EMA revised guidelines applicable to pandemic vaccines.
Table of contents

• Regulatory pathways for pandemic vaccines  
  *(Regulatory module of the influenza guideline)*

• Scientific requirements  
  *(Clinical module of the influenza guideline)*

• Summary of the existing pandemic vaccines
EMA guideline on influenza

- Revision of the regulatory framework and scientific requirements for influenza vaccines
- Include the lessons learnt exercise post-2009 exercise
- 3 integrated Modules
  - Regulatory and procedural requirements
  - Quality requirements
  - Non-clinical / clinical requirements
Validation of the model for a Pandemic Preparedness Vaccine

- **Problem statement:**
  - Emergency + unpredictability: lack of time to generate data
  - Anticipate by investigating pandemic scenario and has already a vaccine authorised
  - Pre-assess data (adjuvant,...)

- **Regulatory Module**
  - Confirmation of the approach - Allowed accelerating authorisation of the pandemic strain vs. other procedures
  - Emphasis on the possibility to use different strains to support the potential pandemic strain
Offering a wide range of regulatory pathways to authorise a pandemic vaccine

- **Problem statement:**
  - Mass vaccination -> availability
  - Different types of vaccines / different types of technology / different strategies from manufacturers

- **Regulatory Module**
  - Prioritisation of the Pandemic Preparedness Vaccine
  - Other routes of authorisation possible if needed
    -> wide range of options to engage with all manufacturers and cover max of situations
Pandemic preparedness strategy – Centralised procedure

INTERPANDEMIC PERIOD

- ‘Pandemic preparedness’ vaccine
  - a MA granted in advance of a pandemic containing a potential pandemic strain
  - To save time, better prepare pandemic and avoid confusion

**Pandemic declaration**
(actual pandemic strain identified)

PANDEMIC PERIOD

- Seasonal vaccine
  - Back-up plan if no pandemic preparedness vaccine
  - Platform has to be similar

- Pre-pandemic (zoonotic) vaccine
  - intended to be used to immunise against a zoonotic strain
  - Use is independent of a Pandemic.

- Pandemic vaccines
  (based on existing MA)
  - Waivers of some requirements as laid down in art.21

- Pandemic vaccines
  (based on new MA)
  - ‘Emergency’ Procedure
  - Back-up plan if no pandemic preparedness vaccine
Others changes to streamline regulatory activities

- Streamlining the initiation of the pandemic activities and the switch from pandemic to seasonal settings
- Streamlining the post-authorisation modifications to the MA (e.g. prioritisation depending on the urgency of the change, several Opinions combined in one Decision, USR may be used depending on the urgency of the situation)
- Implementation of exemptions for labelling (article 63(1) and (3) of Directive 2001/83/EC)
Table of contents

- Regulatory pathways for pandemic vaccines  
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  *(Clinical module of the influenza guideline)*

- Summary of the existing pandemic vaccines
Mock-up vaccines for pandemic influenza

**Principles for data requirements for authorisation**

- “CORE DOSSIER” provides safety/immunogenicity data for a vaccine construct containing a potential pandemic strain (poorly immunogenic strain - majority of humans immunologically naïve, e.g. H5N1) to allow for identification of a dose regimen that is likely suitable should the next pandemic be due to such a strain (worst case scenario).

- Manufacturing, antigen content, adj and adj/antigen, route of admin → same as pandemic vaccine
- Data to be generated at least in healthy adults >18 years (no major ethical limitations – acceptable risk in an interpandemic period for an investigational product).
2009 H1N1 pandemic (11 June 2009)

Mock up vaccines H5N1

**GSK**
- Adjupanrix (split, Dresden, 2008)
- Daronrix (whole virion, 2007)

**BAXTER**
- Pandemic vaccine Baxter (whole virion, 2008)

**NOVARTIS**
- Foclivia (subunit, 2007)

Pandemic vaccines H1N1

**GSK**
- Pandemrix (CHMP OP 24 Sept 09)

**BAXTER**
- Celvapan (CHMP OP 01 Oct 2009)

**NOVARTIS**
- Focetria (CHMP OP 24 Sept 2009)

**Pandemic Vaccines via emergency procedure**

**SANOFI**
- Humenza (H1N1 split) → CHMP OP February 2010
  Data submitted in a rolling review fashion since June 2009

**GSK**
- Arepanrix (H1N1, split, Quebec) → CHMP OP January 2010
  Data submitted in a rolling review fashion since July 2009

MA: Marketing Authorisation
Mock up vaccines H5N1

GSK

• Adjupanrix (split, Dresden, 2008) • yes

• Pumarix (split, Quebec, 2011)  ---

• Daronrix (whole virion, 2007)  ---

BAXTER

• Pandemic vaccine Baxter (whole virion) • yes

NOVARTIS

• Foclivia (subunit) • yes

Pandemic Vaccines HxNx

MA duplication & variation

MA via emergency procedure

SANOFI

• Humenza (H1N1) ➔ withdrawn 2010

GSK

• Arepanrix (H1N1) ➔ withdrawn 2010

Pandemic Vaccines H1N1(09)

• Focetria

• Celvapan

• Pandemrix

MA: Marketing Authorisation
Future pandemic preparedness vaccines and new requirements for authorisation

New guideline for influenza vaccines

• Public consultation closed (July 2014 - end of January 2015)
• Currently under revision based on comments received
• Approx date of publication of the final document: end of 2015
• Entry into force: TBC – approx 6 months after publication

• Changes to improve clarity: covering all flu vaccines and all epidemiological scenarios in one document; modular structure: 1) Quality; 2) Non-clinical and Clinical; 3) Regulatory/procedural

• Changes to improve evaluation of future vaccines: revised requirements based on current knowledge and past experience
Pandemic preparedness vaccines (former mock-up vaccines)

MAA - Requirements for authorisation

• Target population: data from healthy adults >18 years; recommended: at least some data from subjects >60 years. **NEW**
• As far as may be possible, data should be obtained also from other age and population groups, particularly healthy children. **NEW**

• The total size of the safety population should consist of at least 3000 individuals (for rare AEs - as for any influenza vaccine) – follow up 6m. **NEW**

• An adequate subset of the safety population is tested for immunogenicity.

• Existing data for the same construct with other pandemic/zoonotic/seasonal strains should be submitted – investigate two or more strains strongly recommended. **NEW**
Pandemic preparedness vaccines

Data to be generated post-authorisation

• Study in immunocompromised, elderly and frail (e.g. need for booster dose?) → RMP (interpandemic period)
• Vaccine effectiveness and safety will be evaluated during the pandemic → RMP. Such data should be collected in populations that were and were not included in the studies in the core dossier (e.g. pregnant women – via registries).
• Large scale safety data are expected from field use to assess rates of local and systemic reactions immediate post-vaccination, and specific (very) rare AEs
• Plans for enhanced safety surveillance to be performed during the pandemic period (real time collection of data within a month from start of vaccination).

NEW (to be further discussed)
• Accumulation and sharing of immunogenicity/safety/efficacy data (rapid sharing, rapid review: implications for dosing and future strategies)
Requirements for applications to change vaccine composition
(pandemic strain change variation)

• it may include quality data only -- recommended that some clinical data indicative of the likely immunogenicity of the pandemic strain are included in the strain change variation dossier. NEW
• Immunogenicity/protection studies in animals could be supportive if human data not available. LAIV: only protection studies relevant.

• Immune data in all age group and in risk groups required as specific obligations to the MA, to be submitted within specified timelines.

• At this time the RMP plans for estimating vaccine effectiveness/safety should be activated and results should be reported in the pre-agreed timeframes.
Live attenuated Pandemic preparedness vaccines NEW

MAA- Requirements for authorisation

• Similar principles as for inactivated vaccines apply
• Immunogenicity could be measured after a dose of inactivated non-adj vaccines (same strain) given after 1 dose of LAIV (booster effect)
• Any other data generated with seasonal or other strains should be submitted

Pandemic vaccines via Emergency procedure

MAA- Requirements for authorisation

• Dataset required to be discussed on case by case based on the knowledge of the construct
• Novel vaccine: more data than a well known vaccine
• Contact reg authorities ASAP
An important change in the evaluation of future influenza vaccines

Correlates of protections (inactivated HA vaccines)

So far:

- HI titre 1:40 represented a reasonable CoP for efficacy of 50-70% against influenza
- Since 1970s, evidence indicates need to better define CoPs, may vary according to e.g. specific age group or vaccine type

NEW recommendations:

- Efforts in development encouraged to support identification of CoPs
- Immunity against HA: HI/SRH and VN; HI titre 1:40 no longer sufficient for approval, distribution of titres across population and % of vaccinees above specified cut off levels; GMTs, SC, pre/post-vacc comparisons;
- Broader investigation of immune responses by measure of anti-NA and CMI, especially in elderly;
- **Pandemic**: % achieving predefined justified antibody threshold levels, plus additional analysis to evaluate titres distribution across population, including potential of vaccine to cross-protect against similar viruses.
Zoonotic influenza vaccines (former pre-pandemic vaccines)

Principles for data requirements for authorisation

• intended for immunisation in outbreaks of zoonotic influenza viruses with pandemic potential, including use in specific groups like veterinarians or laboratory personnel and when there is anticipation of a possible pandemic due to the same or a similar strain → different benefit/risk evaluation to pandemic vaccines

• The dossier should include strain-specific and population-specific data, which will form the indication → different to the pandemic preparedness vaccine for which the indication is open to the whole population.

• Authorised vaccines (H5N1): Aflunov (subunit), Vepacel (whole virion), Prepandrix (split)
Zoonotic influenza vaccines

MAA - Requirements for authorisation

• Immune responses to the vaccine should be fully characterised within each age/risk group for which an indication is sought (including preferably data on antibody persistence and responses to booster doses, if not pre: RMP).

• Safety → at least 3000 individuals and age stratification is based on the indication sought.

• Post-authorisation: if used in zoonotic outbreak, data should be gathered from field use (RMP).
Seasonal Vaccines to immunise against seasonal strains

Zoonotic Vaccines intended to be used to immunise against a zoonotic strain. Use is independent of a Pandemic.

Pandemic Preparedness Vaccine
a MA granted in advance of a pandemic containing a potential pandemic strain

Pandemic Declaration
Pandemic variation submitted to introduce the actual pandemic strain

Pandemic vaccine

Pandemic vaccine
(new MAA applied for during a pandemic)
BACK UP plan
Emergency Procedure

Conclusions

- Pandemic Preparedness Vaccines (PPVs) are so far the best tool to prepare for a pandemic in advance
- 3 PPVs authorised; one procedure ongoing
- PPVs are not ‘empty’ virtual files; dossiers are authorised based on adequate amounts of data to allow for posology and safety recommendations
- New guideline aims at improving evaluation of future influenza vaccines, including PPVs
Thank you for your attention

Further information

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Link to revised influenza guideline:

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Glossary

- LAIV: live attenuate influenza vaccine
- TBC: to be confirmed
- AEs: adverse events
- RMP: Risk Management Plan
- MA: Marketing Authorisation
- MAA: Marketing Authorisation Application
- HA: Haemagglutinin
- HI: Haemagglutinin Inhibition assay
- SRH: single-radial-haemolysis assay
- VN: virus neutralisation assay
- GMTs: geometric mean titres
- SC: seroconversion
- NA: neuraminidase
- CMI: cell-mediated immunity