Regulatory issues related to stockpiling of pandemic flu vaccines - abstracted from a draft WHO document "Regulatory preparedness for pandemic influenza vaccines" (currently under development, April 2007)

Introduction

Over the last year, WHO, Health Canada, and the US Food and Drug Administration and have jointly convened and supported two workshops on regulatory preparedness for pandemic influenza vaccines. The first of the workshops was held in Ottawa, Canada, 8-11 March 2006 and the second in Bethesda, Washington, 12-13 June 2006. This process, has led to development of a draft WHO document which aims to promote regulatory convergence for assessment of human pandemic influenza vaccines, and thus facilitate rapid global access to such vaccines. In addition the process has created a global network of key regulators engaged in pandemic influenza vaccine regulation. The document will be subject to a two-day consultation in June 2007 and, after further revision, submitted to the WHO Expert Committee on Biological Standardization in October 2007.

Although not yet established as WHO guidance for regulators, the draft document provides useful pointers to current regulatory thinking. Therefore relevant sections have been abstracted and reproduced below to inform the SAGE during their deliberations on an influenza vaccine stockpile.

The numbering of the sections corresponds to the numbering of the complete document. The complete document is not provided since it runs to over 100 pages, but can be made available on request.

1. Regulatory Pathways

1.6 Criteria for Emergency Use

It is recognized that, since the timing of a pandemic or how quickly it may spread cannot be predicted, a high probability exists that the full licensure process requirements will not be able to be met before vaccine is needed and that some sort of Emergency Use authorization process will be required.

While it may seem desirable that internationally accepted criteria for an emergency use release be established, this is difficult for a number of reasons. Firstly, within each jurisdiction, existing laws and regulations will dictate what, if any, emergency options are available. While some NRAs may have a range of regulatory options which could be used in an emergency, other countries may be restricted in this area. It is recommended that countries carefully
review their available options and, as a matter of urgency, implement any corrective measures that may be needed as soon as possible. Secondly, once it is determined that an emergency option needs to be invoked, which options to be used will depend on how much and what type of data has been generated on the vaccine, if any, and to what extent the vaccine needs to be distributed under this option. Although a developing country at the source of the pandemic may need to commence a large scale immunization campaign, other countries may need to use the emergency option only for certain groups of people who need to be immunized on a priority basis. Therefore, rather than establishing data criteria for the use of an emergency option, it is the data available which will dictate which emergency use option is most suitable.

- **Standard Process**

A proposed process to guide jurisdictions in the use of an emergency option is provided as Appendix III to this document.

**2. Scientific and Clinical Assessment**

**2.1 Introduction**

Whatever manufacturing strategy is used, the production and handling of live influenza viruses during the initial stages of manufacture of an inactivated vaccine, and throughout the manufacture of live attenuated influenza vaccines, requires the availability of an appropriate containment facility (BSL 2+ for modified prototype strains; BSL3 for wild virus) as defined in WHO TRS 941 Annex 5 (2007), and independent evidence that vaccine manufacture is in compliance to the appropriate biosafety standard.

**2.3 Stability criteria applicable to human pandemic influenza vaccines**

Independent from the substrate used for virus growth and from the method of production, storage periods assigned to intermediates, to the drug substance and to the drug product should be justified by real time real condition data and should further be supported by stability studies conducted under elevated temperatures. Pandemic influenza vaccines for stockpiling will need a particularly well defined stability testing program in order to justify the selected design of the stockpile and to ensure continued immunogenicity and safety throughout the stockpiling period. Vaccine components (e.g. bulk antigen and adjuvant) might be stored separately.
Periodic non-clinical and/or clinical reinvestigation of a stockpiled vaccine might be necessary. The final stability testing program should be agreed on by the NRA.

2.6 Special considerations for human pandemic influenza vaccines intended for use before the pandemic is declared

Several countries are (mid-2006) exploring pandemic preparedness options that include use of human pandemic influenza vaccines in the pre-pandemic phase. The economic incentive of such an approach to manufacturers could stimulate vaccine production by immediately using pandemic candidate vaccines in specific parts of a population or whole populations thus ensuring short-term returns on investments made by manufacturers. The public health benefit could be significant but relies on a number of parameters which are difficult to predict such as the match of influenza virus subtype present in the vaccine and the actual pandemic strain, or the affected age group. In the ideal case a vaccinated population will benefit from a primed immune system by either being completely protected from pandemic influenza virus infections, or experiencing less severe disease outcomes after exposure to the pandemic virus. This may be accomplished by rapidly responding to booster vaccination or exposure to pandemic influenza virus. Potential risks linked to pre-pandemic use of pandemic candidate vaccines are adverse drug reactions induced by a vaccine that provides no immediate benefit or no benefit at all in case the vaccine virus strain does not match with the actual pandemic strain, or the vaccine has no cross protective potential against drift variants of the original vaccine strain.

Given the need for regulatory preparedness for all possible intended uses of human pandemic influenza vaccines, regulatory considerations for the following scenarios will be outlined:

- Use of a human pandemic influenza vaccine in pre-pandemic phases in selected parts of a population or whole populations
- Prime/boost concepts with a first dose given in the interpandemic phase followed by revaccination(s) once a pandemic has been confirmed (which means that the effect of booster dose(s) must be shown in clinical trials to demonstrate that “priming” was effective if this strategy is chosen)

This guideline does not address the requirement for development and authorisation of live attenuated influenza vaccines intended for use in the pre-pandemic period.
The data presented in a regulatory dossier for human pandemic influenza vaccines intended for pre-pandemic use shall all be derived from a vaccine prepared with a variant virus antigenetically and genetically closely related to the influenza virus against which protection is claimed. Any data with other strains that may or may not belong to the same antigenic and genetic group or another subtype could be considered to be supportive. This regulatory pathway is in contrast to the regulatory pathway in one region of the world for vaccines intended for use after the pandemic is declared where, in principle, a regulatory submission may be based on any influenza virus strain to which the study population is immunologically naïve.

In line with WHO policy on multidose presentations, an effective antimicrobial preservative may be needed, based on a risk assessment of possible microbial contamination during use and the maximum recommended period after first use of the vial (in-use shelf life). Tests for the antimicrobial preservative should be included, if appropriate, and, if done, may be conducted on the bulk vaccine. The applicant should investigate any interference of the antimicrobial preservative, if included, with other tests.

Immunogenicity data derived from an accepted animal model that responds well to human influenza vaccine (e.g. ferrets) are expected before commencing human clinical trials. The investigations should include an evaluation of immune responses according to dose and dose interval using vaccine that contains the strain intended for the final product. Immunogenicity studies in relevant animal models are also useful to document consistency of production, in particular during the validation phase of a human pandemic influenza vaccine manufacturing process. Immunogenicity data for the first three batches should be presented to document consistency of production. The choice of immunogenicity assay(s) needs to be approved by the NRA, and the assays need to be appropriately validated and standardized in such a way to enable comparison of data between different studies.

For whole virion, split or subunit inactivated influenza vaccines for human use manufactured from an established production process and formulated to be similar to a licensed interpandemic vaccine (apart from the strain), non-clinical safety investigations need not be repeated, provided that they have been performed in accordance with relevant WHO and national/regional requirements.

Changes relating to the dosage of whole virion, split or subunit human pandemic influenza vaccines derived from a licensed process will also not require non-clinical safety testing unless
a single human dose exceeds 45 µg of HA antigen. This threshold is based on evidence from seasonal pandemic influenza vaccines currently licensed in the one Region of the world which contain 15µg HA of each of the 3 human influenza strains (=45µg). For this amount of HA (plus corresponding impurities) safety has been confirmed over many years with many different influenza drift variants. If a candidate vaccine exceeds this threshold, a study on local tolerance of single and repeated dose administration is required. Investigation of local tolerance of repeated doses administration is also required when the intended vaccination schedule consists of multiple doses of vaccine containing in total more than 45 µg of HA antigen. This threshold is based on the same evidence cited above. Also, in view of the possible use human pandemic influenza vaccines in pregnant women, animal reproductive toxicity studies should be performed.

Human pandemic influenza vaccines derived from a new manufacturer or production process will require a complete non-clinical study program as stipulated in the relevant WHO and national or regional guidelines.

Use of any of the human pandemic influenza vaccine types mentioned above in combination with a well-established adjuvanting system will also only require local tolerance studies following administration of single and repeated doses. New adjuvanting systems where no experience exists in relation to human use need to be specifically investigated for their safety profile, separately and in combination with the influenza virus antigen.

It is expected that non-clinical safety testing should normally be performed with the vaccine candidate that contains a variant virus antigenetically and genetically related to the strain intended for the final product. If some or all of the data have been obtained with seasonal vaccine strains, or other potential pandemic strains the applicant should justify the relevance of these data to the final product. If reference is made to the literature as supportive bibliographic data, this literature should be provided and its relevance to the human pandemic influenza vaccine candidate should be discussed.

For human pandemic influenza vaccines intended for use before the pandemic is declared, protective efficacy cannot be established in human clinical trials. Therefore, challenge studies in appropriate animal models (e.g. ferrets or other relevant animals) to provide evidence regarding the potential protective efficacy of a human pandemic influenza vaccine in man should usually be conducted using the both the wild strain from which the vaccine virus was derived as well as more distant antigenic variant wild type viruses compared to the vaccine
strain. If the applicant submits data from challenge studies performed only with other potential pandemic strains the relevance of the findings to the final product should be justified. It is difficult to provide specifications for such tests until more data become available. Instead a detailed justification for the definition of the non-clinical endpoints selected for the animal studies, e.g. death, weight loss, virus excretion rates, clinical symptoms such as fever, runny nose and eyes, etc. on which estimation of non-clinical efficacy will be built.

In principle, the clinical development of human pandemic influenza vaccines intended for use before the pandemic is declared should be in accordance with the general WHO and relevant national or regional recommendations regarding the clinical development of vaccines. In the pre-submission phase the applicants are encouraged to present and discuss with NRA's the clinical development plan and any interim results.

For a human pandemic influenza vaccine intended for use before the pandemic is declared the indications for use that are initially approved should strictly reflect the characteristics (e.g. age range and/or immunocompetence) of the population(s) in which it is considered that sufficient data are available to support the indication. As with all vaccines, variations to these indications that extend the population in which dose recommendations have been established may be approved if suitable data are provided. However, studies in children and adolescents to evaluate immunogenicity and safety should be initiated only after acceptable data have been obtained from studies conducted in healthy adults. Studies in infants and toddlers should only be initiated when data from older children and adolescents have been found acceptable. It is possible that the manufacturer will not be able to generate data for all age and risk categories. Under these circumstances, some degree of extrapolation might be allowed (e.g. from healthy adults to older and younger age categories). The appropriateness and extent of any extrapolation that is allowed will have to be considered on a case-by-case basis and will depend on the total data available. Applicants seeking such extrapolations should seek advice from the relevant NRA.

The clinical studies should provide a detailed characterization of the immunological responses to the human pandemic influenza vaccine candidate that contains the strain intended for the final product. Data generated during clinical studies conducted with vaccines that contain other influenza strains may be considered to be supportive.

In one region of the world, three immunological criteria ((a) seroprotection, (b) seroconversion and, (c) a sufficient increase in geometric mean titre (GMT)) are evaluated in human clinical
trials every year because of the annual update of seasonal influenza vaccine strain composition (CPMP/BWP/214/96). For a candidate seasonal vaccine in which the only change from a vaccine registered for the previous season is the new strain(s), at least one of these criteria have to be exceeded for the immunogenicity of the new strain(s) to be considered acceptable. For a candidate seasonal vaccine that is new (e.g., from a new producer or based on a new production method such as cell culture rather than eggs) then all three criteria have to be met and a very good justification must be given when this is not the case. This may happen, for example, if a given study population have a very high residual immunity already pre-vaccination that can not be further boosted by the candidate vaccine (or any other influenza vaccine). In mid-2006 the latter approach was being widely used in many countries to evaluate candidate human pandemic influenza vaccines. However, the seroconversion criterion applied in this context, of an HI titre of at least 1:40 after vaccination, is based upon an assumption of a correlation of this titre with a reduction in influenza-like illness, hospitalization and deaths from influenza and its exacerbations under the condition of the presence of some degree of pre-existing immunity against the influenza strains included in the vaccine. This correlation, between HI titre and protection, may not be as strong for human pandemic influenza vaccines for which the human population is immunologically naïve, as would be the case if the vaccine was used before the pandemic was declared, and also for a time afterwards. Evidence suggests that there may be different degrees of reduction in disease linked with the serological performance of the vaccine strain. However, the ratio between these two factors is unknown.

As a general principle, vaccines used for primary immunisation of a previously immunologically naïve population should induce as high an immune response as possible. This principle needs to be balanced, in the special circumstances of a human pandemic influenza vaccine, with the need for an antigen-sparing approach for vaccine formulation to maximize vaccination coverage.

Taking all the above factors into account, human pandemic influenza vaccines intended for use before the pandemic is declared should induce high GMTs and seroconversion rates, most preferably after only two doses. More specifically, it could be argued that all three criteria (seroprotection, seroconversion and sufficient increase in GMT) as defined in guideline CPMP/BWP/214/96 should be exceeded in the target population, with GMT in addition to seroprotection rates being the most important. Based on current (mid-2006) understanding, the public health benefit of a vaccine fulfilling or exceeding these immunological criteria cannot be fully estimated. Although unlikely, it also cannot be excluded that there will be no public health benefit if all these serological criteria are not fulfilled. Applicants should explain and justify the expected public health benefits if a candidate vaccine does not fulfill all serological
criteria specified above. Good data from immunization/challenge trials in animal models (Stohr et al, 2006) would greatly assist in the decision making process.

In addition to HI titres, neutralising antibodies should be measured in at least a subset of vaccinated individuals, using standardized procedures or with reference to an international standard serum. Although additional immunological assessments, such as explorations of cell-mediated immunity and neuraminidase inhibition, are of unknown relevance to protection, these should be explored in a subset of vaccinees to provide more insight into the overall effects of vaccination.

Immune responses should be determined at intervals after completion of the primary series in at least a statistically valid subset of the vaccinated population to investigate the need for revaccination. At the time of initial licensure, these data may be limited (e.g. to 6-12 months and for only a subset of the vaccinated population). It will be expected that applicants will have plans in place to follow antibody levels over time and commitments to this effect should be agreed at the time of first approval.

Also, as part of post-approval commitments, the applicant should investigate antigenic cross-reactivity elicited by each vaccine to circulating influenza viruses with human pandemic potential (i.e. drift variants). However, no clinical claims of cross-protection against drift variants should be made without provision of additional evidence (e.g. cross-neutralizing activity of post-vaccination antisera and/or protection demonstrated in challenge models).

Despite the naivety of the population even a single dose of an inactivated vaccine used before the pandemic is declared, may be sufficient to elucidate an immune response of public health benefit. However, because of the uncertainties a priming schedule with two (or even more) doses of vaccine may be preferential as well as incorporation of an adjuvant. Thus in addition to the need to determine the optimal dose of the antigens, several potentially feasible vaccination schedules should be explored.

The optimal dose and schedule may depend upon:

- Vaccine specific factors, such as type and amount of antigens, content and type of adjuvant
- Population specific factors such as age, immunological naivety to the potential pandemic strain(s)
The circumstances of use. For example, a short duration regimen would be needed to urgently achieve seroprotection of persons who might come in contact with the virus, such as poultry workers.

In general, for each specified target population group at least 50 immunologically naïve individuals should be enrolled into dose finding studies for each vaccine candidate (see table 1). Once the applicant considers that an appropriate formulation and schedule has been identified for healthy adults aged from approximately 18-60 years, the safety and immunogenicity of the final choice of vaccine candidate should be evaluated in larger numbers in a similar 18-60 year old population. The total database for safety in this first population to be studied should be as shown in Table 1 and as discussed below. Depending on the population included in the initial dose-finding studies, sub-stratification by age may be appropriate to obtain more information in under-represented strata. These strata should preferably be predefined. the clinical development program should be agreed on by a NCA.

Extension of the population in which the vaccine may be indicated for use (e.g. by age group and/or risk factors) may be based on studies completed before or after initial licensure. The data requirements are summarised in the table.
Table 1: Dose finding and safety studies by population group

<table>
<thead>
<tr>
<th>Minimum sample size of immunologically naïve individuals to be studied at each dose and/or regimen in studies performed to identify acceptable formulations and schedules</th>
<th>Size of safety database (Based on ADR detection limit)</th>
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</thead>
<tbody>
<tr>
<td>Adults from 18 to 60 years</td>
<td>≤0.1% (To reach an ADR detection limit of &lt; than 0.1% inclusion of approximately 3000 individuals into the safety data base is necessary).</td>
</tr>
<tr>
<td>• At least 50.</td>
<td></td>
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<tr>
<td>Specified age groups (e.g. adults over 60 years of age, adolescents, children, infants)</td>
<td>0.1 – 1% (^1)</td>
</tr>
<tr>
<td>• For each specified age group and for each vaccine candidate investigated, at least 50 immunologically naïve individuals need to be included</td>
<td></td>
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<tr>
<td>Specified risk groups (e.g. immune compromised individuals, chronically ill patients)</td>
<td>≤ 1% (^2)</td>
</tr>
<tr>
<td>• For each specified risk group and for each vaccine candidate investigated, at least 50 immunologically naïve individuals need to be included</td>
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The size of the safety database for each human pandemic influenza vaccine will be different depending on the population studied, as defined in table 1. Follow-up of clinical trial study participants for the evaluation of safety should be at least 6 months and should include specified parameters (for example as defined in guideline CPMP/BWP/2490/00). These data should be submitted as part of the license application. If any new issues regarding safety arise during the clinical development programme, or use, these need to be followed up specifically as part of a risk management plan.

If the human pandemic influenza vaccine contains thiomersal as a preservative, relevant WHO and national or regional guidance should be followed.

\(^1\) The size of the safety database depends on the individual clinical investigation programs. Advice from Authorities should be sought.

\(^2\) For each specific risk group, unless justified.
As mentioned above, at the time of initial licensure plans should be in place to assess antibody persistence, cross-reactivity to new circulating variant viruses (compared to the vaccine strain) and responses to booster doses in cohorts of vaccines from each age and risk group for which registration is sought. There should also be plans ready to assess efficacy after exposure to circulating influenza virus of pandemic potential (see section 4). These plans are important to provide insight as to whether prior vaccination may afford at least some protection against strains that might trigger a pandemic. Whenever the opportunity arises, NRAs should request further information on safety, immunogenicity and efficacy to expand the vaccine database. It is especially recommended to collect additional data in populations which have been studied to a lesser extent in the pre-authorisation clinical trials. In the event of a declared pandemic, attempts should be made to estimate the effectiveness of prior vaccination in persons who do and do not receive a dose of any pandemic vaccine through standardized and well controlled trials. A Risk Management Plan should be provided with safety information for each major population group that have not been studied or have only been studied to a limited degree in the pre-authorisation phase.

As for seasonal influenza vaccines, it might be necessary to change the influenza strain included in a human pandemic influenza vaccine intended for use before the pandemic is declared, especially if antibodies raised against the vaccine strain show no or negligible cross-reactivity against circulating viruses with current pandemic potential. In order to up-date the pandemic vaccine (e.g. to replace H5N1 of clade x with H5N1 of clade y) in such a vaccine, the marketing authorization holder should submit complete manufacturing and quality data related to the new strain. A study in relevant animals should be conducted to demonstrate that immune responses to the new strain in the vaccine are at least as good as were those to the initial strain in the licensed product. Applicants are advised to obtain advice from the relevant NRAs regarding the extent and type of clinical data that would be required. It should be noted that different requirements would likely apply if there was an intent to change the H/N type of strain (e.g. from a H5N1 vaccine to a H7N7 vaccine). Advice from relevant NRAs should be sought on the regulatory framework and data requirements for such a change.
4. Post-Marketing Surveillance

4.3. Special considerations if human pandemic-like influenza vaccines are used before the pandemic is declared

Although very limited knowledge on immunogenicity and safety, and no knowledge on efficacy with regard to cross-protectivity with the pandemic strain, will be available, some governments have plans to create stockpiles of pandemic-like influenza vaccines and may choose to use these vaccines in certain populations considered at risk (e.g. those involved in culling exercises, veterinarians and laboratory workers collecting and processing specimens) before an officially declared pandemic situation. Some countries may also opt to use these vaccines in WHO Phases 4 and 5 for pandemic preparedness (e.g. if a vaccine strain was considered a close-enough match to a virus that had been shown to transmit between humans). If pandemic-like influenza vaccines are used in the pre-pandemic period, this will provide important opportunities to collect data on safety and immunogenicity. Data collection should allow for well-designed and pre-planned analysis of the immunogenicity, including the response to booster doses (if applicable), cross-immunogenicity/protection with other strains as well as the local and systemic short and long-term safety of the pandemic-like influenza vaccines. These data should be assessed for implications on surveillance activities during the pandemic and for the need for any modification of post-marketing surveillance plans.
Appendix III: Emergency use pathways for human pandemic influenza vaccine

**Declaration of Pandemic**

*No data available*

- Proceed immediately to pandemic manufacturing
- Early release of available pandemic vaccine via:
  - animal rule authorization
  - clinical trial in high risk/targeted groups
  - EUA
  - importation of pre-qualified pandemic vaccine

**Declaration of Pandemic*  

*Limited pre-pandemic data available*

- Non-clinical and human clinical trials with pre-pandemic vaccine
- Proceed immediately to pandemic manufacturing
- Determination as to value from use of pre-pandemic vaccine via:
  - animal rule authorization (if only non-clinical trials completed)
  - clinical trial in high risk/targeted groups
  - immediate licensure of pre-pandemic vaccine
  - importation of pre-qualified pre-pandemic vaccine by developing countries
- Early release of available pandemic vaccine as above

**Declaration of Pandemic*  

*Extensive pre-pandemic data available*

- Application for licensure of pre-pandemic vaccine
- Pandemic vaccine manufacturing initiated
- Early release of available pandemic vaccine via:
  - clinical trials
  - EUA
  - importation of pre-qualified pandemic vaccine

**Pandemic spreading quickly/ Vaccine needed**

*No data with pandemic vaccine available*

- Non-clinical and human clinical trials with pandemic vaccine
- Application for licensure of Pandemic Vaccine
- Early release of available pandemic vaccine via:
  - clinical trials
  - EUA
  - importation of pre-qualified pandemic vaccine

**Pandemic spreading quickly/ Vaccine needed**

*Some data available*

- Sale/Use of Vaccine for immunization
- Vaccine Licensure through Accelerated Approval or Early release of available vaccine via:
  - clinical trials
  - EUA
  - importation of pre-qualified pandemic vaccine

*Contingency needed in event that actual pandemic strain differs significantly from pre-pandemic strain. Data determined from pre-pandemic may be of little value for extrapolation to use with pandemic strain*