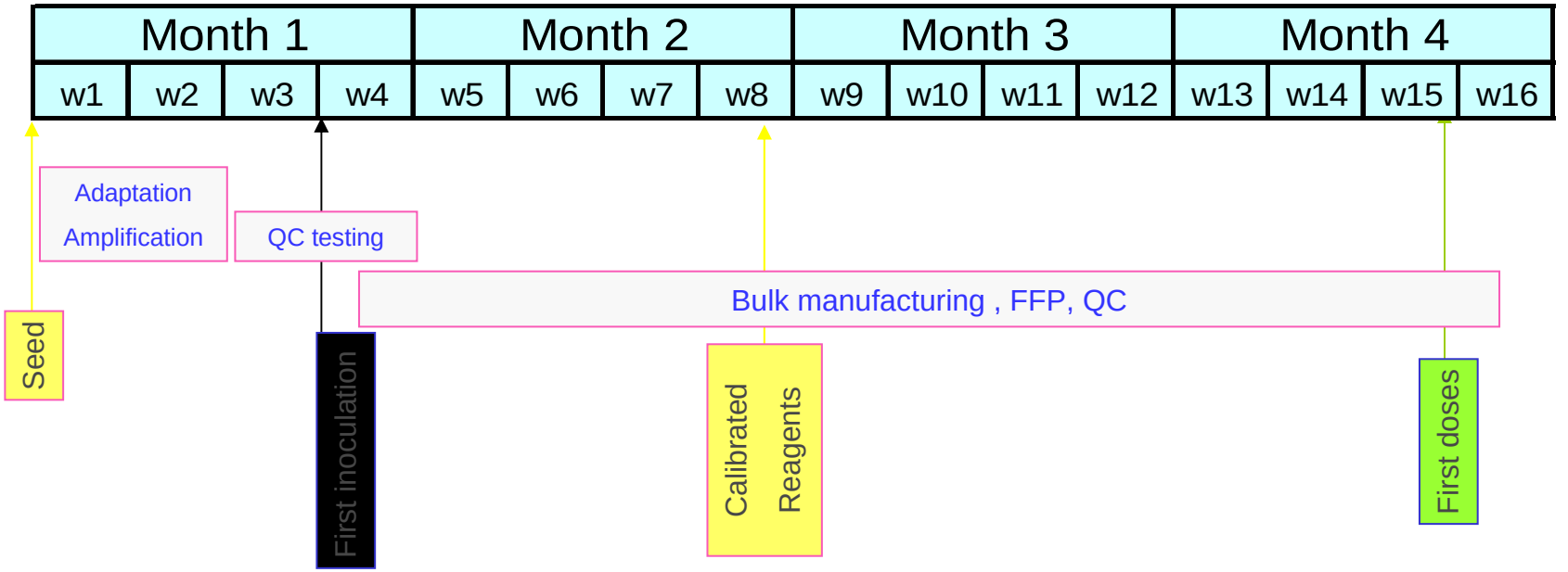
http://www.emea.europa.eu/htms/human/pandemicinfluenza/background.htm


Thank you for your attention

BACK UP SLIDES

Timelines for manufacture of pandemic vaccine

- Assumptions:
  - » **Attenuated strain – Delivery on time**
  - » **Assuming appropriate reagents received on time**



Seed and reagents provided by WHO reference centers

- » **First doses should be issued within the 4th month from the availability of the seed from WHO ref centers**

What is an adjuvant and what is it used for?

- **A vaccine adjuvant in the pandemic vaccine is a component that potentiates the immune responses to the virus antigen**

- **Examples of adjuvants include:**
  - mineral salts, e.g., aluminium hydroxide
  - Oil emulsions such as MF59 (used in Focetria) and ASO3 (used in Pandemrix)

More detailed information on composition of Mock-Up Vaccines

Product name	Comment	Applicant
DARONRIX	**H5N1 whole virus inactivated antigen** **15 μg per dose** **Alum adjuvanted**	**GSK Biologicals SA** **GSK will not use this since it will focus resources on its second generation (improved) product, Pandemrix**
FOCETRIA	**H5N1 virus surface inactivated antigen adjuvanted with MF59** **7.5 μg per dose** ***> Variation expected to the original MA to include H1N1 strain***	**Novartis Vaccines and Diagnostics S.r.l**
PANDEMRIX	**H5N1 split virion, inactivated, adjuvanted with AS03** **3.75 μg per dose** **Variation needed to include H1N1 strain** ***> Variation expected to the original MA to include H1N1 strain***	**GlaxoSmithKline Biologicals SA**
CELVAPAN	**H5N1 whole virion, Vero cell derived, inactivated** **7.5 micrograms per dose non adjuvanted** ***> Variation expected to the original MA to include H1N1 strain***	**Baxter AG**

Pandemic influenza A (H1N1) 2009

Tamiflu (oseltamivir)

&

Relenza (zanamivir)

What has been done as of October 2009 (1)

- **30 April 2009: The EMEA initiated an Article 5(3) procedure to provide recommendations for Tamiflu and Relenza.**

- **The CHMP adopted the following recommendations in May 2009:**
  - during an officially declared influenza A/H1N1 pandemic the benefits of the use of Tamiflu outweigh its risks in the treatment of children under the age of one year.
    - The recommended dosage for treatment is 2 to 3 mg per kg body weight twice daily.
    - The recommended dosage for prophylaxis is 2 to 3mg per kg body weight once daily and should not exceed 10 days.
  - the benefits of using Tamiflu and Relenza in pregnant or breastfeeding women outweigh the risks in case of an Influenza A/H1N1 pandemic.
  - hospitalisation of children below 1 year of age in case of an Influenza A/H1N1 pandemic, including the children below 3 months of age, is recommended by the CHMP. However it should follow recommendations from Member States depending on the local situation.
  - Tamiflu capsules that are already on the market may be used for up to two more years after their current five-year expiry date during a declared pandemic.

What has been done as of October 2009 (2)

- **May 2009: Extension of shelf life of Tamiflu capsules and Relenza from 5 to 7 years.**

- **Bi-weekly Pandemic Safety Reports (PSR) for Tamiflu started 1st of May 2009 are assessed every 2 weeks by the CHMP. The 3rd PSR covering from 1 to 15 June 2009 is currently under review.**

- **The European Pharmacovigilance strategy for antivirals in case of pandemic influenza agreed by the PhVWP and the CHMP in 2006 will be revised according to practical experience.**

  - The MAH has submitted an updated risk management plan (RMP) taking into account the extension of the indication to children between 6 and 12 months of age in case of pandemic influenza. This RMP is currently under review.

What has been done as of October 2009 (3)

- Tamiflu Product Information has been updated with information on pregnancy, lactation and dosage recommendations for children below 1 year of age.
- The CHMP agreed to have a recommended dose of 3mg/kg for treatment of children aged between 6 and 12 months during a pandemic influenza in the Product Information.
- In September, the CHMP has updated the Product information to provide more information on the use of Tamiflu in the treatment of influenza in children < 6 months and in post-exposure prevention of influenza in children < 1 year year during a pandemic influenza outbreak
- The CHMP also recommended the approval of detailed instructions on the preparation and dosing of 'extemporaneous' formulations for children < 1.