Under the *Microscope*

**Regulatory issues in pandemic influenza vaccine development**

The Therapeutic Goods Administration (TGA) is responsible for the licensing of vaccines used in Australia. This includes pre-market evaluation aspects (such as assessing the quality, efficacy and safety of vaccines) and post-market aspects (such as batch release testing and the monitoring of adverse reactions). For inter-pandemic and pandemic influenza vaccines, TGA is also involved in the selection of appropriate vaccine viruses and the calibration and supply of reagents for the production of influenza vaccines. Together with industry, TGA has a responsibility to ensure that all regulatory and good manufacturing requirements (GMP) are met to ensure vaccine safety and efficacy.

Pandemic influenza potentially presents a major global emergency with limited options for intervention. The use of public health interventions and antivirals, as well as the implementation of an effective national pandemic plan, will be crucial in the first wave of the epidemic and beyond to contain outbreaks as they occur. Vaccines, however, will be necessary to curb any pandemic.

Pandemic vaccines will not be immediately available when the pandemic strikes, as it will take time to produce vaccine using an appropriate virus strain(s). The first batches could be produced in a few months but it may take up to a year to produce enough vaccine to cover most of the Australian population. Inter-pandemic vaccine generally has a timeline involving 7-11 months, therefore the development of strategies to shorten the time between the emergence of a pandemic influenza virus and the availability of safe and effective human pandemic influenza vaccines is of the highest priority.

There will be many critical steps for pandemic vaccine development, including the identification of vaccine candidate strains, preparation of seed lots, which may involve reverse genetics, appropriate animal safety data, safety and clinical data on the pandemic influenza vaccine, and finally manufacturing and distribution. Manufacturers will require at least 2-3 months from seed strain availability to production of the first lots of vaccine for laboratory and safety testing.

The whole process is both fickle and fragile, with possible delays occurring during any stage of production from the development of pandemic vaccine seed strains to distribution. Moreover, as the virus is cultured in embryonated hens eggs, there may be a poor virus yield and, depending on the characteristics of the virus, the haemagglutinin content may also be low, resulting in manufacturing difficulties.

Nearly all of the world’s inter-pandemic influenza vaccines are produced in embryonated eggs. Egg-based vaccines offer a long history of safety with few viral and prion safety concerns and are generally efficacious, but there are limits to the quantities that can be produced.

Inter-pandemic influenza vaccines available in Australia are prepared as inactivated, non-adjuvanted vaccines containing antigens from the virus as split virion vaccines or subunit vaccines. Whole virion influenza vaccine is used only in one country at this time; however, while purified influenza virus surface antigens are in general less reactogenic, they are much less immunogenic compared to purified whole virion vaccines in immunologically naive individuals, including small children. Moreover, in individuals with residual immunity, purified influenza virus surface antigens display a booster rather than a primary immunisation effect requiring annual uptake of inter-pandemic influenza vaccines in order to boost the immune system to seasonally circulating strains.

Pandemic vaccines using newer technologies such as cell culture and recombinant protein technology are...
developing and will aid in increasing global vaccine production, but influenza vaccines using these technologies are not currently widely registered. At the present time, further information is needed to determine if these approaches to influenza vaccine production are sustainable in a regulatory framework and there may also be additional regulatory considerations for vaccines produced using recombinant protein technology. While some countries have registered cell culture based influenza vaccines, and the use of qualified cell cultures for influenza vaccine production is accepted by regulators, it is not yet used very extensively. The use of attenuated pandemic vaccines might also be possible in Australia if appropriate safety and clinical data are generated and such vaccines have been safely used in the USA and Russian Federation.

To help speed up the regulatory process in the event of an influenza pandemic, the European Medicines Agency (EMEA) has provided scientific guidance to manufacturers and regulators, requiring a ‘core pandemic dossier’ to be supplied during the inter-pandemic period. Such a dossier would contain quality, safety and efficacy data for a ‘mock-up’ vaccine, where virus strains with pandemic potential or related viruses are used to generate safety and efficacy data (e.g. H5, H9, H7, H2 and H1 viruses). TGA has accepted the EMEA guideline.

The ‘mock’ vaccine would include viral antigen(s) to which humans are immunologically naïve and the antigen in ‘mock-up’ vaccine would be different from those in the inter-pandemic influenza vaccines. Clearly, clinical data from inter-pandemic vaccine cannot be extrapolated to a pandemic situation as inter-pandemic vaccines contain three viruses given as one dose with 15μg concentrations of each virus without adjuvant, whereas a pandemic vaccine would likely contain one virus strain, have a different antigen content and concentration, be adjuvanted, possibly preserved and have a different dosing schedule. Moreover, some manufacturers may choose to produce the virus using novel production systems. Therefore regulators will require studies with potential pandemic viruses to determine their safety and efficacy.

Ideally, the ‘mock-up’ vaccine would be produced in same way as intended for pandemic vaccine whether it be cell culture or egg derived. Comparisons would be made between whole virion and split or subunit vaccines; it would have similar antigen content as any future pandemic vaccine; it would have the same adjuvant system (if used) as the future pandemic vaccine; preclinical testing to establish safety and immunogenicity would be available; and clinical trial data with the

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**Figure 1.** Steps involved in the development and approval of southern hemisphere inter-pandemic and pandemic influenza vaccines (thanks to Christopher Boswell and immunobiology staff at TGA Laboratories for assistance with the figures).
‘mock-up’ vaccine would be generated. If all these parameters were met then the safety, efficacy, dose and dosing schedule could all be quickly assessed by the regulator when a pandemic is declared.

During a pandemic a variation would be submitted to the TGA which would require the submission of quality data only related to the pandemic influenza strain and a commitment from the sponsor to gather clinical information during a pandemic. This would provide a faster approval process (Figure 1).

Industry itself has taken significant steps to improve its pandemic preparedness, including the construction of new production plants meeting higher biosafety standards, investigation of various antigen sparing technologies, the use of different adjuvants, and the development of libraries of candidate vaccine prototypes. Some of these steps may also influence the quality, safety and efficacy of inter-pandemic influenza vaccine production.

Laboratory tests for potency and safety may not be the same for inter-pandemic and pandemic influenza vaccines. For inter-pandemic vaccines, the haemagglutinin and neuraminidase of seed viruses are identified by immunological tests. For a pandemic vaccine, it is likely that vaccine production will be underway before reagents are available for identity testing and PCR-based tests will be needed for identification.

Vaccine potency is normally assessed by single radial immunodiffusion (SRID) tests. This test requires strain-specific antigen and antiserum reagents, which normally require 3 months to prepare. In the absence of SRID reagents, alternative potency tests such as protein, SDS PAGE, dot blot or ELISA may have to be used and these would need to be validated by vaccine manufacturers and regulators prior to the pandemic. SRID tests should be done on final product but, if there are difficulties due to presence of adjuvant, alternative validated potency tests would need to be developed (Figure 2).

Endotoxin tests are required for batch release and the limulus amoebocyte lysate (LAL) test is generally used, but there may be interference from adjuvant, requiring the LAL test be done on the bulk vaccine before the addition of adjuvant. Vaccine stability would need to be determined and a modified batch release programme, including protocol and QC data evaluation, may need to be considered by regulators.

In the battle against pandemic influenza, vaccines will be essential and their production and availability will rely on strong partnerships between industry, regulators, WHO and national health authorities.

Reference