

## **Influenza Pandemic Preparedness**

### **EVM Proposal for an Action Plan to ensure availability of effective vaccines in the event of an influenza pandemic (May 2006)**

In order to ensure adequate and timely supply of vaccines to protect against an influenza pandemic, the European vaccine industry issued in March 2004 a report intended to provide concrete proposals for building a long-term commitment between European Vaccine Manufacturers (EVM\*) members and Member States with the support of the European Commission ([http://www.evm-vaccines.org/pdfs/evm\\_pap.pdf](http://www.evm-vaccines.org/pdfs/evm_pap.pdf)).

Since then, progress has been made in managing some of these issues. Others still need to be addressed. This revised version of the EVM proposal re-states the key requirements of the Action Plan and reflects the developments that have taken place since publication of the first document.

In the view of the EVM, planning for a pandemic threat relies on three main pillars:

1. R&D activities
2. Vaccine production and supply
3. Alternative/complementary vaccination strategies

Additional aspects such as allocation of pandemic vaccines and liability should also be jointly addressed with the Commission and Member States.

#### **1. Strengthen R&D activities**

The development of prototype influenza pandemic vaccines is a fundamental step in influenza pandemic preparedness. It is aimed at shortening the lead-time for regulatory approval of the pandemic vaccines. The EMEA issued in March 2004 guidelines on submission of marketing authorization applications and dossier structure and content for pandemic influenza vaccine. EMEA has agreed to waive the registration fees of the prototype pandemic vaccine files to support the development of such vaccines.

The vaccine industry has undertaken an intensive research effort to develop prototype pandemic vaccines. These vaccines are based on avian strains and the development of specific monovalent formulations, which have to undergo clinical testing before approval. Part of these efforts includes the adaptation of manufacturing facilities to produce pandemic prototype vaccines.

The EVM members are currently engaged in the development of 12 prototype vaccines covering a range of potential pandemic strains and using different technologies and formulations (ref EVM website). As of April 2006, two mock-up

dossiers have been submitted to EMEA and others will follow during the course of the year.

It is important to point out that in Europe R&D efforts are currently performed directly by individual companies. This is in contrast to government support provided in the USA, Japan, Australia and Canada.

In addition to achieving these short-term objectives based on existing know how, other medium and long-term R&D activities are ongoing to develop novel approaches to further improve the efficacy and supply of pandemic vaccines.

Whilst industry is focusing its activities on the development and production of pandemic vaccines, the EVM considers that public health authorities should contribute to activities for which they have expertise and competencies, such as:

- to develop standardised immunological methods for evaluation of pandemic vaccines;
- to explore alternative vaccination strategies, as described in section 3;
- to fund research into, and evaluation of new influenza pandemic vaccines concepts.

## **2. Adapt and prepare production of pandemic vaccines**

Pandemic vaccines will be manufactured in facilities dedicated to seasonal flu vaccine manufacture, so the current capacity for seasonal flu vaccines is an important determinant of pandemic vaccine capacity. Thus, not only is there an immediate health benefit from encouraging broader seasonal vaccination coverage, but over time the global capacity to produce pandemic vaccines will increase as well. In this respect, the EVM supports the WHO coverage objective of 75% of people at risk by 2010, which has also been endorsed by the European Commission and Member States.

Some Member States are already increasing vaccination coverage to reach the WHO objective. Since it takes 3 to 5 years to build and validate a new production site, and it may not be financially viable to build a dedicated vaccines facility that will only be used during a pandemic period, it is essential for Member States to plan in advance their interpandemic needs and share this information with manufacturers, as requested by Commissioner Kyprianou.

Vaccines will be required urgently in the event of a pandemic but their timing and availability will be linked to several factors:

- the amount of antigen per dose, a lower level will enable more doses to be produced per week;
- the production yield of the pandemic virus strain, which could be inferior, equal or superior to seasonal influenza production yield;
- the timing of the availability of vaccine candidate strains and reagents;
- the fast-track release mechanisms by regulatory authorities (batch-release, universal packaging material).

EVM members are currently working on:

- producing H5N1 candidate vaccines on pilot and industrial scale;
- securing the supply of key raw materials (eggs, adjuvants, ...);

- developing vaccines in cell culture production systems;
- studying new vaccine formulations;
- increasing capacity in bulk manufacturing facilities

### **3. Evaluate alternative/complementary vaccination strategies**

A number of alternative/complementary approaches to the one consisting of vaccinating during the pandemic, are currently under evaluation by various public organisations or authorities, including WHO. The strategy of using a vaccine for the actual human pandemic strain has the disadvantage that it will only be available several months after the pandemic has begun.

One of the approaches currently under consideration is to use vaccines prepared using avian strains in anticipation of the pandemic (“pre-pandemic” vaccines). It is based on the assumption that these vaccines could elicit an immune response with a certain degree of cross reactivity with future human pandemic strains. This, of course, needs to be scientifically evaluated.

Alternative strategies, including making the best use of stockpiled vaccines or through pre-emptive vaccination programmes are being considered (figure 1):

1. Using a stockpile of pre-pandemic vaccines in selected populations (to be defined) immediately at the start of the pandemic, without waiting for the pandemic vaccine to become available. A second dose of pandemic vaccine could be given when available. This would represent a first line of defence;
2. “Prime-boost” approach, consisting of a “prime vaccination” with monovalent pre-pandemic vaccines during the inter-pandemic period. At the time of a pandemic, one single “booster” injection of the actual human pandemic vaccine would be given. This would enable a larger proportion of the population to be immunised more quickly.
3. Stand-alone vaccination programmes consisting of two doses of pre-pandemic vaccines given in advance of a pandemic. This would spread the vaccination programme across many years, rather than requiring a large surge in capacity at a single point in time. It could represent a long-term approach against several potential pandemic strains.

The scientific evaluation of these strategies requires a better understanding of:

1. the immunological and virological methods to assess the protective efficacy of pandemic vaccines;
2. the cross-protection of vaccines prepared using avian strains against mutated human forms of the virus, for example between the prototype vaccines using the H5N1 Viet Nam 2004 strain and the clade 2 strains isolated in Turkey or Indonesia;
3. the confirmation of the “prime-boost” effect observed in the current studies when two doses of pre-pandemic vaccines (adjuvanted or non adjuvanted) are given several months apart.

To this end, public-private partnership funding should be devoted to establishing the necessary scientific rationale of these strategies. This would also have a major impact

on the regulatory approach, as this means considering full license of "pre-pandemic" vaccines in addition to the "mock-up" approach, with a more comprehensive pre- and post-licensure clinical development.

#### **4. Allocation of Pandemic vaccines**

The vaccine industry is making considerable efforts to expand and maximise production capacity to prepare for a potential influenza pandemic. The implementation of points mentioned above will also lead to an increase in pandemic vaccine availability.

Nevertheless, as MSs will legitimately request pandemic vaccines to protect their entire population, even with these measures in place, it is prudent to assume that the population to be protected will still be greater than the number of vaccination courses available. Moreover, the timeline of the pandemic vaccine production will not make it possible to meet all vaccine orders in a short timeframe. Consequently, this will have an impact on the allocation of pandemic vaccines.

The industry role is to produce as much pandemic vaccine as possible, but the EVM considers that it is not its role to allocate pandemic vaccine doses beyond contractual agreements. This situation raises important political issues about allocation of supply in the event of an influenza pandemic.

As regards developing countries, the EU Commission, together with the Member States, should explore the creation of a Flu Fund aimed at supporting those countries most in need of pandemic vaccine.

#### **5. Liability**

In normal circumstances, vaccine manufacturers/Marketing Authorisation Holders are responsible for the legal liabilities arising from the use of vaccines that are manufactured and administered according to the Marketing Authorisation.

In the exceptional event of a flu pandemic, tight deadlines will need to be met, and it may be that health authorities in the Member States would urgently require pandemic vaccines for mass vaccination. At that time, it is assumed that the pandemic vaccine will have been evaluated and given a positive opinion by the EMEA, but that clinical experience will be limited to the mock-up vaccine containing another viral strain.

Manufacturers' liability protection from any vaccine adverse experience in these circumstances needs to be put in place by the competent authorities with the coordination of the EU before the production and delivery of pandemic vaccines.

Today the discussion in Europe has not led to any concrete proposal, although some MSs have accepted a liability waiver as part of the contractual agreements with vaccine manufacturers. In other countries, such as USA and Australia, specific liability measures have been implemented.

## Conclusion

Since the publication of EVM's first Proposal for an Action Plan in February 2004, industry has moved forward with the development of prototype pandemic vaccines and research is ongoing to optimise vaccine formulation and increase production capacity.

At the same time, there have been some initiatives by the European institutions, mainly focused on regulatory issues. Some Member States are supporting the development of vaccines, through contractual agreements with manufacturers to provide pandemic vaccines or to deliver prototype vaccines for stockpiling.

Industry will continue working on R&D and industrial challenges, but collaborative efforts are urgently needed to face the pandemic threat including:

- EU support for additional research and development activities;
- MSs implementation of WHO 75% coverage objectives for interpandemic influenza vaccination;
- The evaluation of alternative/complementary vaccination strategies

In addition to these major issues, other aspects such as allocation of pandemic vaccines and liability should be jointly addressed by the Commission, Member States and the industry.